A novel explanation for the role of dietary fiber in colorectal cancer

A high intake of dietary fiber is associated with a substantially reduced risk of colorectal cancer, but the mechanisms behind this association are far from clear. Nguyen *et al*. hypothesized that the beneficial effects of dietary fiber might be mediated by butyrate, one of the principal short-chain fatty acids produced by microbial fermentation of fiber in the gut. Butyrate is known to have anticancer effects *in vitro* that resemble the tumor-suppressive effects of transforming growth factor β (TGF-β).

Nguyen and colleagues' *in vitro* study examined the effects of butyrate in a non-neoplastic rat intestinal epithelial cell line (RIE-1), as well as in transformed RIE-1 cells and six human colorectal cancer cell lines. The authors showed that even low levels of butyrate potentiated some tumor-suppressive actions of TGF-β. This effect of butyrate on TGF-β signaling resulted from selectively increased expression and activation of SMAD3 (but not SMAD2) protein. Butyrate strongly inhibits histone deacetylases and, thus, modulates transcription by inducing conformational changes in chromatin; the authors suggest that this mechanism could explain the increased SMAD3 expression. Butyrate also increases activation of SMAD3 and, therefore, upregulates transcription of TGF-β-responsive genes after activated SMAD3 translocates to the nucleus.

Paradoxically, TGF-β also has tumor-promoting effects. The authors noted that butyrate inhibited one tumor-promoting effect of TGF-β, namely the induction of cyclooxygenase 2 expression. Further *in vitro* and *in vivo* studies by the same team are underway.

Original article Nguyen KA *et al.* (2006) Dietary fiber enhances a tumor suppressor signaling pathway in the gut. *Ann Surg* **243:** 619–627

Lymphoma risk is elevated even in new-onset inflammatory polyarthritis

Lymphoma is more than twice as likely to occur in patients with inflammatory polyarthritis than in the general population, a UK study has shown—supporting previous findings of a causal link between the incidence of inflammatory polyarthritis (which includes rheumatoid arthritis [RA]) and lymphoma. Whether lymphoma develops as a consequence of immunosuppressive treatment, or of the characteristics of RA or inflammatory polyarthritis, however, remains unclear. So, Franklin *et al.* measured lymphoma risk in an unselected cohort of patients with inflammatory polyarthritis, and evaluated the effects of disease severity and treatment history on this risk.

This prospective, primary-care-based study recruited 2,105 patients enrolled on the Norfolk Arthritis Register (NOAR) between 1990 and 1999, who were recently diagnosed with inflammatory polyarthritis, and had accessible hospital records. During annual follow-up, data on prescription drug use and disease severity were collected.

After a total follow-up of 15,548 person-years, the incidence of lymphoma was 7.07 cases per 10,000 person-years. Lymphoma risk was highest in patients who had ever tested positive for rheumatoid factor, those ever diagnosed with RA, or those who had ever received disease-modifying antirheumatic drugs. Methotrexate use carried the highest risk (~5 times that of the general population), although all these factors were interrelated.

The small number of lymphoma cases, however, meant that the authors could not draw definitive conclusions about the effects of disease severity and drug exposure on lymphoma risk. They highlight the need for appropriate control groups in future studies that explore the effects of antirheumatic drugs on lymphoma risk.

Original article Franklin J *et al.* (2006) Incidence of lymphoma in a large primary care derived cohort of cases of inflammatory polyarthritis. *Ann Rheum Dis* **65:** 617–622

TNF inhibitors plus cyclophosphamide could increase patients' cancer risk

Tumor necrosis factor (TNF) induces apoptosis in several tumor types. TNF inhibitors have become a mainstay of treatment in many inflammatory conditions, although it has been suggested that these agents could increase patients' risk of developing cancer. To date, these concerns have principally focused on lymphoma; however, Stone *et al*. now report that patients treated with both a TNF inhibitor and cyclophosphamide might have an increased