Dietary Factors May Modify Cancer Risk by Altering Xenobiotic Metabolism and Many Other Mechanisms\textsuperscript{1,2}

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Expanded Abstract

The frequently asked question is “What is the relationship between alteration in xenobiotic metabolism and cancer risk?” Based on the two expanded abstracts by Drs. J. S. Felton and R. H. Dashwood as well as many publications, we can answer the question by stating: Dietary manipulations that alter xenobiotic metabolism leading to decreased carcinogen activation and enhanced carcinogen elimination are expected to reduce cancer risk.

We also know that a specific chemical may affect the metabolism of different carcinogens differently, and dietary chemicals may trigger other molecular events that could decrease or increase cancer risk. Therefore, information on the biological effects of dietary substances based on inadequate or inappropriate studies on biomarkers could be misleading.

Carcinogen metabolism was an active area of research in the 1970s and 1980s. In many earlier studies on the effects of dietary factors on carcinogenesis, carcinogen metabolism was a key target for study, and indeed, many dietary chemicals were found to affect Phase I (mainly cytochrome P450 enzymes) and Phase II xenobiotic metabolism enzymes (1,2). For example, inhibition of cytochrome P450-catalyzed carcinogen activation has been proposed as the mechanism of cancer prevention by organosulfur compounds such as diallyl sulfide and phenethyl isothiocyanates (2). Induction of Phase II enzymes that enhance the elimination of carcinogens has been proposed as the chemopreventive mechanism for sulforaphane and other compounds (3). However, recent studies also showed that these isothiocyanate compounds have other biological activities, such as induction of apoptosis and inhibition of histone deacetylase (4,5).

Indeed, many mechanisms of cancer preventive activity by dietary chemicals proposed in recent years are not related to carcinogen metabolism. These data were obtained when dietary chemicals were administered to animals in the postinitiation stage, that is, when the animals were no longer exposed to carcinogens or in studies with genetically modified mice in which exposure to carcinogens was not needed. In these studies, even for a single compound, many mechanisms have been proposed, including many signal transduction pathways that are related to cell proliferation, apoptosis, and angiogenesis. How do we determine which of the mechanisms are relevant and which are irrelevant for cancer prevention? This will be the topic of the remaining part of this article.

How do we distinguish relevant mechanisms from irrelevant information?

Mechanistic understanding of the chemopreventive actions of dietary chemicals is extremely important. It helps us to extrapolate information obtained from laboratory studies to human situations and in the development of useful biomarkers for health effects. The literature in this area, however, is rather confusing. For the compound (\textasciitilde)epigallocatechin-3-gallate (EGCG), the most abundant and biologically active polyphenolic compound in green tea, as an example, >50 targets or mechanisms have been proposed (6). Some of them are illustrated in Figure 1. It is possible that different mechanisms may be involved in different animal model systems for cancer prevention. Even for a specific experimental system, multiple mechanisms may be involved. But it is likely that only some of these proposed mechanisms are relevant to cancer prevention, whereas others are irrelevant or artificial. Many of the proposed mechanisms are based on studies in cell lines, some using concentrations (10–100 \textmu M) that were much higher than those achievable in animals or humans after consumption of tea or EGCG.

In general, if a biological effect can be caused by an agent in cell culture at concentrations that can be observed in animal blood and tissues, then we may expect a similar effect in vivo. Thus, among the different proposed mechanisms, the ones that are caused by low concentrations of the agent are more likely to be physiologically relevant. However, there are problems in determining the effective concentrations of an agent in vitro and in vivo and in making comparisons. For example, if we put 50 \textmu M EGCG in a cell culture system, the intracellular concentration may be much lower as a result of the instability and poor cellular uptake of this compound, whereas in a situation in vivo,
EGCG is more stable, and the intracellular concentration may approximate the tissue or plasma concentrations. These factors need to be seriously considered in future research.

The cell culture environment is quite different from the environment in vivo. For instance, the cell culture system is under rather high oxygen partial pressure (152 mm Hg). Redox-sensitive compounds, such as EGCG and other phenolic compounds, are not stable in most cell culture conditions. They are readily oxidized to generate superoxide radicals and H$_2$O$_2$, and these reactive oxygen species can induce apoptosis and inactivate membrane receptors. Some of these effects can be blocked by the addition of superoxide dismutase and catalase in the culture medium. The superoxide dismutase stabilizes EGCG by inhibiting its autooxidation. It is not known whether the autooxidation-induced changes occur inside of the animal tissue because most of the tissues are endowed with antioxidative enzymes and are under lower oxygen partial pressure (<40 mm Hg). Because of these factors, it is important to demonstrate the proposed mechanisms in animal models or appropriate human tissues. Immunohistochemistry, Western blot, and other molecular approaches are being used for this purpose.

**Literature Cited**