Lessons from the European Prospective Investigation into Cancer and Nutrition (EPIC) Study for the Development of Cross-Country Nutritional Epidemiologic Research in East Asia

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Summary The European Prospective Investigation into Cancer and Nutrition (EPIC) study is a prospective cohort study with about 520,000 study participants enrolled from 23 centers in 10 western European countries (Greece, Spain, Italy, France, Germany, Netherlands, United Kingdom, Denmark, Sweden, and Norway). This study is unique in that food frequency questionnaire-based dietary assessment methods are tailored to different eating habits in different countries, while maximum efforts were made for standardization of the food composition database and dietary intake calculations. Such an international collaboration project has not been conducted in East Asian countries, where dietary habits are considerably different from those in European and other countries. Accurate assessment of dietary intake in Asian countries is particularly challenging, as Asian diets are generally complex, consisting of many variations of composite and mixed dishes. Nevertheless, these large variations in dietary habits warrant thorough investigation into the association between dietary factors and chronic diseases within each country. On the other hand, with technological advancement, more and more large-scale prospective cohort studies have used repeated measurements of dietary intake based on a more detailed dietary assessment method, such as multiple-day dietary records, which have not been incorporated in EPIC. Here, the author briefly summarizes the experiences and considerations in the conduct of EPIC as well as the current situation of dietary habits and research methodology in East Asian countries, and then discusses the importance of the development of cross-country nutritional epidemiologic research in East Asia in the near future.

Key Words nutritional epidemiology, international collaboration, dietary assessment, Europe, East Asia

During the past few decades, interest in the relationship between diet and the risk of chronic disease has resulted in a substantial number of prospective epidemiologic studies, providing a wealth of scientific evidence on preventive and detrimental dietary factors on a range of health outcomes. One of the largest successful studies is the European Prospective Investigation into Cancer and Nutrition (EPIC) (1). This study is unique in that different dietary assessment methods (country-specific dietary assessment questionnaires) were used in each country, while maximum efforts were made for standardization of the food composition database and the calculation of dietary intakes. Such an international collaboration project has never been conducted among East Asian countries, where dietary habits are considerably different from those of countries in Europe. Here, the author briefly summarizes the experiences and considerations in the conduct of EPIC as well as the current situation of dietary habits and research methodology in East Asian countries so that development of cross-country nutritional epidemiologic research in East Asia can be further explored in the near future.

A brief overview of EPIC: its rationale and dietary assessment methodology

EPIC is one of the largest prospective cohort studies in the world, with more than half a million (about 520,000) participants enrolled from 23 study centers in 10 European countries: Greece, Spain, Italy, France, Germany, Netherlands, United Kingdom, Denmark, Sweden, and Norway (1). EPIC was designed to investigate the relationships between diet, nutritional status, lifestyle and environmental factors, and the incidence of cancer and other chronic diseases. Due to the geographical spread of the countries, from northern to southern Europe, variation in dietary intake was large, which makes it possible to study the impact of diet across a wide range of intakes. This is important because, for example within the Netherlands, saturated fat intake is traditionally quite high and homogenous, so to study the impact of saturated fat, we need more variance, which in EPIC is the case due to the Mediterranean countries. For dietary assessment, information on the usual diet was collected by country-specific dietary assessment questionnaires at enrollment in 1992–2000 (2). To calibrate dietary measures, a standardized, computer-assisted 24-hour dietary recall was also conducted at each study center on stratified ran-
dom samples of the participants (approximately 37,000 individuals) (3). To improve comparability of nutrient databases across 10 European countries, a harmonized nutrient database was developed, containing 26 major nutrients and their related components between 550 and 1,500 foods per country (about 10,000 foods in total). EPIC represents the largest single resource available today world-wide for prospective investigations into the etiology of cancers and other diseases that can integrate questionnaire data on lifestyle and diet, biomarkers of diet and of endogenous metabolism and genetic polymorphisms (1), and so far more than 1,600 scientific articles have been published based on EPIC.

**How different are dietary habits and eating patterns between East Asian and European countries? Findings from Japan**

Mainly due to their possible contribution to long life expectancy, much attention has been focused on the characteristics of Japanese dietary habits. Compared with those in Western countries, the Japanese diet typically includes a high consumption of refined grains, soybean products, seaweeds, vegetables, fish, and green tea and a low consumption of whole grains, nuts, processed meat, and sugar-sweetened beverages (4). Further, the proportion of daily energy intake consumed at breakfast, lunch, dinner, and snacks is, on average, 23%, 30%, 40%, and 8%, respectively, in Japan, while the ranges of corresponding values are 9% to 20% (median 16%), 16% to 42% (26%), 24% to 40% (32%), and 10% to 35% (26%), respectively, in the 10 European countries in the EPIC study (5). These large differences in dietary habits warrant thorough investigation on the association between dietary factors and chronic diseases within a specific population.

**What we can learn from EPIC: a vision for East-Asia collaboration from the European experience**

While EPIC is undoubtedly one of the major sources for generating evidence regarding diet-health relationships, one always has to have in mind that the approach of assessing diet in this consortium is reflecting the state of the late 1980s with some small but strategically important innovations. In EPIC, the diet of all participants was assessed once by country-specific structured food frequency questionnaires (FFQs) based on a suggested list of key food and nutrient variables. It was immediately seen that the diversity of actually used food frequency questionnaires (FFQs) might have hampered proper EPIC-wide diet-health analyses due to differences in assessment quality including mean and variation. Thus, a calibration instrument was subsequently introduced in a small subgroup (n=36,000) comprising one 24-h recall per subject that should act as an EPIC-wide reference assessment. An approach based on so-called linear calibration was used in many publications but the tendency was inevitable to report calibrated and uncalibrated results often into confusion for the readers. The major difficulty to publishing calibrated results only was the insight that after center-specific calibration, the mean could be considered as reflecting the reference mean of the center populations but not the variation. The variation reflected the variation measurable by the various FFQs but not the variation existing in the population.

At the time of flourishing EPIC-results, statistical progress led to models identifying the error structure of the assessment instrument. The models needed at least two measurements per subject. The increasing complexity of such error identification models obtained in subsamples could be one of the reasons that they hardly were used in full cohort analysis. In EPIC, the group got funding by the EU for developing a common web-based FFQ for all EPIC centers including a small calibration study for the participating centers. However, the application of the instrument was not funded in subsequent applications, thus leaving EPIC with one measurement and linear calibration until now.

A clear learning experience from EPIC can be seen in the fact that standardization should be done from the beginning and that fixing approaches at later stages always requires optimal conditions which will often not exist. In this context, it seems that modelling of the error structure within subsudies and subsequent application in the full study to correct the diet-health estimates does not serve as a solution due to uncertainty of transfer and the hampering effect of the long duration of such studies. In addition, it is always questionable to initially present weak data that by statistical magic gain credibility.

The world is nowadays different compared to the start of EPIC, particularly in respect to collecting substantial data amounts, and use of digital devices, and AI. Web-based only cohort studies such as the NutrNet Sante Study (6) have been established with the collection of several selfadministered 24-h recalls. In addition, well developed web-based 24-h recalls for self-administration are provided by some groups. Statistical modelling could show that the combination of short-term (24-h recalls) and longterm assessment instruments (FFQs) generates results better than either of the two single approaches. This could be a general principle for future dietary assessment strategies by using a number of different sources of information for modelling individual diets. In the modelling framework described above, the FFQ (that could be applied several times) has still an important role as prime covariate information, and a longterm assessment instrument is particularly good at improving the estimates for rarely consumed foods. Further, hybrid solutions are being established trying to combine the best elements of the approaches (7). In the last approach, it was the aim of the modelling to generate simultaneously high internal and external validity of the dietary data.

It seems as if diet is not a subject of ex-post approaches to organize meta-analyses, since precisions are often replaced by compromises. Instead, only “a priori” coordination of potential common analysis in the future should be organized. The coordination should clearly cover a common detailed food code such as
FoodEx2, a common web-based 24-h recall, a common FFQ, and a clear modelling strategy. An important feature of the coordination should be that the core elements of the assessment could be extended but not compromised by novel developments. Additionally, the ability of the 24-h-recall to record time and meal context of each food consumption offers the possibility to include timing of food consumption into the risk analysis, leading to a more extended understanding of eating.

**Potential barriers and opportunities for the development of cross-country nutritional epidemiologic research in East Asia: experience in Singapore**

Generally speaking, accurate assessment of dietary intake in Asian countries is challenging, as Asian diets are generally complex, consisting of many variations of composite and mixed dishes. This is particularly relevant in multi-ethnic cosmopolitan settings, such as Singapore. Nevertheless, such settings would provide a good opportunity for investigating the relationship between diet and disease, given that the variation in dietary intakes would be larger in multi-ethnic populations than in homogeneous populations (but also risk confounding due to differences between these ethnic groups with respect to other lifestyle habits). In Singapore, a food frequency questionnaire was developed for multi-ethnic populations (8). This is a good example to highlight that dietary assessment questionnaires need to be substantially more elaborate to cover different Asian ethnic cuisines, in this case Indian, Malay, and Chinese cuisines. This food frequency questionnaire was successfully validated against 24-h dietary recalls and blood and urine biomarkers (9). This kind of methodological development is valuable given that recent research suggests that effects of selected food groups or nutrients may differ between Asian and Western populations. For example, the effect of moderate alcohol consumption on cancer risk may be more detrimental in some East Asian populations (10). This justifies further research focusing on East Asian populations.

**Conclusions**

Although an establishment of cross-country nutritional epidemiologic research in East Asia may be challenging, particularly because of the complex nature of dietary intake and eating behaviors, it would not be impossible if experiences from other countries such as EPIC as well as technological development were fully appreciated. Such research would advance more nutrition research.

**Disclosure of state of COI**

No conflicts of interest to be declared.

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