

implementation and quality control. Although what has been found are associations between coronary care and a decline in occurrence of events rather than cause and effect, confirmation that these associations exist and that they are positive across a wide range of treatment settings is important. As the researchers point out, what would the implications be if the associations were in the opposite direction (ie, suggesting that evolving improvements in clinical care were not beneficial), or if clinical care seemed to do more harm than good?

The value of the ecological analyses surrounding risk factors is best summarised by figures 1–3 in the article by Kuulasmaa and colleagues. Despite a weak association between coronary events and individual risk factors or global risk scores, most of the populations with a decline in the prevalence of risk factors also experienced a reduction in events. Data from large cohort studies and randomised clinical trials suggest that community-wide risk-factor reduction should translate into lower coronary-event rates. However, this conclusion is based on the assumption that risk factors identified in one setting, such as Framingham, Massachusetts, are generalisable to other countries. Although there are data suggesting that risk factors maintain their relative importance among different western populations, there is less information from eastern European or Asian settings.^{13–15} Until large prospective cohort studies are completed in these countries, the WHO-MONICA results suggest that risk factors are risk factors irrespective of the community in which they occur. More importantly, modification of those amenable to change, such as blood pressure, blood lipids, and smoking, can result in risk reduction outside of clinical trials done under idealised conditions.

The main message of the WHO-MONICA Project thus seems to be one of generalisability. Despite incomplete understanding of the causes of cardiovascular disease, some modifiable risk factors that remain important irrespective of the individual's nationality or place of residence have been identified. There also seems to be progress in efforts to prevent this disease and reduce the disability and mortality associated with it across a wide range of medical settings.

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Towards post-genomic investigation of colorectal cancer

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Molecular markers of colorectal cancer are of potential use in classification, indication of disease spread at diagnosis, prediction of therapeutic response to therapy, population screening, and prognostic evaluation.¹ Confusion surrounds the ability of molecular markers to establish prognosis, largely because information is based on studies most of which have been underpowered and that have yielded different findings, have assessed only one marker at a time across all stages of disease, and have used univariate statistical analysis.

Dukes' staging has withstood the test of time, but is being supplanted by the tumour-node-metastasis (TNM) system, which will be the gold standard against which novel prognostic markers are compared. However, any new marker that is being proposed for clinical use should provide additional information, such as whether patients are in the high-risk subgroups of stage II and thus might benefit from adjuvant therapy.

A range of markers and their relation to outcome of colorectal cancer is shown in the panel. However, there is no consensus on their relevance, and the identification of a marker that provides information independent of that from TNM staging is rare. For example, although many studies suggest an association between tumour p53 mutation and poor prognosis, a recent study that confined multivariate analysis to patients with tumour-free margins at resection showed no independent effect of the p53 mutation.²

In today's *Lancet*, Anthony Heaney and colleagues report their results on the use of the pituitary-tumour transforming gene (*PTTG₁*) as a prognostic marker of colorectal cancer. The low expression of *PTTG₁* in normal tissue compared with its high expression in cancerous tissues prompted the researchers to wonder whether *PTTG₁* expressivity might correlate with invasiveness and subsequent metastasis. Studying 68 serially collected tissue samples, Heaney and co-workers found that, compared with its expression in normal tissues, *PTTG₁* was overexpressed in all 48 colorectal

Postulated prognostic indicators		
Group	Marker	Suggested contribution to prognosis
Oncogenes	Ras-mutated	Poor prognosis Valine codon 12 mutation—worst prognosis
	TGF α -low expression	Poor prognosis
	TGF β -positive staining	Poor prognosis
	Her-2,neu-strong staining	Poor prognosis
	EGRF-strong staining	Poor prognosis
	c-myc-amplification	Predicts response to 5FU
	Overexpression in the presence of wt p53	Good prognosis
Tumour-suppressor genes	p53—mutations	Poor prognosis—particularly mutations in the zinc binding domain. Also predict poor therapeutic response to radiotherapy and chemotherapy
	DCC—loss of expression	Poor prognosis (stage II tumours behave like stage III tumours)
Apoptosis pathways	p27kip1—loss of expression	Poor prognosis
	Bcl-2—high expression	Good prognosis
Angiogenesis/ metastasis/invasion	PDEGF-positive staining	Poor prognosis
	VEGF-positive staining	Poor prognosis
	MMP 1,2, and 9-positive staining	Poor prognosis
	CD44-immunoreactivity	Poor prognosis
	E-cadherin—low expression	Poor prognosis

For a comprehensive review of the evidence, see reference 1. TGF=transforming growth factor; EGFR=epidermal growth factor receptor; DCC=deleted in colon cancer; PDEGF=platelet-derived epidermal growth factor; VEGF=vascular endothelial growth factor; MMP=matrix metalloproteinases.

cancers and in 19 (95%) of 20 polyps. Furthermore, invasion through the bowel wall, metastasis, and vascularity were associated with high *PTTG_i* expression. The investigators suggest that *PTTG_i* may be a novel marker of invasive colorectal cancer. Certainly their observation that *PTTG_i* can regulate secretion of basic fibroblast-growth factor suggests a mechanism by which invasiveness may be influenced. Their results, however, are preliminary and show only a correlation between *PTTG_i* expression and Dukes' staging. A longer follow-up of a larger series of patients, with investigation of confounding variables, is needed before a conclusion can be reached about whether *PTTG_i* expression is an independent marker.

What does the future hold for prognostic evaluation for colorectal cancer? Further genomic information arising from completion of the Human Genome Project will provide a static picture of the human nucleus, with no information on differential gene expression between normal and cancerous cells. Two post-genomic strategies are being explored that might give a more integrated predictive picture. One of these strategies is expression profiling, or transcriptomics, which consists of the identification of mRNAs expressed by the genome at a given time and yields a snapshot of the active genes under the cellular conditions then prevailing. A tumour "cellular soup" from a patient would be analysed on microarrays containing thousands of complementary DNAs (cDNAs) derived from cellular genes. mRNAs in the lysate are identified from their binding to their complementary cDNA. The limitations of this technique include the differing rates of intracellular degradation for individual mRNAs and proteins and post-translational modification. The latter process occurs in many proteins, with the result that one mRNA can translate into more than one form of a protein.

The other strategy, proteomics, or finding out the full complement of proteins expressed by a cell at any one time, also has its advocates. Proteins, derived from serum or cells, are separated by charge and mass on two-dimensional gel electrophoresis. Gels can separate

between 2000 and 11 000 proteins, which are then stained with Coomassie blue dye, silver stains, fluorescent dyes, or radiolabels and quantified by spectroscopic or radiographic techniques. The advantage of proteomics over transcriptomics is the derivation of the true protein content of the cell.

The key to both of these techniques is pattern recognition rather than identification of specific proteins, and correlation of such patterns with outcome. Since both methods will generate hundreds or thousands of individual datum points, complex pattern-recognition programs will be required to read the assays, allied to advanced mathematical models that transcend conventional multivariate analysis. Artificial neural networks are computer programs that can be trained to discover complex relations within data sets that cannot be detected by linear statistical analysis. New prognostic factors can be easily integrated into established neural networks, and neural networks "trained" within one institution remain reliable and accurately predict outcome when applied by another unrelated institution.^{3,4}

For the more immediate future, though, efforts continue to be focused on molecular biomarkers and, in view of the biological rationale for a relation between *PTTG_i* and invasion, the role of this gene as a marker is worth further investigation.

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