Raloxifene reduces breast cancer, but not cardiovascular, risk in women

In 1998, the Raloxifene Use for The Heart study was launched to investigate whether the selective estrogen-receptor modulator raloxifene reduces the risk of clinical coronary events and/or invasive breast cancer.

This randomized, double-blind trial recruited 10,001 postmenopausal women (mean age 67.5 years) with established coronary heart disease (CHD) or multiple CHD risk factors. Of these women, 5,044 were randomly allocated to receive 60 mg raloxifene daily; the rest received placebo. The incidence of invasive breast cancer and coronary events (including death from coronary causes, hospitalization for an acute coronary syndrome, and nonfatal myocardial infarction) was recorded over a median follow-up of 5.56 years.

Raloxifene treatment approximately halved the risk of invasive breast cancer (absolute risk reduction 1.2 cases per 1,000 women treated for 1 year), and was associated with a 33% lower incidence of all breast cancer, compared with placebo. Markedly fewer clinical vertebral fractures occurred in patients given raloxifene than in controls. Raloxifene treatment did not affect the risk of primary coronary events, but treated patients were nearly 1.5 times more likely to suffer venous thromboembolism or fatal stroke than controls. Hot flashes, leg cramps, and peripheral edema were also associated with raloxifene treatment.

The authors conclude that, although raloxifene treatment reduces the risk of invasive breast cancer, it does not reduce risk of coronary events in postmenopausal women with, or at increased risk for, CHD. Patients and clinicians must consider both the benefits and risks of raloxifene when contemplating its use.

Original article Barrett-Connor E *et al.* (2006) Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. *N Engl J Med* **355:** 125–137

Model identifies DNA mismatch-repair mutations in patients with colorectal cancer

The early identification of patients carrying germline mutations in the DNA mismatch-repair genes is vital to the successful management of colorectal cancer, as progression from adenoma to carcinoma occurs rapidly in these individuals. Given the expense of genotyping, a clinically driven method for identifying likely carriers could help optimize the use of resources.

Barnetson *et al*. present a model that identifies likely mutation carriers among patients newly diagnosed with colorectal cancer. The researchers used a prospective population-based approach to recruit 870 patients in Scotland with early-onset colorectal cancer. Data on several clinical variables were recorded for each patient, and family history was established following enrollment. Germline DNA from each participant was examined for DNA mismatch-repair mutations, and tumor samples were analyzed for microsatellite instability and by immunohistochemistry. A two-stage model was developed from these data using multivariate logistic regression. The first stage involves univariate analysis of clinical variables to identify likely carriers of mismatch-repair mutations. Tumor samples from these individuals are then tested to refine the carrier prediction. The model has a sensitivity of 62%, with an 80% positive predictive value, and has been validated in an independent cohort.

Among the original study participants, 38 mutations were identified. Carrier frequencies were two times higher in men than in women. Survival over 2,938 patient-years of follow-up did not differ between carriers and noncarriers. The authors suggest that this model (available at http://www1.hgu.mrc.ac.uk/Softdata/MMRpredict.php) could facilitate genetic testing decisions in patients with early-onset colorectal cancer.

Original article Barnetson RA *et al.* (2006) Identification and survival of carriers of mutations in DNA mismatch-repair genes in colon cancer. *N Engl J Med* **354:** 2751–2763

Close or positive margins in breast-conserving surgery: is re-excision always necessary?

A recent study by Chism and co-workers has addressed some of the controversies surrounding the importance of margin status and re-excision in breast-conserving treatment for early breast cancer.

Patients with stage I–II breast cancer and a close (±2 mm) or positive margin after initial excision were assigned to one of three groups: