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**LETTERS TO THE EDITOR**

**Confounders in Asian studies**

**Amy Luke**

Dear Sir:

Epidemiologic studies of salt in Asia deserve attention because the Asian population has twice as high an intake of salt as US or European populations (1). Therefore, the articles by Takachi et al (2) and Umesawa et al (3), which appeared in recent issues of the Journal, and any other studies of salt from Asia deserve consideration in future reviews. The report by Takachi et al is particularly important because it included cardiovascular disease (CVD) and cancer as the outcomes. However, at least 2 points should be considered in future reviews.

First, the studies may involve residual confounding of associations of total salt intake with diseases risks. Takachi et al (2) reported that salted-fish consumption was one of the sources of salt and was significantly associated with a 14% lower risk of CVD or a 34% lower risk of myocardial infarction. As discussed by the authors, the findings supported cardioprotective roles of omega-3 polyunsaturated fatty acids (n–3 PUFAs). The authors identified correlations between intakes of salted fish and salt (r = 0.1–0.3). The associations between CVD and fish and salt intake indicated that conclusions on the basis of total salt intake were confounded by n–3 PUFA intake.

Similarly, phytoestrogen may be a residual confounder of associations between total salt intake and cancer risks. Other studies that used the Japanese cohort of Takachi et al (2) previously related salt and phytoestrogen to cancer outcomes (4–6). One of the dietary sources of phytoestrogen and salt is miso soup, which is a typical feature of the Japanese diet; Takachi et al (2) reported a positive correlation between miso soup and total salt intake (r = 0.4). Thus, analyses of associations between total salt and cancer may need adjustment for phytoestrogen intake.

Cumulative observations suggested that n–3 PUFAs and phytoestrogen may confound associations of total salt with chronic diseases in Japan. Notably, 90% of Japanese adults consume >1.0 g n–3 PUFAs/d and >3.0 g sodium/d, whereas 75% of US adults consume <0.8 g n–3 PUFAs/d and <4.0 g sodium/d (1, 7). Intakes of phytoestrogen, teas, or other culture-specific foods show similar characteristics. Therefore, Takachi et al and other investigators in Asia should carefully consider covariates for different disease outcomes and mutual confounding by multiple dietary factors.

The second concern about these studies is that their analyses do not take into account their cohort design. The cohorts of Takachi et al (2) and Umesawa et al (3) were from nationwide multicenter studies, and analyses were often performed without adjustment for the multiple centers. Takachi et al argued that adjustment for regions could have masked associations. However, the attenuation is not necessarily a bias. After adjustment for regions, the authors would be able to obtain more valid results without bias or ecological fallacy due to unmeasured confounders, such as regional socioeconomic environments.

Moreover, the multicenter designs could cause nondifferential misclassification due to the difference in validity of any assessments across regions. In the cohort of Takachi et al (2), amounts of sodium intake, validity of dietary assessments, and disease incidence were different across regions (8, 9). An extreme example of the Japanese study is the consumption of pickled vegetables, which was positively associated with gastric cancer in the study of Takachi et al. In validation analyses, energy-adjusted correlation coefficients for pickled vegetable consumption between dietary records and food-frequency questionnaires ranged from −0.19 to 0.49 across regional

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areas (8). Pooling all individuals without adjustment for regions, the ecological approach reasonably showed a higher correlation coefficient, 0.54 (8). Therefore, with regard to the regional difference in outcomes (2), Takachi et al may have provided results with non-differential misclassification. These issues may be present in other multicenter cohort studies (3), and thus future reviewers should interpret such studies carefully.

In conclusion, studies from Takachi et al (2), Umesawa et al (3), and others undertaking similar analyses may provide results with unadjusted regional and dietary confounding. Additional studies, or even reanalyses of the nationwide cohorts, are needed to provide valid results of associations between salt and diseases. Minimizing such potential biases will allow valid inference about benefits by reducing salt intake without reducing intakes of beneficial nutrients, such as n–3 PUFAs, or without moving across regions. Investigators and reviewers for the Journal should be aware of the aforementioned methodologic issues based on cultural backgrounds and relatively complex study designs.

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Reply to F Imamura

Dear Sir:

In our study (1), we did not adjust for n–3 polyunsaturated fatty acid (PUFA), which is abundant in dried and salted fish, or isoflavones, which are major phytoestrogens in miso soup, because we were concerned that entering the 2 variables into multivariable models would have led to overadjustment due to collinearity. Further adjustment for n–3 PUFA and isoflavones as suggested by Imamura, however, did not change our principal findings materially: original and reanalyzed multivariable hazard ratios (HRs) of total cancer for the highest compared with lowest quintiles were 1.15 (95% CI: 1.04–1.27; P for trend = 0.01) and 1.16 (95% CI: 1.04–1.28; P for trend = 0.01), respectively, for salted fish roe, and 1.04 (95% CI: 0.93–1.16; P for trend = 0.61) and 1.05 (95% CI: 0.93–1.18, P for trend = 0.57), respectively, for sodium. Findings for cardiovascular disease (CVD) also showed no material change, with corresponding HRs of 0.86 (95% CI: 0.74–0.99; P for trend = 0.04) and 0.82 (95% CI: 0.70–0.96; P for trend = 0.01), respectively, for dried and salted fish, and 1.19 (95% CI: 1.01–1.40; P for trend = 0.06) and 1.20 (95% CI: 1.01–1.43; P for trend = 0.07), respectively, for sodium.

We usually adjust for study area in Japan Public Health Center–based prospective studies (2) but chose not to do so in this article on the basis that, although the study areas had wide variation in sodium intake, validities of intake were relatively low and different for individual areas, with narrow variations, albeit that they were reasonable for the study as a whole. Differential correlations according to study areas between consumption of sodium or salted foods estimated by our food-frequency questionnaire and those calculated by diet records were chiefly within the range of random variation caused by the relatively small number of subjects in the validation study in each area (n = 51–61). Furthermore, the correlations were not generally associated simultaneously with regional differences in sodium or salted food intake and with differences in the incidence of total cancer or CVD. It is therefore unlikely that our choice not to adjust for study area resulted in biased observations due to nondifferential misclassification.

We understand that no observational study can perfectly control potential confounding factors and that caution is therefore required in the selection of variables with regard to both biological and statistical considerations. Furthermore, the possibility of residual confounding should always be acknowledged.

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