Point/Counterpoint

Not the Time to Abandon the Food Frequency Questionnaire: Point

Walter C. Willett and Frank B. Hu

Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts

In a recent editorial, Kristal et al. (1) asked whether it is time to abandon the food frequency questionnaire (FFQ) for studies of diet and cancer. They highlighted three recent ''developments'' to cast doubt on the value of the FFQ. The first is the ''growing lack of consistency both within and across studies examining diet and cancer risk.'' Although some inconsistencies are to be expected in a topic as complex as diet and cancer, due to both chance and true biological interactions, when large prospective studies have been analyzed in a similar manner as is done in the Pooling Project of Prospective Studies of Diet and Cancer (2), there has been remarkably little heterogeneity among studies. Findings from these prospective studies have often been inconsistent with earlier case-control studies, which is most likely due to bias in the latter, as recognized by Kristal et al. This does not seem to be due to greater validity of the more intensive interviewer-administered diet history typically used in case-control studies; when data from such a diet history and from a typical FFQ were both compared with diet records, the correlations with the FFQ were as strong or stronger than those with the diet history (3).

A second ''development'' identified by Kristal et al. is the Observing Protein and Energy Nutrition study, in which intakes of energy and protein assessed by FFQ and 24-hour recalls were compared with corresponding biomarkers (4). Correlations for absolute intakes were low and lower than seen between the 24-hour recalls and FFQ. The authors concluded that the correlations between FFQ and 24-hour recalls were erroneously high due to correlated error and that the estimates of FFQ validity in previous studies had been overstated. As discussed elsewhere (5), the findings of this study are open to question because there was no realistic assessment of within-person variability in the biomarkers, which can create the false appearance of correlated error between the FFQ and diet recalls. Despite this serious limitation, the validity of energy-adjusted protein intake assessed by FFQ in the Observing Protein and Energy Nutrition study was nearly identical to what we have earlier reported (5). In addition, FFQs have been shown to have good correlations with biomarkers of fatty acid intake (linoleic acid, long-chain *n*-3 fatty acids, and *trans*-fatty acids) measured in adipose tissue (6). These biomarkers are more likely to reflect time-integrated long-term intake because of slow turnover of adipose tissue.

The third ''development'' cited by Kristal et al. was a small cohort study (168 cases) from the United Kingdom (7), in which a very strong association (even without adjustment for measurement error) between total and saturated fat and risk of breast cancer was reported using a 7-day diet record [for highest versus lowest quintile, relative risk (RR) = 1.79; 95% confidence interval (95% CI), 0.89-3.56; P_{trend} = 0.05 for total fat; RR = 1.98; 95% CI, 1.05-3.72; P_{trend} = 0.005 for saturated fat], whereas a weaker and nonsignificant association was seen using a FFQ (for highest versus lowest quintile, RR = 1.31; 95% CI, 0.65-2.64; P_{trend} = 0.52 for total fat; RR = 1.35; 95% CI, 0.69-2.61; P_{trend} = 0.23 for saturated fat). On this basis, Kristal et al. suggest that an important association with dietary fat and breast cancer has been missed in other cohort studies. The findings of Bingham et al., however, seem doubtful in light of the results of the Women's Health Initiative (8) trial (for low versus high fat groups, RR = 0.91; 95% CI, 0.83-1.02); if the United Kingdom findings were correct, the Women's Health Initiative trial should have stopped years ago. Moreover, the validity of dietary total fat assessed by FFQ has been evaluated by comparison with lipid biomarkers and found to be high (9). In addition, with the massive numbers of cases in the prospective studies (7,329 cases, for 5% of energy increase in total fat multivariate, RR = 1.00; 95% CI, 0.98-1.03), it is quite unlikely that an association of the magnitude reported by Bingham et al. for total or saturated fat intake during midlife or later life has been missed due to measurement error.

Underlying the concerns of Kristal et al. seems to be the lack of support in large prospective studies for several favored diet-cancer hypotheses. However, using the same questionnaires and populations, clear and consistent associations have been seen between various aspects of diet and risks of coronary heart disease and type 2 diabetes (10, 11) and with biomarkers that likely mediate these relationships (12). Thus, although it is possible that small effects have been missed, the lack of hypothesized associations in large studies of diet and cancer and particularly the pooled analyses is not simply due to insensitivity of FFQs to differences in diet or to lack of variation in diet within the populations studied. One possibility is that the hypotheses for which no associations have been found are not true. Another possibility is that the temporal relationship between diet and cancer has not yet been addressed adequately; both latency and specific ages of susceptibility may be important. The complex nature of cancer causation is very different than for cardiovascular disease; for the latter, many lines of evidence indicate that most exposures act quite proximal to diagnosis (but not exclusively proximal). The challenges for research on diet and cancer are illustrated by the fact that the latency between the onset of smoking and lung cancer is ~30 years and that intense exposure to ionizing radiation in the American atomic bombing of Japan had virtually no effect on breast cancer risk for women exposed after age 40 (13). Thus, if dietary factors act to block the action of these or other genotoxic events, they would have been missed in the vast majority of epidemiologic studies or randomized trials published thus far. Our finding that intake of animal fat among young premenopausal women was positively associated with breast cancer risk (14), whereas no

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Requests for reprints: Walter C. Willett, Department of Nutrition, Harvard School of Public Health, 665 Huntington Avenue, Boston, MA 02115. Phone: 617-432-4680; Fax: 617-432-0464. E-mail: walter.willett@channing.harvard.edu

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association was seen among older women using the same FFQ, further suggests that examination of diet during this and earlier periods of life may be critical. Further, most published prospective reports on diet and cancer have had ≤10 years of follow-up. Finally, our findings that overall dietary patterns and diet quality indices were associated with the risk of estrogen receptor–negative breast cancer, but not overall breast cancer risk, further underscore the complexity of diet-cancer relationships (15, 16). Future studies will need to analyze subtypes of cancer and also examine the role of overall diet.

Questioning of our measurement methods is of course healthy, and hopefully, this would lead to improved precision. Kristal et al. suggest several alternatives, which would be worth investigating. However, even a perfect measurement of diet during a short interval, such as a 7-day diet record, will have considerable error as a measure of long-term intake; the correlations for energy-adjusted intakes over ~1 year tend to be in the range of 0.5 to 0.7 and decline with time, meaning that repeated assessments will be needed to capture long-term intake well. The efficiency and ease of completing the FFQ is an advantage in this regard, and we have seen that repeated measurements do provide greater validity and, thus, stronger associations and narrower CIs (17). For example, in comparison with the average of diet records collected in 1980 and 1986 from participants in the Nurses' Health Study, deattenuated correlation coefficients for energy-adjusted intakes of total and saturated fat were 0.57 and 0.70 using only the 1980 FFQ but 0.83 and 0.95 when using the average of 1980, 1984, and 1986 FFQs.[1] Consistent with this finding, important associations between cardiovascular disease and diabetes would have been missed in our cohort studies if we had only used our baseline dietary assessment rather than the cumulative average of questionnaires updated every 4 years (18, 19). When considering improvements of dietary assessments, one important option is to build into FFQs more detailed information to focus on specific hypotheses; this can be done whether the format is printed page or electronic. For example, the hypothesis that *trans*-fatty acids increase risk of coronary heart disease was an aim of our research since 1980. We therefore collected detailed information on types of cooking fats and type and brand of margarines every 4 years and repeatedly analyzed commonly used margarines and other foods for fatty acid composition to account for changes in manufacturing. With this detailed information, we were able to show clear associations for coronary heart disease, type 2 diabetes, blood lipids, and inflammatory markers (20-24). Similarly, more detailed information may be needed for cancer-related hypotheses, such as methods of cooking meat, to address the role of heterocyclic amines. We should not assume that a single FFQ is appropriate for all applications and in all populations.

When evaluating new methods, it will be important to consider the temporal relation between biomarkers and short-term methods when the interest is in long-term intake; if the two are assessed close in time, their correlation will tend to be overstated, which can be viewed as a form of correlated error. For example, in the Cambridge European Prospective Investigation into Cancer and Nutrition study, the correlation with plasma vitamin C level was considerably higher with a 7-day diet record than with a FFQ when they were all assessed at the same time (25). However, the correlation with plasma vitamin C level measured ~1 year earlier, which addresses the validity of long-term intake, and the correlations of the biomarker with energy-adjusted intake of vitamin C assessed by diet record and FFQ were virtually identical (26). Other data using biomarkers with appropriate temporal comparisons also suggest that the FFQ and repeated 24-hour recalls have similar validity (27, 28). Although incorporation of biomarkers into diet-cancer studies will undoubtedly enhance the study design, biomarkers are complementary to, rather than a replacement for, FFQs in large epidemiologic studies. Although improvement of dietary assessment methods is a worthy pursuit, to abandon the FFQ, which is highly informative in epidemiologic applications, before alternatives are shown to be superior would be unwise.

[1] Unpublished data.

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