with first-line therapy, and patient preferences. While maintenance therapy might be appropriate for some patients, it might be less preferable for others.

Maintenance therapy with erlotinib represents an important modality to improve patient outcomes in advanced NSCLC. The ability to use a biomarker to select therapy represents a new treatment paradigm, and provides hope that new agents will be discovered to improve outcomes for patients with NSCLC.

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1 Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* 2004; **304:** 1497–500.
2 Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2004; **350:** 2129–39.
3 Cappuzzo F, Ciuleanu T, Stelmakh L, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. *Lancet Oncol* 2010; published online May 20. DOI: 10.1016/S1470-2045(10)70112-1.
4 European Medicines Agency. Summary of opinion (post authorisation). http://www.ema.europa.eu/pdfs/human/opinion/TarcevaII_8608010en.pdf (accessed March 18, 2010).
5 Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009; **361:** 947–57.
6 Rosell R, Moran T, Queralt C, et al. Screening for epidermal growth factor receptor mutations in lung cancer. *N Engl J Med* 2009; **361:** 958–67.
7 Ciuleanu T, Brodowicz T, Zielinski C, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. *Lancet* 2009; **374:** 1432–40.

Beyond steroid hormones: the new cancer endocrinology

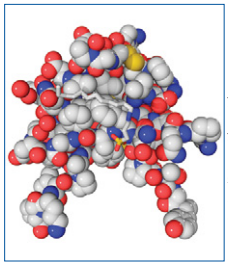
The meta-analysis[1] by the Endogenous Hormones and Breast Cancer Collaborative Group of studies investigating the relation between the concentration of circulating insulin-like growth factor 1 (IGF1) and risk of breast cancer in this issue of *The Lancet Oncology* concludes that higher concentrations of this peptide hormone are associated with a moderate increase in breast-cancer risk. This comprehensive analysis, which involves more than 14 000 participants, broadly substantiates the conclusions of the first prospective study of this topic reported 12 years ago,[2] and provides important additional insights.

Ovarian steroids provide a well-known precedent for an affect of hormones on breast-cancer risk. Key and colleagues noted a 28% overall increased risk among women at the upper compared with the lower end of the broad normal range of circulating IGF1 concentration. The authors correctly point out that this might be a conservative estimate because of noise arising from the use of a single measure to estimate IGF1 concentrations. At least as important in this regard is the possible imprecision of the many assays used to measure IGF1, particularly if there is variation in the handling of blood samples.

The findings are biologically plausible, as models of mammary gland carcinogenesis[3] are affected by IGF1 concentration, and because IGF1 is known to favour both the survival and proliferation of cells, even if DNA damage is present. Furthermore, circulating IGF1 concentration is associated with previously known risk factors for breast cancer for which the underlying physiological basis was unclear, such as height, age at menarche, and mammographic breast density, suggesting that these may be linked to risk at least in part because they act as surrogates for IGF1 concentration.

Although previous studies have been inconsistent about the relative importance of IGF1 concentration as a breast-cancer risk factor for premenopausal compared with postmenopausal women, this new meta-analysis suggests that concentrations are related to risk among all women, but only for oestrogen receptor (ER)-positive cancers. This finding will motivate further research. It is clear that at least some ER-negative breast cancers are responsive to IGF1,[4] although IGF1 receptor concentration tends to be positively correlated with ER concentration. The distinction between carcinogenic pathways that lead to ER-positive compared with ER-negative cancers is the subject of considerable ongoing investigation.

While the variation of breast-cancer risk across the range of circulating IGF1 concentrations is modest compared with the risk associated with *BRCA* mutations, the burden of disease attributable to this risk factor could still be substantial, since a relatively large proportion of the population falls into the range of circulating IGF1 concentration associated with increased risk.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Furthermore, the underlying biology might be relevant to several common cancers, as recent meta-analyses[5,6] have confirmed trends seen in the earliest prospective studies[7,8] that concluded that a high IGF1 concentration is associated with increased risk of prostate and colorectal cancer.

There are important unanswered questions of potential clinical relevance. It is now recognised that many cancer cells and cells at risk for transformation incorporate not only IGF1 receptors, but also insulin receptors and hybrid receptors. It will therefore be important to examine jointly the effects of variation in IGF1 and insulin concentrations on cancer risk and prognosis. This research might be relevant to understanding recent retrospective findings[9] that suggest that use of metformin, a drug that lowers insulin concentrations, is associated with reduced cancer risk in patients with type 2 diabetes, while prolonged insulin therapy might be associated with an increase in cancer mortality.[10] The hypothesis that variation in IGF1 concentration affects penetrance of genetic cancer-risk factors is another area of active investigation.

The identification of a risk factor often does not imply an immediately applicable method of risk reduction. Drugs that reduce IGF1 concentrations or interfere with IGF1 signalling are now under investigation for cancer treatment rather than prevention. It is not certain that pharmacological approaches to IGF1 reduction would be appropriate for long-term use in the context of prevention, or that dietary modification to lower IGF1 concentrations would be practicable, clinically. Furthermore, low IGF1 concentrations have been associated with an increased risk of cardiovascular disease, and frank IGF1 deficiency is associated with many undesirable outcomes. More work is needed to determine whether specific subsets of women (eg, those with dense breasts) might benefit from interventions that reduce IGF1 concentrations or bioactivity. Nevertheless, one immediate implication from both rapidly advancing basic research[11] and the meta-analysis by the Endogenous Hormones and Breast Cancer Collaborative Group is that the healthiest circulating IGF1 concentration is probably not at the high end of the normal distribution, so for clinical conditions where long-term growth hormone therapy is indicated, it might be unwise to achieve circulating IGF1 concentrations higher than the age-specific population mean.

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1 The Endogenous Hormones and Breast Cancer Collaborative Group. Insulin-like growth factor 1 (IGF1), IGF-binding protein 3 (IGFBP3), and breast cancer risk: reanalysis of 17 prospective studies. *Lancet Oncol* 2010; published online May 17. DOI:10.1016/S1470-2045(10)70095-4
2 Hankinson SE, Willett WC, Colditz GA, et al. Circulating concentrations of insulin-like growth factor-I and risk of breast cancer. *Lancet* 1998; **351:** 1393–96.
3 Pollak M, Blouin MJ, Zhang JC, Kopchick JJ. Reduced mammary gland carcinogenesis in transgenic mice expressing a growth hormone antagonist. *Br J Cancer* 2001; **85:** 428–30.
4 Law JH, Habibi G, Hu K, et al. Phosphorylated insulin-like growth factor-i/insulin receptor is present in all breast cancer subtypes and is related to poor survival. *Cancer Res* 2008; **68:** 10238–46.
5 Rinaldi S, Cleveland R, Norat T, et al. Serum levels of IGF-I, IGFBP-3 and colorectal cancer risk: results from the EPIC cohort, plus a meta-analysis of prospective studies. *Int J Cancer* 2010; **126:** 1702–15.
6 Rowlands MA, Gunnell D, Harris R, Vatten LJ, Holly JM, Martin RM. Circulating insulin-like growth factor peptides and prostate cancer risk: a systematic review and meta-analysis. *Int J Cancer* 2009; **124:** 2416–29.
7 Ma J, Pollak MN, Giovannucci E, et al. Prospective study of colorectal cancer risk in men and plasma levels of insulin-like growth factor (IGF)-I and IGF-binding protein-3. *J Natl Cancer Inst* 1999; **91:** 620–25.
8 Chan JM, Stampfer MJ, Giovannucci E, et al. Plasma insulin-like growth factor-I and prostate cancer risk: a prospective study. *Science* 1998; **279:** 563–66.
9 Bodmer M, Meier C, Krähenbühl S, Jick SS, Meier CR, Meier CR. Long-term metformin use is associated with decreased risk of breast cancer. *Diabetes Care* 2010; published online Mar 18. DOI: 10.2337/dc09-1791.
10 Bowker SL, Yasui Y, Veugelers P, Johnson JA. Glucose-lowering agents and cancer mortality rates in type 2 diabetes: assessing effects of time-varying exposure. *Diabetologia* 2010; published online Apr 21. DOI:10.1007/s00125-010-1750-8.
11 Kenyon CJ. The genetics of ageing. *Nature* 2010; **464:** 504–12.

Towards individualised treatment in childhood leukaemia

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The results of treatment of childhood acute myeloid leukaemia (AML) are slowly improving, and some groups report a prognosis that is nearly as good as for childhood acute lymphoblastic leukaemia (ALL), as in the AML02 multicentre study by Rubnitz and colleagues[1] in this issue of *The Lancet Oncology*. The 3-year overall survival of 71% and event-free survival (EFS) of 63% are among the highest yet recorded, although only marginally higher than survival outcomes reported by groups that had 5-year or 7-year follow-up, so the results are not fully comparable.[2] Some of the older protocols stratified patients by response to the first block of therapy, as assessed by conventional morphological bone-marrow examination (≥5% malignant cells in a specimen),