IN THIS ISSUE

Long-term Antioxidant Supplementation for Cancer Prevention

Although epidemiologic studies have suggested that a diet high in fruits and vegetables, and thus certain antioxidants, may be associated with a lower risk of cancer, this finding has not been confirmed in randomized clinical trials. The discrepancy between clinical trial results and observational studies might result from insufficient follow-up, failure to evaluate antioxidants in combination, or other factors.

The Women's Antioxidant Cardiovascular Study, a double-blind, placebo-controlled 2x2x2 factorial trial, included about 8,000 cancer-free women who were assigned to take vitamins C, E, beta carotene, or placebo. After analyzing the trial data, **Lin et al. (p. 14)** found that supplementation with these antioxidants, alone or in combination, for an average of 9.4 years did not reduce the risk of developing cancer and dying from cancer.

In an accompanying editorial, **Albanes (p. 2)** discusses the many chemoprevention trials that were based on epidemiologic observations that suggested possible cancer-preventative roles of various nutrients. He suggests that, because controlled trials allow for the unbiased examination of multiple hypotheses, they will continue to shed light on the complex causes of cancer, even when they fail to show anticipated cancer prevention effects.

Integrating Genetic Association Results

The number of reports of associations between genetic variants and cancer is increasing rapidly. Because of this, a way to systematically appraise the evidence from these studies is needed. Using a database of studies that addressed associations between variations in DNA repair genes and specific cancers, **Vineis et al. (p. 24)** performed meta-analyses on 241 associations that had been addressed in at least two independent studies. The strength of each association was assessed.

They found that 31 associations reached a nominal level of statistical significance. These associations were also graded on the amount of evidence, extent of replication, and protection from bias. To do so, the authors used a recently developed grading system. Relatively few associations received high overall grades. When more stringent P values were required to account for multiple testing, only two genetic variants showed statistically significant associations with the risk of cancer. The authors suggest that this could be used as a model for identifying the evidence for such associations and assessing the strength of that evidence.

In an accompanying editorial, **Yesupriya et al. (p. 4)** outline the efforts of the Human Genome Epidemiology Network to develop a roadmap for identifying credible associations in which networks of investigators, including 14 groups focusing on cancer, will develop field synopses based on meta-analyses.

Cisplatin, Oxaliplatin, and a Mechanism of Hearing Loss

Patients treated with the chemotherapeutic agent cisplatin often experience hearing loss (ie, ototoxicity). However, those treated with oxaliplatin, another platinum-based chemotherapeutic agent, rarely lose their hearing. **Hellberg et al. (p. 37)** used HCT116 carcinoma cells and a guinea pig model to investigate cytotoxic and ototoxic mechanisms for cisplatin and oxaliplatin.

The authors found that cisplatin, but not oxaliplatin, induced apoptosis in cancer cells through pathways involving superoxide anions and calcium ions. In guinea pigs treated with equimolar concentrations of either cisplatin or oxaliplatin, the concentration of total platinum in cochlear tissue and the level of active drug in perilymph were higher in animals treated with cisplatin than those treated with oxaliplatin.

The authors conclude that cisplatin and oxaliplatin appear to induce different apoptotic pathways and that the lower cochlear uptake of oxaliplatin, compared with cisplatin, appears to be a major explanation for the lower ototoxicity of oxaliplatin.

Insulin, Insulin-Like Growth Factor-I, and Breast Cancer

Obesity has been linked to high circulating insulin and estrogen levels and to an increased risk of postmenopausal breast cancer. However, it is unclear whether circulating levels of insulin and/or insulin-like growth factor-I (IGF-I), a related hormone, are directly associated with the risk of breast cancer independent of estrogen level.

To investigate this question, **Gunter et al. (p. 48)** conducted a prospective case–cohort study of incident breast cancer among 93,676 nondiabetic postmenopausal women who were enrolled in the Women's Health Initiative Observational Study. The authors examined associations between incident breast cancer and fasting levels of insulin, total and free IGF-I, and estradiol and baseline characteristics (including body mass index and hormone therapy use).

Hyperinsulinemia and high endogenous estradiol levels were independent risk factors for postmenopausal breast cancer. These factors largely explained the association between obesity and the risk of breast cancer in postmenopausal women who were neither diabetic nor using hormone therapy.

Anti-EpCAM and Detection of Circulating Breast Cancer Cells

Identification of breast cancer cells in the peripheral blood of patients, which can provide important information about metastasis and the patient's prognosis, requires a method that can recognize all tumor cell types. **Sieuwerts et al. (p. 61)** investigated whether a commercially available test (the CellSearch Circulating Tumor Cell test, which uses antibodies against epithelial cell adhesion molecule [EpCAM] to isolate circulating breast cancer cells) can detect all five subtypes of breast cancer cells, including normal-like, basal, HER2-positive, and luminal A and B types.

The authors added 50-150 cells from 19 breast cancer cell lines (15 luminal, nine normal-like, five basal-like, and five HER2-positive), whose subtypes had been determined by gene expression profiling, to blood samples from a single blood donor and subjected the mixture to the CellSearch test.

The test did not recognize breast cancer cell lines with a normal-like subtype but did recognize the four other subtypes. The authors conclude that, because normal-like breast cancer cell have aggressive features, new tests are needed that include antibodies that specifically recognize normal-like breast cancer cells in peripheral blood.