



This Week in the Journal

November 14, 2002

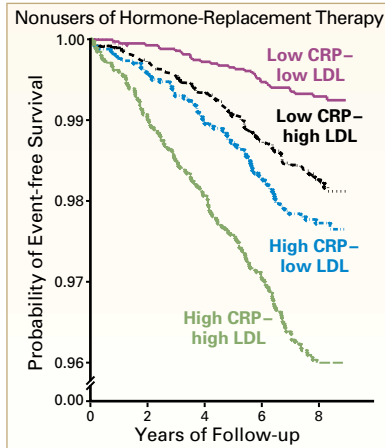
“Dexamethasone should be initiated before or with the first dose of antibiotics.”

Dexamethasone Treatment to Improve Outcomes in Bacterial Meningitis

Can adjuvant treatment with dexamethasone reduce morbidity and mortality in adults with acute bacterial meningitis? In this randomized, double-blind trial, which involved 301 patients, the outcomes were clearly better in the group that received dexamethasone for four days, in addition to antibiotics, than in the group that received placebo and antibiotics. With dexamethasone treatment, the risk of an unfavorable outcome was greatly reduced (relative risk, 0.59), and mortality was reduced from 15 percent to 7 percent.

This carefully controlled trial will have an important effect on the treatment of adults with bacterial meningitis. The greatest benefits were in patients with pneumococcal meningitis. There was no significant increase in the risk of gastrointestinal bleeding among patients treated with dexamethasone.

see page 1549 (editorial, page 1613)

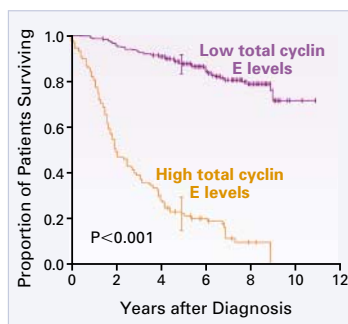


C-Reactive Protein in the Prediction of First Cardiovascular Events

Studies have suggested that C-reactive protein, a marker of inflammation, may predict the risk of cardiovascular events, including coronary events. In this study of nearly 28,000 women, C-reactive protein levels were found to predict the risk of subsequent cardiovascular events independently of other known coronary risk factors. C-reactive protein and low-density lipoprotein cholesterol levels were found to be complementary in the prediction of risk.

The prediction of cardiovascular risk is an important goal. The use of C-reactive protein measurement as a screening test for this risk is under discussion.

see page 1557 (editorial, page 1615)



Cyclin E and Survival in Breast Cancer

The level of cyclin E, part of a molecular network that controls the cell cycle, is increased in breast-cancer cell lines. In breast-cancer tissue, high levels of cyclin E correlated with a poor outcome, whereas low levels correlated with a good outcome.

If this work is substantiated, measurement of cyclin E will be used to obtain prognostic information in patients with breast cancer. An obvious clinical reason to measure cyclin E will be to stratify patients with breast cancer who are enrolled in therapeutic trials.

see page 1566 (Perspective, page 1546)

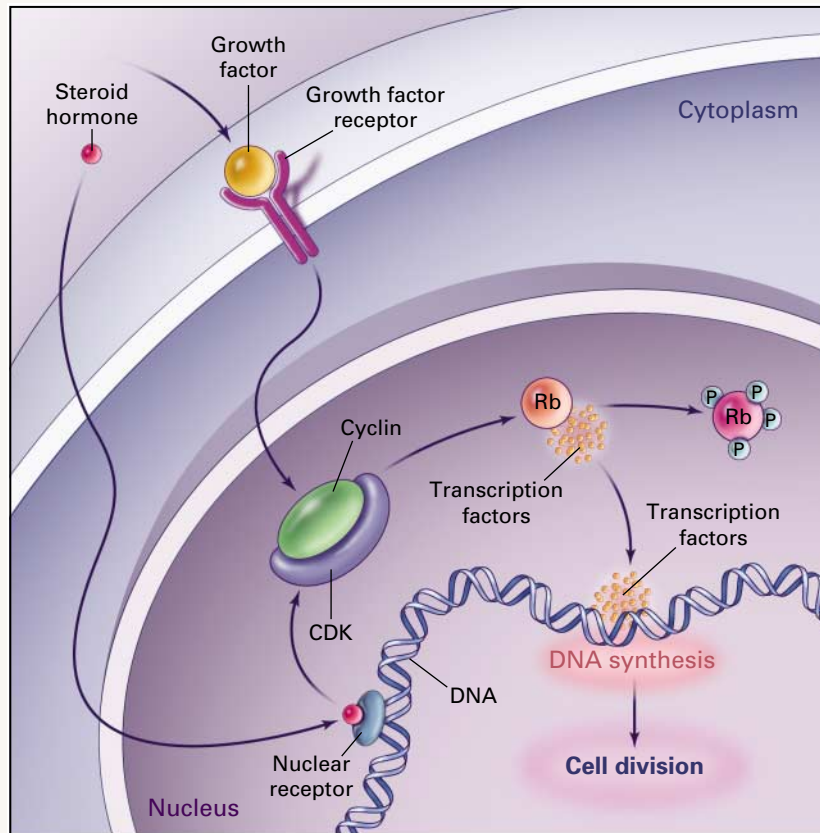
PERSPECTIVE

Cyclin E and Prognosis in Patients with Breast Cancer

An early and essential event in the evolution of cancer is loss of the normal control mechanisms responsible for the orderly progression of cells through the cell cycle, with consequent reduced fidelity of DNA replication and inappropriate cell division. Cyclins are the regulatory partners of the cyclin-dependent kinases (CDKs), which form the molecular control mechanisms responsible for cell-cycle progression.

An advanced understanding of cell-cycle control has evolved over the past decade, since it became apparent that the underlying machinery of this fundamental biologic process was conserved during evolution. Indeed, the importance of these control mechanisms and their relevance to human disease was recognized with the award of the Nobel prize to their discoverers, Drs. Paul M. Nurse, R. Timothy Hunt, and Leland H. Hartwell, in 2001. Their seminal work has not only led to a deeper understanding of normal cell-cycle control, but has also allowed unprecedented insights into the roles of several known and potential oncogenes and tumor-suppressor genes in the evolution of cancer. The gene for cyclin E is one such gene; others include the related D-type cyclins, the CDK target pRb (the product of the retinoblastoma tumor-suppressor gene), the CDK inhibitors p16^{INK4a} and p27^{Kip1}, and p53 and p14^{ARF}, which link cell-cycle progression to apoptosis.

Cyclin E has a pivotal role in transducing the mitogenic response of diverse hormone, cytokine, and growth-factor mitogens. After their cognate cell-surface or intracellular

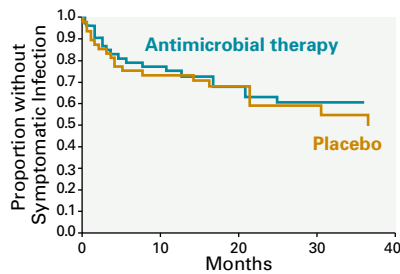


Cyclins and Cell Proliferation.

In the resting, nondividing state, cells are prevented from beginning DNA synthesis by the retinoblastoma protein (Rb), which sequesters transcription factors that are essential for the expression of genes required for DNA synthesis. Mitogenic stimulation of breast epithelial cells with steroids, growth factors, or both activates their receptors, induces expression of cyclin genes, and stimulates the formation of active enzyme complexes through the binding of cyclins to cyclin-dependent kinases (CDK). Active cyclin-CDK complexes phosphorylate Rb and liberate Rb-bound transcription factors, initiating the gene transcription essential for DNA synthesis and subsequent cell division.

receptors have been activated, these mitogens induce transient expression of cyclin E, formation and activation of cdk2 complexes, phosphorylation of pRb, and the release of transcription factors essential for transition to DNA synthesis (see Figure). In this issue of the *Journal*, Keyomarsi et al. (pages 1566–1575) report that abnormal expression of cyclin E, as measured by Western blotting of tumor lysates, is a powerful predictor of poor outcome in patients with breast cancer. In a retrospective analysis of 395 patients

with breast cancer with a median follow-up of 6.4 years, the authors demonstrate that high levels of truncated or total cyclin E correlate with poor disease-specific survival. Among patients with stage I disease, all of those with low levels of cyclin E were alive at seven years, as compared with none of those with expression of high levels of cyclin E. In a multivariate analysis, the hazard ratio for death from breast cancer associated with a high level of cyclin E was significantly greater than that associated with any other



Asymptomatic Bacteriuria in Women with Diabetes

In women with diabetes, treatment of asymptomatic bacteriuria has been recommended to prevent complications. In this trial, 55 women with diabetes and asymptomatic bacteriuria were randomly assigned to receive antimicrobial therapy and 50 to receive placebo. After a mean follow-up of 27 months, the rates of symptomatic urinary tract infection were similar: 42 percent in the treated group and 40 percent in the placebo group. There were also no significant differences between the two groups in the rates of pyelonephritis or hospitalization for urinary tract infection, although the 95 percent confidence intervals for these differences were wide.

Among women with diabetes, a policy of screening for and treating asymptomatic bacteriuria leads to many courses of antibiotics but does not appear to prevent complications. The findings of this controlled study call such a policy into question.

see page 1576 (editorial, page 1617)

clinical or pathological risk factor that has been identified to date.

What is known about the biology of cyclin E in breast cancer that might explain these remarkable findings? Cyclin E is overexpressed in a substantial proportion of breast-cancer cell lines and primary cancers, suggesting that it may have a role in the initial loss of normal growth regulation that is characteristic of cancer. Support for this conclusion comes from studies in transgenic mice, in which cyclin E overexpression targeted to the mammary gland induces mammary tumors.

The relatively low frequency (approximately 10 percent) and long latency of these tumors does, however, imply that additional genetic events are essential for tumor development. Stimulation of the proliferation of breast-cancer cells by estrogens and growth factors is accompanied by increased cyclin E levels and the formation of active cyclin E-cdk2 complexes. Conversely, inhibition of growth by antiestrogens and progestins involves the inactivation of cyclin E-cdk2 complexes. Overexpression of cyclin E accelerates the transition into

DNA synthesis, but in breast-cancer cells, this results in only a slight decrease in sensitivity to the growth-inhibiting effects of antiestrogens and progestins, indicating that the overexpression of cyclin E is unlikely to markedly affect sensitivity to systemic endocrine therapies.

A more relevant feature of the pathobiology of cyclin E overexpression may be its ability to induce chromosomal instability in human breast-epithelial cells, since chromosomal rearrangements are a feature of all solid tumors and increase with progression of the disease process. Indeed, it is metastasis, not the rate of proliferation of the primary tumor, that causes death from breast cancer.

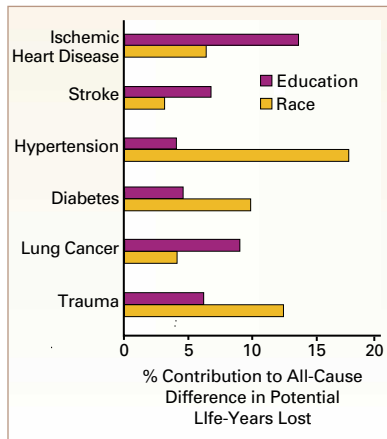
An important feature of the study by Keyomarsi et al. is the relation between the outcome of breast cancer and the overexpression of low-molecular-weight isoforms of cyclin E. These proteins lack varying amounts of the amino terminal of the native molecule and are reported to be hyperactive in terms of cell-cycle progression, but there are, to date, no data on their ability to induce chromosomal abnormalities. Since these isoforms appear to be

generated by proteolytic cleavage, and various proteases have been implicated in breast-cancer metastasis, it is possible that the truncated cyclin E isoforms are a surrogate marker of another biologic process that is more directly related to disease progression and metastasis.

Irrespective of the underlying mechanisms, the observation that cyclin E overexpression is the most powerful predictor of the outcome of breast cancer that has been identified to date will undoubtedly engender new interest in this and functionally related molecules in breast cancer. The most pressing issues are whether these data can be replicated in other cohorts of patients and whether an immunohistochemical assay can be developed for simultaneous assessment of total cyclin E and its low-molecular-weight isoforms that would be suitable for use in routine clinical practice.

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Special Article: Contribution of Major Diseases to Disparities in Mortality

Mortality from all causes is higher for persons with less education and for black persons. This study examined cause-specific mortality to estimate the relative contribution of major health problems to these educational and racial disparities in life expectancy. The diseases that contributed most to the educational disparity were smoking-related diseases. Ischemic heart disease accounted for 12 percent of the disparity, lung cancer 8 percent, stroke 6 percent, congestive heart failure 5 percent, and lung disease 5 percent. The racial disparity was not driven by mortality from smoking-related illness but by hypertension, human immunodeficiency virus infection, diabetes, and trauma.

Public health and educational efforts to eliminate health disparities should focus on the specific diseases that contribute most to racial and educational differences in health outcomes.

see page 1585

“The disruption of a limited number of pathways is sufficient to impart a tumorigenic phenotype.”

Mechanisms of Disease: Human Tumor Cells

The apparent complexity of the genetic, biochemical, and physiological changes in cancer cells threatens to stall the elucidation of the origins of cancer and the development of new treatments for malignant diseases. The authors propose a considerably simplified scheme in which only five alterations are required to transform cells from a normal to a malignant phenotype.

see page 1593

“External reporting allows lessons to be shared so that others can avoid the same mishaps.”

Health Policy Report in the Patient Safety Series: Reporting of Adverse Events

Systems for reporting adverse events can reduce medical errors by uncovering remediable problems in processes of care; however, current reporting systems are neither widely used nor highly effective. Reporting systems work best when they are confidential and easy to use, provide expert analysis of reports, and give timely feedback.

If voluntary reporting systems are modified and expanded, they have the potential to improve patient safety.

see page 1633