effects, but it does not reconcile with table 3, in which biometric modelling effectively attributes all effects to genetic factors for all but two of the haemostatic factors. If shared-environment effects are allowed for, the monozygotic and dizygotic pair correlations presented in table 2 would be consistent with heritability estimates that are much more in line with those derived from analyses of the family data.

Analyses of individual haemostatic factors may tell only part of the story. That ten individual haemostatic components from complex biochemical cascades might show evidence of genetic control (as in de Lange’s study) does not imply that the same genes are involved in haemostasis, or that they are functioning in the same direction, although these issues could have been addressed by multivariate twin analyses. It is possible that high levels of one factor might be counter-balanced by low concentrations or activities of factors upstream or downstream. de Lange and colleagues have not reported on the nature of the relations between plasma concentrations of haemostatic factors that might help assess these possibilities. However, Souto and colleagues provide some insight in this regard by including in their suite of 27 traits functional assays of blood clotting. Particularly interesting was the heritability of 83% for the activated partial thromboplastin time (APTT) and of 71% for the composite phenotype known as activated protein C resistance (APCR). These extraordinarily high values were well above the heritabilities for many of the individual factors contributing to the APTT and APCR phenotypes. These findings suggest coordination of genetic control and raise the possibility that the same genes influence several traits simultaneously. At face value, they provide strong justification for genomic searches for such genes, which may take advantage of dizygotic twin pairs.15

In general, the heritability estimates for haemostatic factors are not far removed from those for other cardiovascular risk factors such as blood pressure, cholesterol control, and might be reported in combined twin and family studies.13,14 However, establishing the role of the genetics of haemostasis in acute coronary syndromes and stroke is still some way off. Optimism comes from the fact that some haemostatic traits have been associated with these disorders16 and that particular genes have been shown to influence these traits.1 However, the pessimism is that these genes may be bit-players in a much bigger picture that includes complex genetic control of a myriad of cardiovascular risk factors and that is clouded by gene–environment interactions. The confidence of de Lange and Souto and their colleagues will be vindicated if common functional genetic variants that modulate haemostatic risk factors comprise a robust and significant proportion of the complete cardiovascular disease equation.

*Stephen B Harrap, John L Hopper

*Department of Physiology, and Centre for Genetic Epidemiology, University of Melbourne, Victoria 3010, Australia (e-mail: s.harrap@physiology.unimelb.edu.au)

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Aspirin for primary prevention of cardiovascular events

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Whether general practitioners should recommend aspirin to their patients to reduce the risk of heart attack and other cardiovascular events has been confusing, even though large trials have shown that the compound has a protective effect. What is it in the report on the Primary Prevention Project (PPP) by Maria Carla Roncaglioni and colleagues in today’s Lancet that provides general practitioners with the evidence they need to recommend aspirin?

The difficulties in applying evidence derived from randomised controlled trials (RCTs) to individual patients in general practice have been identified.1,2 Conducting clinical trials in general practice addresses many of the concerns, but for the results to be generalisable the trial has to be designed and conducted in such a way as not to disrupt usual practice patterns.3 A barrier to the application of clinical-trial evidence in general practice is the use of highly selected study populations, usually with a specific single problem. In general practice co-morbidity is common.4 Extensive exclusion criteria in most RCTs reduce the applicability of the results in general practice. So does the fact that most RCTs are conducted in tertiary-care hospitals. Yet results derived from RCTs, often combined for meta-analysis, are generally the best evidence that general practitioners and their patients have to help in decision-making.

Roncaglioni’s findings are derived from a well-organised RCT conducted in 315 general practices and 15
hospital-based hypertension clinics. The recruitment of 4258 patients from the community with at least one of several risk factors for coronary heart disease overcomes the criticism of studies based on selected populations. The exclusion criteria were few and reasonable. The rigour of the trial meant that 92·3% of participants were followed up and that analyses were based on outcomes obtained for over 99% of participants. The results of exceptional follow-up rates are probably related to the fact each general practitioner recruited an average of 14 patients (range 1–65); exceptional levels of cooperation are possible when physicians know their patients well.

The PPP study was stopped after about 3·5 years of follow-up because the two other studies5,6 of low doses of aspirin showed a significant beneficial effect of the drug. The PPP results showed that 100 mg daily of entericoated aspirin had a protective effect in people with one or more cardiovascular risk factors; with this regimen the relative risk of death was 0·56 (95% CI 0·31–0·99) and that for total cardiac events was 0·77 (0·62–0·95). Together the results from the three studies should give general practitioners the confidence to recommend low doses of aspirin (80–100 mg daily) for primary prevention in individuals who have one or more risk factors but whose blood pressure is contained within the normal range. All three studies also highlight that fact that in hypertensive patients the blood pressure must be well controlled because the higher the blood pressure the greater the risk of haemorrhagic strokes. The other important finding highlighted is that aspirin should be prescribed in low doses to avoid bleeding complications.

The second segment of the PPP, that of the effect of vitamin E, did not provide evidence that the vitamin reduces cardiovascular risk. These findings are congruent with those obtained in a more traditional RCT.7 What general practitioners can confidently advise their patients is that any beneficial effect that vitamin E might have is weak and awaits discovery.

The ability to advise patients confidently is essential in a patient-centred approach to decision making, which includes personal beliefs and values as well as family and life experience. Better outcomes are obtained when decisions are made jointly with the patient than when they are made by the doctor alone.8

Walter W Rosser
Department of Family and Community Medicine, Faculty of Medicine, University of Toronto, Toronto, Ontario M5G 2C1, Canada (e-mail: w.rosser@utoronto.ca)


Relation between dermatomyositis and polymyositis and cancer

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I first became interested in the relation between dermatomyositis and malignancy when I read the now classic review by Bohan and Peter1 in 1975, during my medicine residency. In the summary Fact, Fancy and Fiction, they listed the relation between dermatomyositis and malignancy under Fancy and wrote:

“There may be an association between dermatomyositis and neoplasia, especially in men in the tumor-age group. (The data, however, are epidemiologically unreliable.) The case is less convincing for such an association with polymyositis than for dermatomyositis.”

On taking up dermatology, I embarked on a project with a rheumatologist to define the relation more thoroughly. During our retrospective review2 of cases of polymyositis and dermatomyositis at the University of Michigan Medical Center, Barnes published a review of the literature3 that for several years was cited as the authoritative reference. She had noted the possible overrepresentation of ovarian cancer. We reported a relation between this cancer and dermatomyositis but not polymyositis.2

It was not until 1992 that Sigurgeirsson and colleagues4 reported the findings of an epidemiologically sound study in Scandinavia showing an increase in the occurrence of cancer in patients with dermatomyositis, but only a slight increase in patients with polymyositis. They believed that the finding was true for dermatomyositis but thought that the association with polymyositis might be accounted for by a bias due to diagnostic suspicion. Studies from Denmark and Finland that showed essentially the same association were published later.5 The Danish study suggested that the risk of malignancy was highest during the first year after diagnosis, and returned to baseline levels in the third year. These studies have all suggested that there is an overrepresentation of ovarian cancer, and the Danish study suggested that lung and lymphoproliferative neoplasia were also over-represented.

This issue of The Lancet contains another chapter in the quest to define the exact relation between the skin disorders and cancer and the types of tumours that might occur. It is an updated analysis of data from all three Scandinavian countries. Catherine Hill and colleagues have again found that dermatomyositis is associated with cancer but that polymyositis is weakly associated. The relation between polymyositis and cancer in this study is higher than in previous reports, but the tumour sites differ from those observed in patients with dermatomyositis. The researchers conclude that bias resulting from a more extensive search for malignancy in patients with polymyositis affected their results.

What practical questions should the clinician ask when faced with a newly diagnosed case of dermatomyositis? First, what is the risk that this newly diagnosed patient has cancer? Second, are there any specific cutaneous findings that the patient has an increased likelihood of harbouring a cancer? Third, where is the cancer most likely to be found and how should the search be conducted? And finally, if a cancer is not found at the time of diagnosis, how should