Biomarkers as Indicators of Cancer Risk Reduction Following Dietary Manipulation

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Background
The U.S. government has convened several public meetings and workshops to explore the role of biomarkers as tools for cancer detection and for assessing cancer risk. In 1999 NIH and FDA held a workshop entitled Biomarkers and Surrogate Endpoints: Clinical Research and Applications. In 2004 NCI and FDA sponsored a workshop on Research Strategies, Study Designs, and Statistical Approaches to Biomarker Validation for Cancer Diagnosis and Detection. Most recently, FDA's Center for Food Safety and Applied Nutrition, the Division of Cancer Prevention, NCI, NIH, and the Office of Dietary Supplements at NIH organized the currently reported workshop on “Biomarkers as Indicators of Cancer Risk Reduction Following Dietary Manipulation.”

Dietary interventions have the potential to significantly reduce the cancer disease burden, and validated biomarkers would be invaluable tools to facilitate research in this area. Biomarkers of exposure could be used to better assess intake of dietary constituents of interest and also provide an indication of exposure of key metabolites at cellular and molecular target sites. Markers of biological effect could lend plausibility to diet-cancer relations and contribute to our understanding of mechanisms of action. A variety of biomarkers are increasingly being used with the goal of identifying individuals susceptible to specific dietary exposures. Finally, validated biomarkers could result in more cost-effective and more feasible randomized controlled intervention trials and could also be used in observational studies.

Biomarkers could be used to address important research questions and ultimately be translated into public health recommendations. Although the number of biomarkers with potential relevance to diet and cancer has exploded in recent years, tests of their validity have not kept pace, and the interpretation of biological effect is often equivocal.

Purpose of meeting
There continues to be considerable interest and debate about the identification and use of validated biomarkers for evaluating the relation between diet and the risk of chronic diseases. The workshop was held to examine the use and misuse of potential biomarkers used to assess cancer risk.

The overall workshop goals were to identify potential biomarkers for cancer risk reduction that may be influenced by diet, identify and discuss the process needed to validate biomarkers, consider the potential pitfalls and misuse of biomarkers for cancer risk reduction, and recognize the research gaps and needs for validating biomarkers for cancer risk reduction.

These goals were addressed through a series of questions and topics that looked at the importance of biomarkers across the cancer continuum, particularly for cancer risk reduction and its relation to dietary component exposures.

Workshop questions/topics
- What are the strengths and weaknesses of cytological and histopathological indicators of cancer risk?
- What is the relation between alterations in xenobiotic metabolism and cancer risk?
- What does DNA (oxidative) damage and repair indicate about cancer risk?
- What do shifts in indicators of proliferation, differentiation, and apoptosis indicate about the cancer process?
- Emerging new and promising biomarkers.

Highlights and future research directions
Perhaps the most overarching conclusions from this conference underscored an appreciation of the essentiality, complexity, and value of validated biomarkers for making significant progress in understanding the diet-cancer prevention relations. Currently, very few validated markers exist; however, a number of potential biomarkers hold promise. Validation of useful biomarkers will likely require the conduct of large clinical studies of long duration, the very studies the use of validated biomarkers will, we hope, replace.

The conference identified several broad categories of biomarkers and a number of issues that needed to be addressed in the process of validating biomarkers for understanding the role...
of dietary components in cancer risk reduction. Additionally several research strategies were discussed to further the study of biomarkers.

**Categories of potential biomarkers**
- Tissues (colorectal adenomas, cervical intraepithelial neoplasia 3).
- Cells (proliferation, apoptosis, DNA adducts).
- Infection (human papilloma virus infection, *Helicobacter pylori* antibodies).
- Imaging (mammographic density, ovarian ultrasound abnormalities).
- Blood analytes (estrogen, prostate-specific antigen).

**Research strategies needed for validating biomarkers for cancer risk reduction**
- Characterize the healthy as well as the disease condition when identifying specific biomarkers.
- Demonstrate that the biomarker is associated with the cancer and the dietary manipulation.
- Study diet–gene interactions to gain a better understanding of the role and impact of genetic polymorphisms.
- Study the effect of the biomarker on chronic versus acute exposures of dietary factors.
- Evaluate dose and employ dose-ranging studies.
- Assess the timing of the dietary intervention in cancer progression and the effect on the biomarker.
- Identify appropriate compliance biomarkers for monitoring background exposure and intervention.
- Evaluate the whole organism when evaluating biomarkers modified by dietary manipulation; different dietary factors can alter many metabolic pathways, cancer sites, and organs.
- Standardize the methodological techniques for biomarkers.
- Use randomized clinical trials to validate promising biomarkers.

**Future research directions**
- Create a multidisciplinary group of scientists with representatives from many health outcomes and research foci to identify potential biomarkers for validation.
- Investigate a panel of biomarkers that could predict risk reduction for one or more cancers.
- Standardize methods for assessing the biomarkers, as well as the exposure of the dietary manipulation.
- Expand the use and availability of transgenic, knockout, and alternative animal models for the identification and validation of biomarkers.
- Expand the use of bioinformatics systems and tools for evaluating complex nutritional information, data analysis, and archiving.
- Expand the availability of databases for nutritionally related biomarker analysis and archiving.
- Maximize the potential of using existing studies for useful data in the future via storage of tissue samples for later study.

**Literature Cited**