The evidence on trial: cholesterol lowering and cancer

A M Tonkin, A Forbes, S J Haas

In an ideal world, medical care would be informed by a complete evidence base, implemented through supportive and appropriately funded systems and enacted by patients who, after being fully informed about the overall potential net benefits and any personal costs, complied with their recommended therapies.

The reality is in stark contrast. The evidence is usually incomplete, many governments do not "value" prevention, while the time pressures on professionals hinder their ability to deliver evidence-based care. In addition, the general population may be becoming increasingly sceptical about some aspects of medical treatments, particularly in relation to the ever-growing incidence of adverse events leading to product withdrawals. This is often because of cultural factors and, at times, the sensational reporting by media of any safety concerns, disproportionately to the benefits of a treatment. As a consequence, full compliance of patients with recommended therapies infrequently occurs.

The recently published Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study has again ignited controversy related to the possibility that cholesterol lowering may be associated with cancer.[1] The question is a very important one. Cholesterol-lowering agents, particularly statins, are among the most commonly prescribed drugs, and their initiation may translate to potential exposure for 30 years or more. This article examines the scientific evidence base underlying such discussions and this topic in particular.

SEAS STUDY

Ezetimibe inhibits the intestinal absorption of cholesterol by binding to the Niemann–Pick CI-like 1 protein. The combination of ezetimibe and an HMG CoA reductase inhibitor ("statin") is logical. This is because statins lower low-density lipoprotein (LDL) cholesterol by inhibition of cholesterol synthesis and upregulation of the hepatic LDL receptor which clears cholesterol from the vascular compartment, but at the same time, they increase the intestinal absorption of cholesterol.

In the double-blind controlled SEAS trial, 1873 patients with asymptomatic mild-moderate aortic stenosis and no indication for statin therapy were randomised to receive the coformulation of simvastatin 40 mg and ezetimibe 10 mg daily or matching placebo. The study was based on previous observational data relating cholesterol and cholesterol lowering to progression of aortic stenosis and the known associated pathology of the aortic valve in this condition, which resembles atherosclerosis.

Despite a large reduction in LDL cholesterol of 61% to a mean of 53 mg/dl (1.3 mmol/l) at 8 weeks, and a 54% reduction over total follow-up (of a mean of 4.1 years), treatment with simvastatin and ezetimibe failed to reduce the primary end-point, a composite of aortic valve disease events and ischaemic cardiovascular events (hazard ratio 0.96; 95% CI 0.83 to 1.12; $p = 0.59$). Results concerning secondary endpoints were mixed, with a significant reduction in ischaemic cardiovascular events, but not aortic valve disease events alone.

Why the controversy? In the group assigned simvastatin and ezetimibe, incident cancer was diagnosed in 105 patients (11.1%) compared with 70 patients (7.5%) among those assigned placebo ($p = 0.01$). The excess cancers in those randomised to simvastatin and ezetimibe were not clustered at any particular site. Further analysis showed that the risk of incident cancer was not associated with the degree of LDL-cholesterol lowering. Fatal cancers occurred in 39 patients (4.1%) of those randomised to simvastatin and ezetimibe, and 23 (2.5%) of those randomised to placebo. The hazard ratio for cancer-related mortality was 1.67; 97% CI 1.00 to 2.79; $p = 0.05$ using the prespecified Cox proportional hazards model ($p = 0.06$ with Yates' logrank continuity correction). Notably, neither cancer incidence nor mortality was designated as a primary or secondary endpoint in SEAS, and these results arose from analyses of possibly a large set of safety endpoints and thereby are at greater risk of being merely a chance finding.

These unexpected results in an unplanned endpoint could only be considered as hypothesis generating, rather than being definitive. Realising this, the pooled interim analysis of cancer data from two ongoing placebo-controlled trials of simvastatin and ezetimibe[2] accompanied the SEAS publication, along with two editorials.[3 4]

The two trials in the pooled interim analysis were the Study of Heart and Renal Protection (SHARP) study[5] and the Improved Reduction of Outcomes: Vytorin Efficacy Intervention Trial (IMPROVE-IT).[6] These trials are ongoing in patients with chronic kidney disease and following acute coronary syndromes, respectively. The SHARP study is a placebo-controlled trial of simvastatin 20 mg and ezetimibe 10 mg, and 9264 patients with a mean follow-up of 2.7 years and IMPROVE-IT (testing simvastain 40 mg and ezetimibe 10 mg) including 11 353 patients with a mean follow-up of 1.0 year at the time of the pooled analysis of cancer data. In the combined analysis of SHARP and IMPROVE-IT, there was no increase in either all incident cancers (313 on simvastatin and ezetimibe vs 326 on placebo, risk ratio 0.96; 95% CI 0.82 to 1.12; $p = 0.61$) or cancer at any organ-specific site.[2] There was a non-significant excess in cancer deaths (97 vs 72; $p = 0.07$) in those randomised to receive simvastatin/ezetimibe but fewer non-fatal cancers (216 vs 254; $p = 0.08$).

There was also no evidence of a trend in the risk of incident or fatal cancer with increasing duration of follow-up in this pooled analyses of the SHARP study and IMPROVE-IT.[2] This might be expected if the treatment were related to cancer risk. Together, these point towards the increased cancer incidence and mortality in SEAS being merely a chance finding. The authors concluded that "the available results … do not provide credible evidence of any adverse effect of ezetimibe on rates of cancer."[2]

SCIENTIFIC EVIDENCE BASE

In general, the evidence related to benefit or harm of specific interventions is derived from multiple sources. These include:

Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia

Correspondence to: Dr A M Tonkin, Cardiovascular Research Unit, Department of Epidemiology and Preventive Medicine, Monash University, Alfred Hospital, Melbourne, Australia 3004; andrew.tonkin@med.monash.edu.au

basic science which can elucidate putative mechanisms; epidemiological observational studies which identify associations; clinical research and large-scale randomised clinical trials to establish efficacy, net benefit and inform cost-effectiveness analyses; randomised clinical trials to establish safety[4] and outcomes research and long-term surveillance data, to allow an estimate of outcomes and effectiveness in usual clinical practice.

Each of these sources of evidence is important but also has some limitations.

Basic science in laboratory animals suffers from potential different mechanisms of action to that in humans, so that results in animals need not necessarily apply to humans. Observational epidemiological studies suffer from a myriad of selection and confounding biases, in which persons being treated may differ systematically in important but unmeasured (or unmeasurable) prognostic factors from those not being treated. Unless the mechanisms underlying the prescription of treatment are well defined and measurable, these biases are difficult, if not impossible, to remove analytically. Randomised and blinded clinical trials, with no loss to follow-up and analysed using the intention-to-treat principle, provide the gold standard for evaluation of the benefits of *assignment* to treatment. However, in the face of treatment non-compliance, assessment of efficacy of treatment *received* must take into account selection biases akin to those of observational studies. In addition, assessment of rare and long-term adverse events is not reliable in randomised trials designed to assess relative short-term efficacy due to the paucity of such events observed during the trial's duration.

CASE OF CHOLESTEROL LOWERING AND CANCER

Tumours in experimental animals

Data from studies of statins in experimental animals are controversial. Early in the testing of statins as therapeutic agents, carcinogenic potential was reported for several statins in rodent studies (malignant lymphomas (pravastatin), and cancers of the lung (simvastatin and lovastatin), thyroid (simvastatin and fluvastatin) and liver (lovastatin, pravastatin, and simvastatin)[7]). These findings were appreciated at the time when the first statins were approved for marketing. Similar findings have been observed with "second generation" agents.

Two-year dietary studies with ezetimibe alone in mice and rats have shown no evidence of carcinogenic potential.

Carcinogenicity in rodents is generally assumed to indicate risk for humans, particularly when compounds are genotoxic in both rats and mice, and several sites are involved. In the case of statins, it was accepted that the hepatic carcinogenicity observed in rodents was related to a non-genotoxic mechanism[7] which involved the induction of peroxisomal proliferation. Fibrates (including nafenopin), and substances such as phthalate plasticisers used in medical devices, produce similar effects.[8] However, human hepatic cells are quite resistant to drug-induced peroxisomal proliferation.[8] What has not been clear is why statin administration can lead to the development of tumours in rodents at other sites where peroxisomal proliferation has not been observed. In addition, although there has been a substantial margin of safety when clinical doses are compared on a mg/kg body weight to the lowest statin doses producing tumours in rodents,[9] the margins are less when statin blood concentration areas under the curve (AUC) data are compared.[7]

Other basic science: potential for protective effects of statins and adverse effects of ezetimibe?

Experimental data have also suggested that statins may protect against cancer by stimulation of apoptosis,[10–12] modulation of the inhibitory effects of vascular endothelium-derived growth factor (VEGF) on apoptosis, promotion of cell cycle arrest and reduction in tumour cell adhesion and migration.[13 14] Inhibition of enzymatic processes for signalling proteins such as Ras may also prevent further growth of existing cancers and tumour metastases, possibly by effects on angiogenesis.[15 16]

In the case of ezetimibe, the editorials[3 4] accompanying the publication of SEAS (1) and the pooled analysis of the SHARP study and IMPROVE-IT (2) suggested a note of caution. This is because ezetimibe blocks not only the absorption of cholesterol but also phytosterols and other molecular substances that have been linked to protection against cancer.[17–19] However, animal studies have not shown that low phytosterol levels are associated with development of tumours.

Epidemiological studies

Data from epidemiological studies are also conflicting, and some studies suggest that statins may protect against cancer. Representative among these analyses:

- A case-control study from the USA reported an overall relative risk for any cancer among statin users of 1.0 (95% CI 0.9 to 1.2) compared with the reference exposure group.[20] Analysis was restricted to subjects followed for at least 3 years (median 6.4 years). Marginally significantly increased risks of colon cancer and rectal cancer were reported among current statin users of 5 years or longer, with a relative risk of 3.5 (95% CI 1.1 to 10.9) and 4.2 (95% CI 1.0 to 16.6), respectively.
- A prospective cohort of 2781 patients with definite or possible familial hypercholesterolaemia was compared with the expected mortalities in the general population. A standardised mortality ratio for the cohort of 0.6 (95% CI 0.4 to 0.8) was observed (32 cancer deaths in total) over an 18-year period.[21] In this study, widespread statin usage did not occur until half-way through the study recruitment period.
- A large ongoing prospective cohort study of male health professionals in the USA reported a relative risk for prostate cancer of 0.41 (95% CI 0.19 to 0.77) among participants reporting the use of "cholesterol lowering agents" (which were predominantly statins but without direct identification of brand, type or dose of agent used), compared with never users, monitored over a 12-year period to the beginning of 2002.[22] It is most likely that widespread statin usage did not occur in this study until about half-way through follow-up, and results could possibly be influenced by selection bias induced by 22% of eligible participants being excluded from analysis due to not reporting baseline medication use.
- A case-control study in Massachusetts with a follow-up of just under 4 years estimated an odds ratio of 0.92 (95% CI 0.78 to 1.09) of developing colorectal cancer among participants who had utilised statins regularly for at least 3 months.[23]
- A Danish population-based cohort study reported adjusted rate ratios for cancer among statin users of 0.86 (95% CI 0.78 to 0.95) compared with 0.73 (95% CI 0.55 to 0.98) for non-statin users.[24] The mean follow-up period was 3.3 years for the statin cohort and 5.1 years for non-statin users. This possible protective effect of statins was observed despite the older age of those on statins.
- Linkage of a community pharmacy-based database to hospital discharge

records for residents of eight Dutch cities concluded that statins were protective against cancer when used for longer than 4 years (adjusted odds ratio 0.64; 95% CI 0.44 to 0.93).[15] Unfortunately, the mean duration of the postmarketing surveillance was only slightly over 7 years.

- In the Molecular Epidemiology of Colorectal Cancer case-control study of 1953 patients in northern Israel who received a diagnosis of colorectal cancer between 1998–2004 and 2015 matched controls, statin use for at least 5 years (compared with non-use) was associated with significant reduction in the adjusted odds ratio of colorectal cancer (0.50; 95% CI 0.40 to 0.63).[25] Self-report of statin use was confirmed by examining prescription records in 95.6% of a subgroup. The use of fibric-acid derivatives was not associated with reduced risk (adjusted odds ratio 1.08; 95% CI 0.59 to 2.01).[25]
- A US case-control study showed that after adjustment for other potential risk factors, statin use was associated with a significant reduction in prostate cancer risk (odds ratio 0.38; 95% CI 0.21 to 0.69) and specifically more aggressive prostate score (Gleason score ⩾7).[26]
- The methodology differed in these studies examining possible associations of cholesterol lowering and cancer. Confounding also remains a potential problem, even after attempts were made to minimise this using approaches such as propensity analysis.

Clinical trials

Large-scale clinical trials have established beyond any reasonable doubt that cholesterol lowering, particularly with statins, reduces atherothrombotic events.[27]

Two individual statin trials had previously raised concern about a possible association of statin treatment with cancer.

In the Cholesterol and Recurrent Events (CARE) trial, with a mean follow-up of 4.9 years, breast cancer occurred in nine patients who were randomised to pravastatin 40 mg daily and none assigned placebo.[28] However, this result was not replicated in the larger Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study which tested the same dose of pravastatin;[29] nor was there an excess of breast cancer in those randomised to placebo in the analysis by the Cholesterol Treatment Trialists' Collaboration (risk ratio 1.01; 95% CI 0.73 to 1.40; p = 0.6).[27]

In PROSPER, another trial of pravastatin in individuals aged 70 years and over at baseline, over a mean of 3.2 years' follow-up, there was an excess of cancers in those randomised to active treatment (245 vs 199 persons; uncorrected p = 0.02).[30] Again, this was also not replicated in similar patients in the Cholesterol Treatment Triallists Collaboration (risk ratio 1.03; 95% CI 0.91 to 1.16; p = 0.4).[27]

Longer-term data concerning clinical trial patients exposed to statin therapy come from extended follow-up in the Scandinavian Simvastatin Survival Study (4S),[31] the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) study[32] and the West of Scotland Coronary Prevention Study (WOSCOPS).[33] These have not shown any association of statin treatment with either incident cancer or cancer death (table 1).

Meta-analyses

Contemporary meta-analyses of the association between statins and all malignancies have typically produced overall *neutral* results for all cancers.[27 34–36] There were also no significant associations for organ-specific malignancies such as breast cancer[37] and melanoma,[38] nor for pravastatin[39] and atorvastatin[40] as individual agents, although one recent meta-analysis reported an increased risk of cancer among elderly patients treated with pravastatin.[41]

The Cholesterol Treatment Trialists Collaboration[27] is noteworthy because of the availability of individual patient data from 14 statin trials involving more than 90 000 patients in whom total cholesterol was lowered by about 1 mmol/l (40 mm/dl). The CTTC analysis showed no evidence of increased cancer risk among a total of 5614 patients who had incident cancer after randomisation to the particular trial (risk ratio 1.00; 95% CI 0.95 to 1.04); nor were there any differences in cancer deaths (in 2163 patients, relative risk 1.01; 95% CI 0.91 to 1.12) or signal that cancer incidence was increased in those with lower cholesterol levels or with a longer duration of treatment.

A more recent meta-analysis included 15 randomised controlled statin trials with more than 100 person years of follow-up (average follow-up 4.5 years) and 5752 new cases of cancer.[42] A higher incidence of cancer was found among patients achieving lower low-density lipoprotein cholesterol (LDL-C) levels. This is consistent with observations in previous epidemiological studies but confounding factors related to cancer and LDL-C, as well as the context of the trials involved, may have influenced the results observed.[43] To support this, subjects randomised to treatment with a placebo rather than a statin demonstrated the same association between low LDL-C and cancer risk.[44] Of most interest, though, the cancer incidence was higher among patients utilising lower doses of statins (p = 0.003 and p = 0.007 for comparisons between low and high dose, and intermediate and high dose, respectively). This may represent a chance finding, but one possible explanation could be potentially biphasic effects of statins on angiogenesis, in which they may enhance and inhibit angiogenesis at low and high doses, respectively.[45 46]

The duration of treatment in the randomised trials was only approximately 4–6 years, much less than the length of potential exposure to drug therapy. In addition, these neutral results would be expected for any solid tumour carcinogen where the duration of exposure was substantially less than the latency period.

BROADER IMPLICATIONS AND THE NEED FOR PHARMACOVIGILANCE STUDIES

Conclusions regarding these aspects may be informed in a variety of ways, but ultimately, infrequent events such as cancer require preplanned longer periods of data collection. Randomised controlled trials are the most reliable way to minimise confounding and bias, and to estimate treatment effects. However, as mentioned earlier, they are much less effective in establishing whether or not an intervention is associated with a serious adverse event.

The placebo-controlled trials of statins and published longer-term follow-up of such trials provide some reassurance regarding the safety of statins with respect to any association with cancer. However, the placebo-controlled data are limited by the relatively short period of exposure and also because analysis is made on an intention-to-treat basis. For example, the usual time for induction of lung cancer by smoking is many years longer.[47] Longer-term follow-up of trial cohorts is also somewhat flawed because subjects were/must be offered proven therapies (such as statins) at the end of the controlled trials phase, minimising the differential in exposure to the treatment. For example, in the WOSCOPS, during extended follow-up of the cohort, the percentages of participants being treated with a statin among those initially

Table 1 Trial characteristics and data concerning incident cancer and cancer mortality according to initial treatment allocation (statin or placebo) with extended follow-up of the Scandinavian Simvastatin Survival Study (4S), Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) study and West of Scotland Coronary Prevention Study (WOSCOPS)

Study	4S[31]	LIPID[32]	WOSCOPS[33]
Context	Coronary heart disease patients	Post-acute coronary syndrome	Primary prevention
Borderline cholesterol (mmol/l)	5.5 to 8.0 (total)	4.0 to 7.0 (total)	4.0 to 6.0 (low-density lipoprotein)
No of subjects	4444	9014	6595
Intervention, daily dose	Simvastatin 40 mg	Pravastatin 40 mg	Pravastatin 40 mg
Average follow-up (years)	10.4	8.0	13.2*
Incident cancers (risk ratio)	0.80 (0.73 to 1.05)	0.91 (0.81 to 1.03)	1.05 (0.92 to 1.20)
Cancer deaths (risk ratio)	0.80 (0.60 to 1.08)	Not reported	0.97 (0.82 to 1.15)

Cancer data are somewhat flawed because of the intention-to-treat analysis.
*Follow-up for incident cancer.

assigned to pravastatin and placebo were, respectively, 28.6% and 24.3% at 1 year, 33.6% and 29.4% at 3 years, and 38.7% and 35.2% at 5 years.[35]

New analytical approaches are needed to address problems such as this. Progress has been made recently with statistical methods to assess efficacy associated with full compliance to treatment[48] and assessment of dynamic treatment regimens;[49] however, these methods are necessarily based on strong assumptions.

Many countries have cancer registries and the potential for linkage of administrative datasets utilised in extended follow-up of patients in clinical trials.[33] It is prudent to establish and enhance systems that can link large databases. In the case of statins, one example is provided by the VISN16 database in the USA. Interrogation and case-control analysis in 40 421 women in this database, which contains clinical and demographic information about all veterans (>1.4 million patients) cared for in the fourth Central VA Health Care Network between 1998 and 2004, showed that after appropriate adjustment for age, smoking, alcohol use and diabetes, which were all significant covariates, women using statins were less likely to develop breast cancer (odds ratio 0.49; 95% CI 0.38 to 0.62).[50] Internal consistency was suggested by the fact that increased breast cancer risk was also shown for documented risk factors.

Specifically, pharmacovigilance data during malignancy in patients on long-term cholesterol lowering therapy could be compared with national age-specific incidence and mortality data. Such monitoring could also help ascertain whether any drug-class effect or organ-specific effects exist (deleterious or beneficial). These data-linkage systems should include a variety of stakeholders, including regulatory authorities from different countries and the pharmaceutical industry, all cooperating in the provision of more robust information in this and other important areas of pharmacovigilance. Recent issues surrounding the long-term uncertainty of rosiglitazone, cyclo-oxygenase-2 inhibitors and hormone replacement therapy have further highlighted that medication safety must be proven rather than assumed, especially for very widely used medications utilised for long-term therapy.

At this time, it is considered unlikely that cholesterol-lowering generally is associated with cancer. Since the excess cancer mortality in the SEAS trials was not replicated in the interim data in the SHARP and IMPROVE-IT trials, this conclusion will probably extend to simvastatin/ezetimibe as further data are obtained in the ongoing trials.[5 6]

WHAT SHOULD WE NOW DO WITH PATIENTS TAKING SIMVASTATIN AND EZETIMIBE ("VYTORIN")?

The Data and Safety Monitoring Committees of both IMPROVE-IT and SHARP have reviewed the cancer data, and have discussed and recommended that both trials continue as planned, with particular surveillance concerning future data in this area. Similarly, the Food and Drug Administration in the USA decided that no action was necessary after SEAS was published.[51] Ezetimibe and its coformulation with a statin are important additions to cholesterol-lowering therapies. It appears inappropriate to withdraw them from patients in whom their indication is clear and to await the results of ongoing clinical trials[5 6] and further information concerning cancer which should be derived from these trials and other sources, including long-term surveillance data, which are required because of the typically very long latency period before cancer is diagnosed.

Funding: AT has received funding for studies and speaker's fees from AstraZeneca, Bristol-Myers Squibb, Merck Sharp and Dohme, Pfizer, Schering Plough and Sankyo. The author's work is independent of these sources. SH has received assistance via an Australian National Health and Medical Research Council Public Health Postgraduate Research Scholarship, Scholarship application i.d. #237059. The author's work is independent of this source.

Competing interests: None.

Accepted 27 November 2008

Heart Asia 2009:6–10.
doi:10.1136/ha.2008.000133

REFERENCES

1. **Rossebo AB,** Pedersen TR, Boman K, *et al*. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med* 2008;**359**:1343–56.
2. **Peto R,** Emberson J, Landray M, *et al*. Analyses of cancer data from three ezetimibe trials. *N Engl J Med* 2008;**359**:1357–66.
3. **Drazen JM,** D'Agostino, Ware JH, *et al*. Ezetimibe and cancer—an uncertain association. *N Engl J Med* 2008;**359**:13.
4. **Fleming TR.** Identifying and addressing safety signals in clinical trials. *N Engl J Med* 2008;**359**:13.
5. **Baigent C,** Landry M. Study of Heart and Renal Preotection (SHARP). *Kidney Int* 2003;**63**(84 Suppl):207–10S.
6. **Cannon CP,** Giugliano RP, Blazing MA, *et al*. Rationale and design of IMPROVE IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial): comparison of ezetimibe/simvastatin versus simvastatin monotherapy on cardiovascular outcomes in patients with acute coronary syndrome. *Am Heart J*. In press.
7. **Newman TB,** Hulley SB. Carcinogenicity of lipid-lowering drugs. *JAMA* 1996;**275**:55–60.
8. **Bentley P,** Calder I, Elcombe C, *et al*. Hepatic peroxisome proliferation in rodents and its significance for humans. *Food Chem Toxicol* 1993;**31**:857–907.
9. **Cattley RC,** Illingworth R, Laws A, *et al*. Carcinogenicity of lipid-lowering drugs. *JAMA* 1996;**275**:1479–80; author reply 1481–2.
10. **Shellman YG,** Ribble D, Miller L, *et al*. Lovastatin-induced apoptosis in human melanoma cell lines. *Melanoma Res* 2005;**15**:83–9.
11. **Cafforio P,** Dammacco F, Gernone A, *et al*. Statins activate the mitochondrial pathway of apoptosis in human lymphoblasts and myeloma cells. *Carcinogenesis* 2005;**26**:883–91.
12. **Fromigue O,** Hay E, Modrowski D, *et al*. RhoA GTPase inactivation by statins induces osteosarcoma cell apoptosis by inhibiting p42/p44-MAPKs-Bcl-2 signaling independently of BMP-2 and cell differentiation. *Cell Death Differ* 2006;**13**:1845–56.
13. **Sleijfer S,** van der Gaast A, Planting AS, *et al*. The potential of statins as part of anti-cancer treatment. *Eur J Cancer* 2005;**41**:516–22.

14. **Kaushal V,** Kohli M, Mehta P, *et al*. Potential anticancer effects of statins: fact or fiction? *Endothelium* 2003;**10**:49–58.
15. **Graaf MR,** Beiderbeck AB, Egberts AC, *et al*. The risk of cancer in users of statins. *J Clin Oncol* 2004;**22**:2388–94.
16. **Adjei AA.** Blocking oncogenic Ras signaling for cancer therapy. *J Natl Cancer Inst* 2001;**93**:1062–74.
17. **Bradford PG,** Awad AB. Phytosterols as anticancer compounds. *Mol Nutr Food Res* 2007;**51**:161–70.
18. **Assmann G,** Kannenbert F, Ramey DR, *et al*. Effects of ezetimibe, simvastatin, atorvastatin, and ezetimibe-statin therapies on non-cholesterol sterols in patients with primary hypercholesterolemia. *Curr Med Res Opin* 2008;**24**:249–59.
19. **Imanaka H,** Koide H, Shimizu S, *et al*. Chemoprevention of tumor metastasis by liposomal β-sitosterol intake. *Biol Pharm Bull* 2008;**31**:400–4.
20. **Kaye JA,** Jick H. Statin use and cancer risk in the General Practice Research Database. *Br J Cancer* 2004;**90**:635–7.
21. **Neil HA,** Hawkins MM, Durrington PN, *et al*. Non-coronary heart disease mortality and risk of fatal cancer in patients with treated heterozygous familial hypercholesterolaemia: a prospective registry study. *Atherosclerosis* 2005;**179**:293–7.
22. **Platz EA,** Leitzmann MF, Visvanathan K, *et al*. Statin drugs and risk of advanced prostate cancer. *J Natl Cancer Inst* 2006;**98**:1819–25.
23. **Coogan PF,** Smith J, Rosenberg L. Statin use and risk of colorectal cancer. *J Natl Cancer Inst* 2007;**99**:32–40.
24. **Friis S,** Poulsen AH, Johnsen SP, *et al*. Cancer risk among statin users: a population-based cohort study. *Int J Cancer* 2005;**114**:643–7.
25. **Poynter JN,** Gruber SB, Higgins PDR, *et al*. Statins and the risk of colorectal cancer. *N Engl J Med* 2005;**352**:2184–92.
26. **Shannon J,** Tewoderos S, Garzotto M, *et al*. Statins and prostate cancer risk: a case-control study. *Am J Epidemiol* 2005;**162**:318–25.
27. **Baigent C,** Keech A, Kearney PM, *et al*. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005;**366**:1267–78.
28. **Sacks FM,** Pfeffer MA, Moye LA, *et al*. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996;**335**:1001–9.
29. **The Long-term Intervention with Pravastatin in Ischaemic Disease (Lipid) Study Group**. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998;**339**:1349–57.
30. **Shepherd J,** Blauw GJ, Murphy MB, *et al*. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002;**360**:1623–30.
31. **Strandberg TE,** Pyorala K, Cook TJ, *et al*. Mortality and incidence of cancer during 10-year follow-up of the Scandinavian Simvastatin Survival Study (4S). *Lancet* 2004;**364**:771–7.
32. **The LIPID Study Group**. Long-term effectiveness and safety of pravastatin in 9014 patients with coronary heart disease and average cholesterol concentrations: the LIPID trial follow-up. *Lancet* 2002;**359**:1379–87.
33. **Ford I,** Murray H, Packard CJ, *et al*. Long-term follow-up of the West of Scotland Coronary Prevention Study. *N Engl J Med* 2007;**357**:1477–86.
34. **Bjerre LM,** LeLorier J. Do statins cause cancer? A meta-analysis of large randomized clinical trials. *Am J Med* 2001;**110**:716–23.
35. **Bonovas S,** Filioussi K, Tsavaris N, *et al*. Statins and cancer risk: a literature-based meta-analysis and meta-regression analysis of 35 randomized controlled trials. *J Clin Oncol* 2006;**24**:4808–17.
36. **Dale KM,** Coleman CI, Henyan NN, *et al*. Statins and cancer risk: a meta-analysis. *JAMA* 2006;**295**:74–80.
37. **Bonovas S,** Filioussi K, Tsavaris N, *et al*. Use of statins and breast cancer: a meta-analysis of seven randomized clinical trials and nine observational studies. *J Clin Oncol* 2005;**23**:8606–12.
38. **Freeman SR,** Drake AL, Heilig LF, *et al*. Statins, fibrates, and melanoma risk: a systematic review and meta-analysis. *J Natl Cancer Inst* 2006;**98**:1538–46.
39. **Pfeffer MA,** Keech A, Sacks FM, *et al*. Safety and tolerability of pravastatin in long-term clinical trials: prospective Pracastatin Pooling (PPP) Project. *Circulation* 2002;**105**:2341–6.
40. **Newman CB,** Palmer G, Silbershatz H, *et al*. Safety of atorvastatin derived from analysis of 44 completed trials in 9416 patients. *Am J Cardiol* 2003:670–6.
41. **Bonovas S,** Sitaras NM. Does pravastatin promote cancer in elderly patients? A meta-analysis. *Can Med Assoc J* 2007;**176**:649–54.
42. **Alsheikh-Ali AA,** Maddukuri PV, Han H, *et al*. Effect of the magnitude of lipid lowering on risk of elevated liver enzymes, rhabdomyolysis, and cancer: Insights from large randomized statin trials. *J Am Coll Cardiol* 2007;**50**:409–18.
43. **Jacobs D,** Blackburn H, Higgins M, *et al*. Report of the conference on low blood cholesterol: mortality associations. *Circulation* 1992;**86**:1046–60.
44. **Steinberg D.** Statin treatment does not cause cancer. *J Am Coll Cardiol* 2008;**52**.
45. **Folkman J.** Angiogenesis in cancer, vascular, rheumatoid and other disease. *Nat Med* 1995;1:27–31.
46. **Weis M,** Heeschen C, Glassford AJ, *et al*. Statins have biphasic effects on angiogenesis. *Circulation* 2002;**105**:739–45.
47. **Doll R,** Peto R. Cigarette smoking and bronchial carcinoma: dose and time relationships among regular smokers and lifelong non-smokers. *J Epidemiol Commun Health* 1978;**32**:303–13.
48. **Imbens GW,** Rubin DB. Bayesian inference for causal effects in randomized experiments with noncompliance. *Ann Stat* 1997;**25**:305–27.
49. **Hernan M,** Lanoy E, Costagliola D, *et al*. Comparison of dynamic treatment regimes via inverse probability weighting. *Basic Clin Pharmacol Toxicol* 2006;**98**:237–42.
50. **Kochhar R,** Khurana V, Bejjanki H, *et al*. Statins to reduce breast cancer risk: A case control study in US female veterans. *J Clin Oncol* 2005;**23**(Suppl):514S.
51. **Cox A.** Hypercholesterolemia: clarification from adverse drug reactions agency. *BMJ* 2008;**337**:a1669.