

General

Disease from passive smoking worldwide

The harmful effects of exposure to other people's tobacco smoke are well documented and the World Health Organization has advised that smoking should be banned in all indoor workplaces and public places and on public transport. Despite this, 93% of the world's population live in countries without adequate regulations against exposure to second-hand smoke.

Data about exposure and the damage caused have been reported for 2004 from 192 countries. Around 40% of children, 33% of non-smoking men, and 35% of non-smoking women were exposed to second-hand smoke. This exposure was estimated to have caused 379 000 deaths from coronary disease, 165 000 deaths from lower respiratory infections, 36 900 from asthma, and 21 400 from lung cancer; a total of >602 000 deaths – about 1% of total worldwide mortality. Among the victims, 47% were women, 26% men, and 28% children. About 10.9 million disability-adjusted life-years (DALYs) were lost, 61% of which were in children. These 10.9 million DALYs included 2.84 million from coronary disease, 216 000 from lung cancer, 1.25 million from asthma in adults, 651 000 from asthma in children, 24 900 from otitis media in young children, and 5.94 million from lower respiratory tract infections in young children.

Measures to limit second-hand smoke exposure should be extended worldwide.

Öberg M et al. Worldwide burden of disease from exposure to second-hand smoke: retrospective analysis of data from 192 countries. *Lancet* 2011; 377: 139–46; Wipfli HL, Samet JM. Second-hand smoke's worldwide disease toll. *Ibid*: 101–2 (comment).

Efficacy of antivenom for scorpion stings

Standard treatment for scorpion (*Mesobuthus tamulus*) stings is with prazosin. An antivenom has recently been made available and has been tested in India.

A total of 70 patients at a single hospital in rural Maharashtra were randomised to prazosin plus antivenom or prazosin alone after being admitted with a grade 2 scorpion sting. All patients were older than 6 months and had no cardiorespiratory or central nervous system abnormalities. The presenting features included profuse sweating, ropy salivation, priapism, hypotension or hyperten-

sion, bradycardia or tachycardia, and cold extremities. Complete resolution of symptoms and signs within 10 hours of treatment occurred in 32 patients (91%) in the antivenom group and 8 (23%) in the control group. The mean time to recovery was 8 hours vs 18 hours.

The antivenom caused no mild or severe reactions. The antivenom was safe and effective.

Bawaskar HS, Bawaskar PH. Efficacy and safety of scorpion antivenom plus prazosin compared with prazosin alone for venomous scorpion (*Mesobuthus tamulus*) sting: randomised open label clinical trial. *BMJ* 2011; 342: 153: (210; 341: c7136); Mills EJ, Ford N. Research into scorpion stings. *Ibid*: 115 (c7369) (editorial).

BMI and all-cause mortality

Although the link between overweight and obesity and cardiovascular mortality and deaths from some cancers is established, the association between BMI and all-cause mortality is uncertain, as is the optimum BMI. Now a systematic review and meta analysis has provided some clarification.

The pooled analysis included data from 19 prospective studies (1.46 million white subjects aged 19–84 years). The median BMI at baseline was 26.2. With an average follow-up of 10 years there were 160 087 deaths. Among previously healthy non-smokers there was a J-shaped relationship between BMI and all-cause mortality after adjustment for age, study, physical activity, alcohol consumption, education, and marital status.

The BMI (hazard ratio for death) figures for women were: BMI 15–18.4 (hazard ratio 1.47); 18.5–19.9 (1.14); 20.0–22.4 (1.0); 22.5–24.9 (1.0); 25.0–29.9 (1.13); 30–34.9 (1.44); 35.0–39.9 (1.88); 40–49.9 (2.51). The corresponding figures for men were similar.

The BMI associated with lowest all-cause mortality is 20–24.9 for white adults. Overweight and obesity, and possibly underweight, are associated with increased risk.

De Gonzalez AB et al. Body-mass index and mortality among 1.46 million white adults. *NEJM* 2010; 363: 2211–9.

AIDS

Mobile phone use to improve ART adherence in Kenya

Mobile (cell) phone use and ownership has spread rapidly throughout the world and by 2012 it is expected that

there will be 4.5 billion subscribers. A study in Kenya has shown that use of a mobile phone short message service (SMS) increases adherence to antiretroviral therapy (ART). The study took place at three sites, one in a low-income area and one in a higher-income area, both in Nairobi, and one in a rural district. Adult patients starting ART were eligible if they owned or had ready access to a mobile phone and could communicate via an SMS. Randomisation was to weekly SMS messages from a clinic nurse (with a response expected within 48 hours) or standard care. A total of 538 patients were randomised between May 2007 and October 2008. The rate of self-reported treatment adherence was 62% (SMS) vs 50% (controls), a significant 19% reduction in non-adherence in the intervention group. Viral RNA load suppression (<400 copies per mL at 12 months) was achieved in 57% vs 48%, a significant 16% reduction in virological failure in the SMS group compared with the control group. The numbers-needed-to-treat were nine for >95% adherence and 11 for viral load suppression.

The SMS service improved success rates for patients beginning ART. Mobile phones are widely available in Africa and only 7% of candidates for this study were excluded by lack of access. The probable cost of providing this service would be about US\$8 per patient per year.

Lester RT et al. Effects of mobile phone short message service on antiretroviral treatment adherence in Kenya (WeTel Kenya1): a randomised trial. *Lancet* 2010; 376: 1838–45; Chi BH, Stringer JSA. Mobile phones to improve HIV treatment adherence. *Ibid*: 1807–8 (comment).

Recently acquired HIV infection in breastfeeding mothers: high risk to the infant

In sub-Saharan Africa, more than 60% of HIV infections are in women and in the countries with the greatest HIV burden; women aged 15–24 are three times more likely to be infected than men of the same age. Pregnant and lactating women seem to be particularly likely to become infected with HIV, putting their children at high risk of acquiring the disease. A study in Zimbabwe has confirmed the high risk in the breastfeeding infants of recently infected mothers.

Mother–infant pairs were enrolled within 4 days of delivery into a trial of vitamin A supplementation to prevent mother-to-child HIV transmission: (it didn't). Data from this trial were used to study vertical transmission of HIV. Four groups of HIV-positive mothers were in-

cluded in the analysis: 1625 who were HIV-positive on ELISA testing at baseline and whose infants were HIV-positive at 6 weeks, 2870 who were HIV-positive at baseline but whose infants were HIV-negative on PCR testing at 6 weeks, 334 mothers who seroconverted during breastfeeding, and 17 mothers who were HIV-negative on ELISA testing but HIV-positive on PCR testing at baseline. Among mothers who were HIV-positive at baseline and whose infants were HIV-negative at 6 weeks transmission via breastfeeding occurred at a rate of 8.96 infections per 100 child-years of breastfeeding. Among the infants of mothers who seroconverted during breastfeeding however, the HIV transmission rate was 34.56 infections per 100 child-years during the first 9 months after seroconversion but fell to 9.50 per 100 child-years during the next 3 months and to zero after that. Median plasma HIV concentration in mothers who seroconverted fell from 5.0 log₁₀ copies per ml before seroconversion to 4.1 log₁₀ copies per ml 9 months after seroconversion. Breast milk HIV load was 4.3 log₁₀ copies per ml soon after infection but declined to 2.0 log₁₀ copies per ml at 31–90 days and <1.5 log₁₀ copies per ml thereafter. The infants of mothers who were infected at around the time of delivery did poorly: 75% were infected or died before the age of 9 months. Maternal seroconversion during breastfeeding accounted for 18–20% of all mother-to-child transmissions of HIV.

The risk of mother-to-child transmission of HIV is particularly high among mothers who seroconvert during breastfeeding.

Humphrey JH et al. Mother to child transmission of HIV among Zimbabwean women who seroconverted postnatally: prospective cohort study. *BMJ* 2011; 342: 37 (2010); 341: c6580; Stringer JSA, Guffey MB. Transmission of HIV to infants whose mothers seroconvert postnatally. *Ibid*: 3–4 (2010); 341: c6269 (editorial).

Prophylactic ART for men who have sex with men

A multinational study has shown that antiretroviral drug prophylaxis provides protection from HIV infection in a high-risk group.

At 11 sites in six countries a total of 2499 HIV-negative men or transgender women who have sex with men were randomised to take emtricitabine and tenofovir disoproxil fumarate (FTC-TDF) as a single combination tablet, or placebo, daily. All subjects received risk reduction counselling, condoms, HIV

testing, and management of sexually transmitted infection. Average follow-up was for 1.2 years. During follow-up 36 subjects in the treatment group and 64 in the placebo group became infected with HIV, a significant 44% reduction in the FTC-TDF group. Blood analyses for the antiretroviral drugs were positive in 22 of 43 subjects (51%) who remained seronegative and 3 of 34 (9%) who became seropositive. The antiretroviral prophylaxis was well tolerated.

Prophylaxis with daily FTC-TDF was effective.

Grant RM et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *NEJM* 2010; 363: 2587–99; Michael NL. Preexposure prophylaxis for HIV – another arrow in the quiver? *Ibid*: 2663–5 (editorial).

Cardiology

Cardiovascular safety of NSAIDs: network meta-analysis

There is still uncertainty about the cardiovascular safety of nonsteroidal anti-inflammatory drugs (NSAIDs), both conventional drugs and cyclo-oxygenase-2 (COX-2) inhibitors. A new network meta-analysis has provided more data about seven drugs, showing naproxen to be probably the least harmful.

The analysis included 31 trials with 116 429 patients and >115 000 patient-years of follow-up. Allocation was to naproxen, ibuprofen, diclofenac, celecoxib, etoricoxib, rofecoxib, lumiracoxib, or placebo. Rofecoxib was associated with a significant 2.12-fold increase in risk of myocardial infarction compared with placebo. Naproxen, diclofenac and etoricoxib were associated with nonsignificant reductions in risk of 18%, 18%, and 25% respectively. The other three drugs were associated with nonsignificant increases in risk of between 35% and 100%. Ibuprofen and diclofenac both increased the risk of stroke significantly and etoricoxib and diclofenac were each associated with significantly increased risk of death from cardiovascular causes.

The NSAIDs vary in their cardiovascular efforts. Significant increases in risk were found with rofecoxib for myocardial infarction, with ibuprofen and diclofenac for stroke, and with etoricoxib and diclofenac for cardiovascular death. An editorialist suggests that for patients at high cardiovascular risk COX-2 inhibitors should be avoided and naproxen is

probably the safest NSAID. He calls for greater assessment of alternative drugs.

Trelle S et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. *BMJ* 2011; 342: 154 (c7086); Ray WA. Cardiovascular safety of NSAIDs. *Ibid*: 116–7 (c6618) (editorial).

Drug-eluting stents in large coronary arteries

First-generation drug-eluting coronary stents have reduced the risk of restenosis compared with bare-metal stents but may be associated with late stent thrombosis. The benefits of drug-eluting stents may be less in large arteries of 3.0mm or greater diameter. Now a large trial in four European countries has shown that drug-eluting stents, compared with bare-metal stents, reduce rates of target vessel revascularisation in large coronary arteries.

A total of 2314 patients who needed stents at least 3.0mm in diameter were randomised to everolimus-eluting (EE), sirolimus-eluting (SE), or bare-metal (BM) stents. The primary endpoint (death from cardiac causes or non-fatal myocardial infarction at 2 years) was reached by 2.6% (SE), 3.2% (EE) and 4.8% (BM). There were no significant differences between drug-eluting and bare-metal stents in the primary endpoint or in the rates of late events or death, myocardial infarction, or stent thrombosis. Drug-eluting stents did, however, reduce the rate of target-vessel revascularisation unrelated to myocardial infarction significantly compared with bare-metal stents (SE 3.7%, EE 3.1%, BM 8.9%).

For patients needing stenting for large vessel coronary disease drug-eluting stents are associated with less likelihood of repeat revascularisation than bare-metal stents. In this study sirolimus-eluting and everolimus-eluting stents performed similarly.

Kaiser C et al. Drug-eluting versus bare-metal stents in large coronary arteries. *NEJM* 2010; 363: 2310–9.

Anacetrapib in patients with or at high risk of coronary disease

Inhibitors of the cholesteryl ester transfer protein (CETP) raise serum levels of HDL cholesterol and some CETP inhibitors reduce levels of LDL cholesterol. The first CETP inhibitor, torcetrapib, failed because it was associated with increased mortality and morbidity in a clinical trial. Further studies, however, suggested that the adverse effects were unrelated to CETP inhibition and not necessarily a drug class effect. Anacetrapib is a new potent, selective, CETP inhibitor that has

appeared non-toxic in preliminary studies. A randomised trial has shown anacetrapib to be effective and probably safe.

The trial included 1623 patients with coronary disease or high coronary risk and with an LDL cholesterol level on statin treatment of 1.3–2.6 mmol/L, an HDL cholesterol level of <1.6 mmol/L, and a triglyceride level of no more than 4.5 mmol/L. Randomisation was to anacetrapib 100mg daily, or placebo, for 18 months. At 24 weeks the mean LDL cholesterol level had fallen from 2.1 to 1.2 mmol/L in the anacetrapib group and from 2.1 to 2.0 mmol/L in the placebo group, a highly significant 40% reduction on anacetrapib compared with placebo. Levels of HDL cholesterol increased from 1.0 to 2.6 mmol/L on anacetrapib and from 1.0 to 1.2 mmol/L in the placebo group, a highly significant 2.4-fold increase with anacetrapib compared with placebo. On follow up anacetrapib produced no significant changes in blood pressure, electrolyte, or aldosterone measurements compared with placebo. Cardiovascular events occurred in 2.0% (anacetrapib) vs 2.6% (placebo). There was a 94% predictive probability that anacetrapib would not be associated with the 25% increase in cardiovascular events seen with torcetrapib.

Anacetrapib produced highly significant and favourable changes in LDL and HDL cholesterol levels and appeared to have an acceptable side-effects profile. Within the power limits of this study it did not have the adverse effects associated with torcetrapib.

Cannon CP et al. Safety of anacetrapib in patients with or at high risk of coronary heart disease. *NEJM* 2010; 363: 2406–13.

Tropical

Cost-effectiveness of prereferral rectal artesunate for severe malaria in children

Parenteral artesunate is the preferred treatment for severe malaria but in rural areas of Africa access to parenteral treatment is often poor. In these circumstances rectal artesunate given by lay community health workers has been recommended as first treatment prior to referral to a health facility. Now a cost-effectiveness analysis has shown that such intervention would be cost-effective and life saving.

With a cohort of 1000 infants followed up to the age of 5 years the cost-

effectiveness would depend on the uptake of the intervention and referral compliance. At 25% uptake and referral compliance, 19 disability-adjusted life-years (DALYs) would be averted at a cost of 1173 international dollars per DALY averted. At 100% uptake and compliance 967 DALYs could be averted and the cost would be US\$1.77 per DALY averted.

Prereferral artesunate for children <5 years old with severe malaria would be cost-effective and life saving.

Tozan Y et al. Prereferral rectal artesunate for treatment of severe childhood malaria: a cost-effectiveness analysis. *Lancet* 2010; 376: 1910–15; Lubell Y. Cost-effective use of prereferral treatment for severe malaria. *Ibid*: 1880–1 (comment).

Obs & Gyn

Outcome prediction in pre-eclampsia

Pre-eclampsia remains a leading cause of maternal morbidity and mortality worldwide. The only cure for pre-eclampsia is delivery. The ability to predict adverse outcomes would be a valuable aid to management decisions. Workers in Canada, New Zealand, Australia, and the UK have developed and validated a prognostic model (fullPIERS).

The prospective multicentre study included a total of 2023 women who were either admitted to tertiary obstetric centres with pre-eclampsia or developed it after admission. Of these women 261 (12.9%) had adverse outcomes 106 (5.2%) within 48 hours of admission. There were no maternal deaths. Factors predictive of an adverse maternal outcome included lower gestational age, chest pain or dyspnoea, low oxygen saturation, low platelet count, and raised creatinine or aspartate transaminase levels.

The fullPIERS model derived from these factors predicted adverse maternal outcome within 48 hours of study eligibility and performed well at up to 7 days. The fullPIERS model identified women at increased risk of adverse outcomes up to 7 days before those outcomes occurred and may therefore be used to guide management decisions. Although the present model is only relevant to high-resource tertiary centres it will be a priority to adapt it to middle-and low-income settings

Von Dadelszen P et al. Prediction of adverse maternal outcomes in pre-eclampsia: development and validation of the fullPIERS model. *Lancet* 2011; 377: 219–27; Teela KC et al. The PIERS trial: hope for averting deaths from pre-eclampsia. *Ibid*: 185–6 (comment).

Anthelmintic therapy in pregnancy and infant immunity

Helminth infections are common in developing countries in which viral and bacterial infections are also common and BCG vaccination is less effective. It has been suggested that helminth infections might lower immunity to other infections and that maternal helminth infection in pregnancy might affect the infant's immune responses. Now a trial in Entebbe, Uganda, where helminth infections are common, has shown that giving antihelminthic treatment to pregnant women does not enhance infant responses to immunisation or reduce the infants' susceptibility to infection.

The trial included 2507 women who were randomised in the second or third trimester of pregnancy to single-dose treatment with praziquantel, albendazole, both, or placebo. At 1 year of age the responses of the infants to BCG, tetanus, and measles immunisations were similar in all four groups. Albendazole treatment of mothers with hookworm infection was associated with reduced interleukin 5 and interleukin-13 responses to tetanus toxoid in their infants.

Anthelmintic treatment of the mothers did not alter the susceptibility of their infants to malaria, diarrhoea, or pneumonia, or to vertical transmission of HIV.

Webb EL et al. Effect of single-dose anthelmintic treatment during pregnancy on an infant's response to immunisation and on susceptibility to infectious diseases in infancy: a randomised, double-blind, placebo-controlled trial. *Lancet* 2011; 377: 52–62; Yazdanbakhsh M, Luty AJF. Wormy mothers, healthy babies: case closed or conundrum? *Ibid*: 6–8 (comment).

Male circumcision to reduce female HPV infection

Infection with human papillomavirus (HPV) causes genital warts, penile and anal cancers in men, and cervical cancer in women. More than 85% of the total burden of HPV disease is in developing countries. As well as reducing the risk of HIV infection, male circumcision reduces the risk of HPV infection in men. Its capacity to protect the men's female partners from HPV infection has been unknown. Now two trials in Uganda, reported together, have shown that male circumcision does protect female partners from HPV infection.

A total of 5596 HIV-negative men were randomised to immediate circumcision or circumcision delayed for 24 months (controls). In addition, 1245 HIV-negative female partners (648 of men in the immediate circumcision group and

597 of men in the delayed circumcision group) were assessed at baseline and at 12 and 24 months. After 24 months of follow-up high-risk HPV infection was found in 27.8% of the partners of men in the immediate circumcision group and 38.7% of the partners of men in the control group, a highly significant 28% reduction in the immediate circumcision group. The incidence of high-risk HPV infection in these women was 20.7 vs 26.9 infections per 100 person-years, a significant 23% difference.

The circumcision of male partners reduces the risk of HPV infection in women. Added to the use of HPV vaccines for women, male circumcision could increase female protection against a wider variety of HPV types.

Wawer MJ et al. Effect of circumcision of HIV-negative men on transmission of human papillomavirus to HIV-negative women: a randomised trial in Rakai, Uganda. *Lancet* 2011; 377: 209–18; Giuliano AR et al. Male circumcision and HPV transmission to female partners. *Ibid*: 183–4 (comment).

Infection

Vitamin D in tuberculosis treatment

In 2008 some 1.8 million people died of tuberculosis. Calcitriol, the active metabolite of vitamin D enhances the host response to tuberculosis by binding vitamin D receptors on antigen-presenting cells and active lymphocytes to regulate transcription of vitamin D-responsive genes. There are three genotypes of the Taq1 vitamin D receptor polymorphism (TT, Tt, and tt) and three of the FokI polymorphism (FF, Ff, and ff). Carriage of the t allele of the Taq I polymorphism is thought to enhance the effects of anti-tuberculosis treatment whereas carriage of the f allele of the FokI polymorphism has the opposite effect. A trial in London, England has shown that high-dose vitamin D reduces the time to negative sputum cultures in patients treated for active pulmonary tuberculosis, but only in those with the tt genotype of the Taq I polymorphism.

At 10 centres, a total of 146 patients with sputum smear-positive tuberculosis were randomised to vitamin D3 2.5 mg, or placebo on starting standard antituberculosis treatment and at days 14, 28, and 42. The primary efficacy analysis included 126 patients. Sputum samples were collected for culture at baseline and at 14, 28, 42, and 56 days. Median

time to sputum culture conversion was 36.0 days (vitamin D) vs 43.5 days (placebo), a nonsignificant 39% difference. Among patients with the tt genotype of the TaqI polymorphism there was a significant shortening of the time to sputum culture conversion in the vitamin D group compared with the placebo group (hazard ratio 8.09). FokI genotype did not influence the speed of sputum culture conversion. Most patients had marked vitamin D deficiency (serum 25-hydroxyvitamin D <20 nmol/L in 75/126 and <75 nmol/L in 122/126 at baseline). At 56 days this level was 101.4 nmol/L in the vitamin D group and 22.8 nmol/L in the placebo group. More than 75% of the participants were of Asian or Black ethnic origin. The distribution of TaqI genotypes in the vitamin D group was TT, 48%, Tt, 44%, and tt, 8%. Vitamin D was not effective in patients with the TT or Tt genotypes. Vitamin D reduced the time to sputum conversion only among the 8% of patients with the tt genotype of the vitamin D receptor polymorphism.

The *Lancet* commentator strongly criticises the lack of attention to the question of whether the prophylactic use of vitamin D would prevent the activation of latent tuberculosis.

Martineau AR et al. High-dose vitamin D3 during intensive-phase antimicrobial treatment for pulmonary tuberculosis: a double-blind randomised controlled trial. *Lancet* 2011; 377: 242–50; Vieth R. Vitamin D nutrient to treat TB begs the prevention question. *Ibid*: 189–90.

Household contacts of patients with MDR or XDR tuberculosis

Contact investigation is important after diagnosis of a case of active tuberculosis but may be limited in developing countries by lack of resources. A study in Lima, Peru has shown that the household contacts of patients with multidrug-resistant (MDR) or extensively drug resistant (XDR) tuberculosis are at high risk of similar disease and therefore that household contact tracing in this case is extremely important.

The study included 693 households of index patients with MDR tuberculosis in 1996–2003. In 48 of these households the index patient had XDR tuberculosis. There were 4503 household contacts and 117 (2.6%) of these had active tuberculosis when the index patient began treatment. The risk to contacts was similar whether the index patient had MDR or XDR tuberculosis. Over 4 years of follow-up active tuberculosis was diagnosed in a further 242 contacts and the

risk in XDR households was nearly twice that in MDR households (incidence 2928 cases per 100 000 person-years in XDR households and 1524 cases per 100 000 person-years in MDR households, adjusted hazard ratio 1.88). Resistance testing was performed on isolates from 142 of the 359 household contacts who had active tuberculosis and in 129 cases (91%) the organism was multidrug resistant. The household contacts of patients with MDR or XDR tuberculosis are at high risk of MDR tuberculosis.

Contact investigation should be performed in all cases and any active tuberculosis found should be considered to be MDR tuberculosis in the absence of evidence to the contrary.

Becerra MC et al. Tuberculosis burden in households of patients with multidrug-resistant and extensively drug-resistant tuberculosis: a retrospective cohort study. *Lancet* 2011; 377: 147–52; Cox H, van Cutsem G. Household screening and multidrug-resistant tuberculosis. *Ibid*: 103–4 (comment).

Healthcare-associated infection in developing countries

Healthcare-associated infections are extremely important worldwide; they are perhaps the most frequent threat to patient safety but little is known about the worldwide burden. A systematic review and meta-analysis of relevant studies has added to knowledge about the burden of endemic healthcare-associated infections in developing countries.

The analysis included 220 studies of which 118 (54%) were of low quality. The pooled prevalence of healthcare-associated infections from high quality studies was 15.5 per 100 patients, much higher than the rates reported from Europe and the USA. In adult intensive care units the figure was 48 per 1000 patient-days, at least three times the healthcare-associated infection densities reported from the USA. Surgical-site infection occurred at a rate of 5.6 per 100 surgical procedures. The most common hospital-acquired infections were with gram-negative bacilli. Meticillin resistance was found in 54% of *Staphylococcus aureus* isolates. The pooled incidence of healthcare-associated infections in children was 5.7 per 100 patients.

The burden of healthcare-associated infection in developing countries is high. Improved surveillance and infection control are needed.

Allegranzi B et al. Burden of endemic healthcare-associated infection in developing countries: systematic review and meta-analysis. *Lancet* 2011; 377: 228–41; Rosenthal VD. Healthcare-associated infections in developing countries. *Ibid*: 186–8 (comment).

Oncology

Aspirin and colorectal cancer: 20-year follow-up

Aspirin and COX-2 inhibitors reduce the risk of colorectal cancers but prophylactic use of COX-2 inhibitors is ruled out by increased vascular risk. High-dose aspirin carries a risk of gastrointestinal and other bleeding problems. The possible benefits and harms of low-dose aspirin are uncertain. The results of long-term follow-up of patients from five randomised trials have been presented.

The five trials assessed aspirin for cardiovascular prophylaxis, four comparing aspirin with control and one comparing different doses of aspirin. The first four of these trials included a total of 14033 patients and the overall colorectal cancer risk (aspirin and control groups) was 2.8%. Overall, aspirin reduced the 20-year risk of colon cancer by 24% and mortality by 35% but did not reduce the risk of rectal cancer. It reduced the risk of proximal colon cancer by 55% but did not reduce that of distal colon cancer. Taking aspirin for at least 5 years, however, reduced the risk of proximal cancer by about 70% and of rectal cancer by 42%. Doses of >75 mg daily did not increase the protection but in one trial a dose of 30 mg daily provided less protection against death from colorectal cancer than a dose of 283 mg daily.

Long-term medication with aspirin at a dose of 75 mg or more daily reduces the risk of colorectal cancer, particularly of cancer of the proximal colon.

Rothwell PM et al. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. *Lancet* 2010; 376: 1741–50; Benamouzig R, Uzzan B. Aspirin to prevent colorectal cancer: time to act? *ibid*: 1713–4.

Daily aspirin reduces cancer deaths

About 40% of people in industrialised countries develop cancer at some time in their lives. There is good evidence that aspirin reduces the risk of colorectal cancer but the evidence of an effect on other cancers has been poor. Now an analysis of individual patient data from randomised trials has shown that daily aspirin may reduce the number of deaths from several cancers.

Eight trials (25570 patients 674 deaths from cancer) were included in the analysis. Taking aspirin reduced the risk of death from cancer by 21% overall. Analysis of individual patient data from seven trials

(23535 patients) showed a 34% reduction in deaths from all cancers and a 54% reduction in gastrointestinal cancer deaths, but the benefit was only apparent after 5 years. Aspirin reduced the 20-year mortality by 20% for all solid cancers, and by 35% for gastrointestinal cancers, the benefit increasing with longer aspirin medication: 7.5 years or longer of aspirin reduced the risk by 31% (all solid cancers) and 59% (gastrointestinal cancers). After 5 years there was a significant effect on deaths from oesophageal, pancreatic, lung, and brain cancers and after a longer period deaths from gastric, colorectal, and prostate cancers were reduced. In the lungs and oesophagus only adenocarcinoma deaths were reduced. The 20-year mortality from adenocarcinoma was reduced by 34%. Any aspirin dose of at least 75 mg daily was effective. Sex and smoking did not affect the benefit which increased with age.

Daily aspirin reduces the risk of death from several cancers. It is calculated that, taking into account all the pros and cons, daily aspirin for 5–10 years would reduce all-cause mortality during that time by about 10%. A *Lancet* editorialist sounds a note of caution.

Rothwell PM et al. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. *Lancet* 2011; 377: 31–41; Jacobs E. Will an aspirin a day help keep fatal cancer away? *Ibid*: 3–4 (comment).

Rituximab maintenance treatment for follicular lymphoma

Follicular lymphoma is the second most common type of lymphoma. Response to initial treatment is often good but relapse usually occurs after several years and recurrent relapses then typically occur with shortening subsequent disease-free periods. Now an international trial has shown that 2 years of maintenance treatment with rituximab (an anti-CD20 monoclonal antibody) after a good response to first-line therapy is able to prolong progression-free survival.

The study, at 223 centres in 25 countries, included 1217 patients with previously untreated follicular lymphoma and high tumour burden. After induction with chemotherapy and rituximab, 1019 patients had a complete or partial response and were randomised to rituximab (375 mg/m² every 8 weeks) or no maintenance therapy for 2 years. The average duration of follow-up was 36 months. The 3-year progression-free survival rate was 75% (rituximab) vs 58% (controls, a highly significant 45% improvement in the rituximab group com-

pared with the control group. The rate of confirmed or unconfirmed complete response at 2 years was 72% vs 52%. There was no significant effect of treatment on overall survival. There were more grade 3 or 4 adverse events in the treatment group (24% vs 17%). Infections occurred in 39% of the treatment group and 24% of the control group.

Maintenance therapy with rituximab prolonged progression-free survival. Questions remain about the role and affordability of maintenance therapy.

Salles G et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. *Lancet* 2011; 377: 42–51; Friedberg JW. Rituximab maintenance in follicular lymphoma: PRIMA. *Ibid*: 4–6.

Iniparib for triple-negative breast cancer

Breast cancer that is oestrogen-receptor (ER)-negative, progesterone-receptor (PR)-negative, and does not over-express human epidermal growth factor receptor type 2 (HER2), has high rates of metastasis and a poor prognosis compared with hormone receptor positive breast cancers. Patients with this 'triple-negative' type of cancer, which accounts of 15–20% of all breast cancers, and metastases have a median survival of about 1 year and there is no standard method of treatment.

These cancers have defects in DNA repair suggesting that inhibitors of poly (adenosine diphosphate-ribose) polymerase 1 (PARP1) a regulator of the DNA base-excision-repair pathway, could be successful in treatment. A trial of iniparib, a drug with PARP inhibitory activity, added to chemotherapy, has shown improved results.

A total of 123 patients with metastatic, triple-negative breast cancer entered the multicentre Phase 2 study and were randomised to chemotherapy (gemcitabine and carboplatin) with or without iniparib on days 1, 4, 8, and 11 of each 21-day cycle. The rate of clinical benefit (complete or partial objective response plus stable disease for at least 6 months) was 56% (iniparib) vs 34% (controls), a significant difference. The overall response rate increased from 32% to 52% and progression free survival from 3.6 months to 5.9 months with iniparib. Median overall survival was 12.3 months (iniparib) vs 7.7 months (control).

Adverse events were similar in the two groups. A Phase 3 trial is in progress. O'Shaughnessy J et al. Iniparib plus chemotherapy in metastatic triple-negative breast cancer. *NEJM* 2011; 364: 205–14; Carey LA, Sharpless NE. PARP and cancer – if it's broke, don't fix it. *Ibid*: 277–9.