Recent findings reported by Brasky et al. (1) contradict the expectation that high consumption of n-3 polyunsaturated fatty acids (PUFAs) would reduce the risk of prostate cancer. A generally held view is that omega-6 fatty acid (n-6FA) promotes tumor development because arachidonic acid–derived oxylipins have proinflammatory and proangiogenic effects. n-3 fatty acids (n-3FAs) are thought to protect from cancer because they are substrates for the same metabolic enzymes used by n-6FA, thus suppressing the formation of the protumorigenic n-6FA–derived oxylipins. Furthermore, n-3FA–derived oxylipins have been shown to have anti-inflammatory and antiangiogenic properties, which provide additional protection against carcinogenesis. Why, then, after decades of research, have n-3FAs not established themselves as effective preventive agents in clinical medicine?

Numerous clinical studies have failed to consistently show an inverse relation between circulating n-3FA and cancer risk, and some studies, including that of Brasky et al. (1), have actually shown that high plasma n-3FA levels are associated with increased cancer risk. We believe that the conflicting data are likely to result from the failure to address the complexity of fatty acid (FA) metabolism. Furthermore, circulating levels of FAs are unlikely to reflect the target tissue exposure to the multiple oxylipins, whose tissue concentration is influenced by an array of environmental and genetic factors. Cellular uptake of FAs is mediated by active transporters, which are differentially expressed and regulated in various cell types.

Metabolism of FAs is mediated by the cyclooxygenases, lipoxygenases, and the less investigated, but important, cytochrome P450 epoxygenases, three distinct but also overlapping pathways that lead to the formation of multiple oxylipins with profound cellular effects (2–4). Equally important are the catabolic pathways, such as prostaglandin dehydrogenase and soluble epoxide hydrolase, which convert oxylipins to less biologically active metabolites. To add to this metabolic complexity, most of the enzymes involved in the synthesis and degradation of oxylipins manifest genetic polymorphisms, which, at least in some cases, have been shown to modify cancer risk (5). Finally, metabolism of FAs has been shown to be affected by body weight and diet because both obesity and high-fat diet are associated with increased adipose soluble epoxide hydrolase expression, which inactivates epoxigenated oxylipins with anti-inflammatory and insulin-sensing properties (6). Collectively, these considerations suggest that n-3PUFAs are not compounds to be shunned, as could be inferred by the inconsistent associations between their plasma levels and clinical outcomes, such as cancer risk. Instead, they are likely to affect cancer risk but within specific autochthonous cellular and host contexts. State-of-the-art lipidomic, molecular, and pharmacologic approaches should be encouraged to unveil not only the antitumor properties of n-3PUFAs but also the characteristics of individuals likely to benefit. This will serve to optimize their clinical use as anticancer agents in the context of personalized medicine. The purpose of our correspondence is to avoid a common tendency in the prevention field to stigmatize a complex and poorly understood field with important potential, a tendency that runs contrary to classical proverbial wisdom that cautions against throwing the baby out with the bath water.

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References

Notes
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