Potter *et al.* prospectively assessed data for 24,999 patients referred from primary care to a specialist breast unit in southeast England from 1999 to 2005. The number of patients referred within 2 weeks rose by approximately 5.8% yearly, increasing from 1,751 in 1999 to 2,490 in 2005; however, during the same period the percentage of patients from this group diagnosed with cancer decreased substantially, from 12.8% to 7.7%. The opposite was seen in routine referrals—the numbers referred decreased by an estimated 4.3% yearly, but the proportion of cancers diagnosed increased alarmingly from 2.5% to 5.3%, meaning that patients in this group were 1.21-times more likely to be diagnosed with cancer year on year ($P<0.001$). Furthermore, waiting times for routine referrals increased with time.

The authors suggest that the need to adhere to the two-week-wait rule is decreasing diagnostic accuracy by undermining the skills and instincts of general practitioners, and call for an urgent review of these guidelines.

Original article Potter S *et al.* (2007) Referral patterns, cancer diagnoses, and waiting times after introduction of two week wait rule for breast cancer: prospective cohort study. *BMJ* **335:** e288

Interleukin-2 induces proliferation of regulatory T cells in patients with ovarian cancer

Interleukin (IL)-2 immunotherapy results in a 16–20% objective response rate in selected patients with cancer. Studies have demonstrated that IL-2 administration increases the pool of regulatory T (T_{REG}) cells in patients with pediatric sarcoma, melanoma and renal cell carcinoma. Wei *et al.* examined the effect of IL-2 therapy on T_{REG} cells in patients with ovarian cancer.

The study included 31 patients with ovarian cancer treated weekly with IL-2 for 16 weeks. IL-2 induced the proliferation of $CD4^+FOXP3^+$ T_{REG} cells *in vitro* in a dose-dependent manner. The administration of IL-2 induced the proliferation of existent $FOXP3^+$ cells. The prevalence of $FOXP3^+$ T_{REG} cells before IL-2 administration was negatively correlated with the potency of IL-2-induced proliferation, suggesting that T_{REG} cells are a key factor in the regulation of self-proliferation. *In vivo,* IL-2 increased the percentages of $CD4^+CD25^{high}$ T cells and induced their proliferation. These $CD4^+CD25^{high}$ T cells were also $FOXP3^+$ and could suppress T-cell activation. IL-2 upregulated the expression of the chemokine receptors CCR4 and CXCR4 on T_{REG} cells, which might enable their migration in response to CCL22 and CXCL12 (the ligands for CCR4 and CXCR4, respectively) in the tumor microenvironment. At 3 weeks after IL-2 treatment cessation, the number of T_{REG} cells was significantly reduced in clinical responders compared with nonresponders, indicating that T_{REG} cell changes might predict response after therapy.

On the basis of these results, the authors conclude that IL-2 induces the proliferation of T_{REG} cells and may promote T_{REG}-cell migration in patients with ovarian cancer.

Original article Wei S *et al.* (2007) Interleukin-2 administration alters the $CD4^+FOXP3^+$ T-cell pool and tumor trafficking in patients with ovarian carcinoma. *Cancer Res* **67:** 7487–7494

Androgen withdrawal improves tumor hypoxia in prostate cancer

Around one-quarter of patients who receive radical treatment for prostate cancer subsequently develop progressive disease. The mechanisms underlying this malignant progression are, however, poorly elucidated. Recently, Milosevic and co-workers have investigated the effects of androgen withdrawal on prostate cancer hypoxia. Androgen withdrawal is known to result in tumor regression in the majority of patients, and is effective in combination with radiotherapy.

Tumor hypoxia is associated with aggressive tumor behavior and the development of progressive disease. The researchers measured pretreatment tumor oxygen concentrations in 248 patients using an ultrasound-guided needle-electrode technique, and detected potentially clinically and biologically significant levels of hypoxia. In total, 22 of these patients received the androgen antagonist bicalutamide (150 mg/day) and consented to a second set of oxygen measurements (performed after 30–145 days). Relative to pretreatment measurements, a significant reduction in prostate hypoxia was observed in these patients after androgen withdrawal ($P=0.005$), although there was considerable variation in individual response. Tumor hypoxia improved