Short cuts

What's new in the other general journals

Heavy smokers who cut down may reduce their risk of lung cancer

Giving up smoking is one certain way of protecting yourself against lung cancer. Everyone knows it, but so few smokers manage to do it. For the majority of smokers who can't or won't stop, cutting down the number of cigarettes they smoke each day may help.

In a large cohort study from Denmark, heavy smokers (≥ 15 cigarettes/day) who managed to cut down by at least half were 27% less likely to get lung cancer over the next 18 years or so, than those who continued smoking heavily (hazard ratio 0.73, 95% CI 0.54 to 0.98). Light smokers (< 15 cigarettes/day) were 56% less likely to get lung cancer than heavy smokers, and former smokers who had quit before the study began reduced their risk by 83%. Predictably, Danes who had never smoked had the lowest risk of all—91% lower than the heavy smokers (0.09, 0.06 to 0.13).

So, although giving up for good is best, doctors can at least tell hard core smokers that cutting down is better than nothing. Unfortunately, there's no evidence that cutting down protects anyone against heart disease or chronic obstructive pulmonary disease, both of which have a greater impact than lung cancer on public health.

JAMA 2005;294:1505-10

Statins: those benefits in detail

A detailed analysis of who benefits from statins and by how much reports that each 1 mmol/l drop in serum concentration of low density lipoprotein cholesterol reduces overall mortality by 12% over five years. It also reduces risk of coronary death or

heart attack by 23%, need for coronary vascularisation by 24%, risk of stroke (fatal or non-fatal) by 17%, and risk of any major vascular event by 21%.

The benefits seem largely independent of age, sex, pre-existing disease, or baseline serum concentration of LDL cholesterol. Statins work even for people with LDL cholesterol concentrations < 2.6 mmol/l, for people with diabetes but no vascular disease, and for people older than 75 years.

This meta-analysis, which included over 90 000 patients from 14 randomised trials, shows that the gains from treatment depend mainly on the size of reduction in LDL concentration, not on baseline values before treatment began. It also suggests that the benefits start early—during the first year of treatment—and increase with time. Patients in these trials were followed up for a mean of five years. A quarter of the participants were women, half had pre-existing coronary heart disease, and 55% had hypertension. Mean serum concentrations of LDL cholesterol at baseline ranged between 3 mmol/l and 5 mmol/l.

The authors could find no evidence of a link between statins and cancer, even

among older patients. Rhabdomyolysis was also extremely rare, and only slightly (and non-significantly) more common among treated patients than controls.

The authors conclude that statins are safe and effective for a wide range of patients, and treatment should be considered for anyone with an increased risk of an occlusive vascular event, including stroke. The goal of treatment should shift away from target concentrations of LDL cholesterol, and focus more on reducing the serum concentration by as much as possible for as long as possible.

Lancet 2005 September 27
doi 10.1016/S0140-6736(05)67394-1

New treatment for CMV in pregnancy looks promising

Cytomegalovirus (CMV) infection during pregnancy is relatively common, usually asymptomatic, and can cause serious congenital abnormalities if passed on to the fetus. There's no treatment, but hyperimmune globulin containing high titres of IgG directed against the virus is one therapeutic possibility. A preliminary study from Italy suggests it can work.

Researchers recruited two cohorts of women with evidence of primary CMV infection in pregnancy, and gave them the option of treatment. The first cohort included 45 women with an infected fetus (diagnosed by amniocentesis), of whom 31 chose treatment. Only one of them had a baby with clinical cytomegalic inclusion disease at birth compared with seven of the 14 women who refused treatment (adjusted odds ratio 0.02; $P < 0.001$). Hyperimmune globulin also protected infants of mothers without documented maternal-fetal transmission, but the results for this second cohort were not as dramatic.

A linked editorial (pp 1402-4) describes these findings as remarkable, not least because 15 of the 31 treated women in the first cohort were carrying a fetus with serious abnormalities. Hyperimmune globulin seemed to cure 14 of them; only one fetus was born with clinical disease.

Serious shortcomings in the design of this study make it hard to be certain of any of the results, however. Women were not randomised, although they could have been. The authors say three ethics

committees would not allow it, but it's hard to see why. We don't know yet whether this treatment works, and only a randomised placebo controlled trial can tell us.

N Engl J Med 2005;353:1350-62

Drotrecogin alfa does not improve survival in low risk patients with severe sepsis

A placebo controlled trial of drotrecogin alfa (activated)—recombinant activated protein C—to treat severe sepsis in patients at low risk of death was stopped early when it became clear that treatment not only did not improve survival but doubled the risk of serious bleeding.

Regulatory agencies in the United States and Europe licensed drotrecogin alfa for high risk patients in 2001, after clinical trials reported it could reduce the risk of death by nearly a fifth. The licence was withheld from lower risk patients pending further work. So researchers planned a megatrial of more than 11 000 patients with severe sepsis but failure of only one organ system or a relatively low clinical risk score (acute physiological and chronic health evaluation (APACHE II) score < 25). In the end, they needed only 2640 patients to show that treatment was probably futile. A fifth of the patients in both the placebo and treatment groups died before they left hospital, and 4% of patients who received drotrecogin alfa had a serious bleed compared with only 2% of patients who received placebo ($P = 0.001$).

The bleeding complications in this trial were no surprise. Drotrecogin alfa is an anticoagulant, among other things. The mortality findings are also confirmatory, following on from subgroup analyses in earlier trials. It's now fairly clear that, for patients with sepsis at the lower end of the risk spectrum, drotrecogin alfa does more harm than good and should not be used.

N Engl J Med 2005;353:1332-41

Phytoestrogens may help prevent lung cancer

Phytoestrogens are weakly oestrogenic compounds found in plant foods such as soya beans, spinach, cabbage, broccoli, grains, tea, and chickpeas. After noticing that hormone replacement therapy seemed to protect women from lung cancer, US researchers did a case-control study to look for similar effects from dietary phytoestrogens. Overall, they found that a high intake of phytoestrogens was associated with a reduction of up to 46% in the risk of lung cancer (odds ratio 0.54, 95% CI 0.42 to 0.7, for highest v lowest intake, divided by quartiles). High intake seemed to benefit people who had never smoked and current smokers, but less so for former smokers. Phytoestrogens from food, rather than from drinks such as tea and coffee, worked best in this study, for both men and women.

The study included 1672 adults with lung cancer and 1735 matched, healthy controls. All participants filled in detailed food frequency questionnaires about what they had eaten in the year before their diagnosis (cases) or interview (controls). Food frequency questionnaires are not ideal, because people don't always remember what they have eaten and when. But despite this, and the other well rehearsed limitations of retrospective studies, the authors conclude that phytoestrogens probably do have a favourable impact on risk of lung cancer. A link is certainly biologically plausible. There are oestrogen receptors in normal and cancerous lung tissue, and phytoestrogens are known to have a particular affinity for both.

JAMA 2005;294:1493-1504

Gene variants predict effectiveness of β blockers in people with acute coronary syndrome

β blockers prolong survival in people with acute coronary syndrome, but a new genetic study suggests they work better for some people than others.

In a cohort of 735 patients admitted to hospital with acute coronary syndrome, mortality at three years among those given β blockers varied between 6% and 20% depending on their β adrenoceptor genotype. More specifically, the authors found a link between survival and variants in the ADRB2 gene, which codes for the β_2 adrenoceptor.

The association was found only among the 81% (597/735) of patients who were prescribed β blockers, and remained significant after adjustment for a whole range of possible confounding factors including age, sex, race, and coexisting chronic diseases such as hypertension

or diabetes (hazard ratio 5.36, 95% CI 1.83 to 15.69, for highest risk genotype v lowest risk). There were 84 deaths in total.

The authors think their findings might eventually be useful for targeting treatment with β blockers to patients most likely to benefit, or stratifying risk so that patients with the least favourable genotype and the poorest outlook get extra treatments.

JAMA 2005;294:1526-33

Prevalence of drug resistant influenza A increases worldwide

Adamantane derivatives such as amantadine have been used to prevent and treat influenza A for decades. Influenza A viruses find it relatively easy to acquire resistance to these drugs, but surveillance studies have always reported low levels of resistance worldwide—typically about 1% among circulating influenza viruses.

That tranquil scene may be changing fast. A recent examination of influenza A virus isolates sent from around the world to a surveillance centre found that 12.3% of them had a gene mutation conferring resistance to adamantanes in 2004. Ten years previously, only 0.4% of isolates sent to the centre had the mutation. Of the 392 resistant viruses found, 84% were identified after 2003, and nearly two thirds of these came from Asia.

The authors describe their findings as alarming and say they almost certainly represent a true and dramatic increase in the prevalence of resistance worldwide. Surveillance methods stayed largely the same over the study period, so better ascertainment is unlikely to have contributed to the observed increases. Governments planning to stockpile adamantanes as a backstop against pandemics of influenza A may want to think again.

Lancet 2005;366:1175-81

Alison Tonks associate editor
atons@bmj.com