

Reflections on nutritional cancer epidemiology

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In this issue of the Journal, no fewer than 5 articles provide new results on the association between diet and cancer (1–5). These articles address different aspects of research on diet and cancers, and a careful discussion of strengths and weaknesses of each study and the implications of their results would go beyond the scope of this editorial. However, their concomitant publication offers the opportunity for some considerations of the general nature on nutritional cancer epidemiologic research.

A first theme, which is illustrated by the results of 3 of the studies, is the importance of stratifying cancers according to clinical and molecular characteristics. In the first study (1), an association with a vegan diet was weaker for advanced prostate cancer, the most relevant form of the disease from a biologic and a clinical viewpoint, than for the whole population of patients, thus detracting from the plausibility of a real association. In the second study (3), an association between meat intake and colorectal cancer survival was suggested for patients harboring a Kirsten rat sarcoma viral oncogene homolog (*KRAS*) mutation. In the third study (5), a protective effect of vegetable intake was suggested for hormone receptor-negative cases of breast cancer. The understanding of the molecular heterogeneity of human cancers has grown enormously in the past decade, leading to major advances in patient stratification and more effective therapeutic interventions (6). Most cancer epidemiologic research previously did not follow this trend, largely because epidemiologists rely on antiquated instruments, such as death certificates and reports of cancer registries, to assess the occurrence of cancer. It is clearly the time to invest a much larger number of resources in the assessment of outcomes, including access to tumor samples and to results of molecular analyses.

The need for increased specificity in the definition of the phenotype leads to a consideration on the role of prospective cohort studies in etiological research on diet and cancer. The current paradigm is that prospective cohort studies provide stronger evidence in support of, or against, a given hypothesis than other study designs, such as the retrospective (case-control) study and the cross-sectional study (7). The main argument in favor of the prospective approach over the retrospective or the cross-sectional approach is the reduced opportunity for bias from selection of study subjects and assessment of dietary exposures. One limitation of cohort studies, however, is the ability to investigate rare outcomes, and the molecular and clinical stratification of cancer patients discussed above poses important challenges in terms of statistical power. For example, in the study of meat intake and colorectal cancer

survival, molecular data were available for 40% of patients, and the group of *KRAS*-mutated cancers accounted for <30% of this group, i.e., 12% of the whole series (3). In a prospective cohort study of colorectal cancer, with cumulative risk in the age range of 45–64 y equal to 2%, 16,000 individuals are needed to achieve 80% power to detect as statistically significant a relative risk of 1.5 because of an exposure with 10% prevalence; in the case of an outcome with cumulative risk of 3.6/1000 (to follow the example of *KRAS*-mutated colorectal cancer), the same power can be achieved with a cohort of 135,000 individuals. One possible solution is the organization of consortia including multiple cohorts (8); however, heterogeneity in the design of the available studies remains an important challenge of consortia. In the face of such constraints, it is important to reassess the contribution of alternative, more efficient approaches, such as the retrospective case-control study: a systematic evaluation of the presence and magnitude of bias in the results of case-control studies, compared with cohort studies, would provide important information on circumstances under which retrospective studies might represent a suitable complementary approach.

Finally, the 5 articles illustrate the methodologic and conceptual complexity of research on nutritional determinants of cancer. Hypotheses with strong biologic rationale, such as that of a protective effect of flavonoids on colorectal carcinogenesis, are not confirmed by more extensive and methodologically solid studies (4), and associations considered well-established, such as the protective effect of vegetarianism on cancer risk, do not always sustain replication (2). These apparently conflicting results are likely to reflect, at least in part, flaws in some of the underlying studies, including dietary misclassification and inadequate control of confounding. It is plausible, however, that they also reflect real heterogeneity in the associations between nutrition and cancer across populations. The genetic background might influence the effect of dietary constituents, the composition of foods, and the whole dietary patterns would affect the biological effects on genetic or epigenetic targets relevant to carcinogenesis, as would interactions with nonnutritional factors. Only a small number of dietary factors exert such a strong effect on human cancer, leading to consistent results across multiple populations:

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the risk of hepatocellular carcinoma from aflatoxin intake (9), and that of head and neck cancer from alcohol drinking (10), are among these strong, replicable associations. Most of the effects of dietary factors on cancer, however, are small in magnitude and depend on an array of host and environmental factors. In these circumstances, the accumulation of the evidence will not follow a unidirectional, monotonic pattern, and any conclusion and evaluation should be considered preliminary and subject to refinement as new data accumulate.

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