

SHORT CUTS

ALL YOU NEED TO READ IN THE OTHER GENERAL JOURNALS

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Aspirin holds promise as adjuvant treatment for colorectal cancer

Aspirin is known to prevent colorectal tumours, and in animal models it has been shown to prevent cancer growth and improve survival. A cohort study of 1279 health professionals with non-metastatic colorectal cancer, with nearly 12 years' median follow-up, suggests that aspirin may improve colorectal cancer specific survival and overall survival. The effect was largely restricted to people who started taking aspirin after the diagnosis and to people whose primary tumours overexpressed the gene encoding cyclo-oxygenase-2 (*COX-2*).

Of the 549 participants who regularly used aspirin after they were diagnosed with colorectal cancer, 81 (15%) died from colorectal cancer during follow-up, compared with 141 (19%) of the 730 participants who did not regularly use aspirin after diagnosis (hazard ratio 0.71, 95% CI 0.53 to 0.95). Overall mortality was also reduced with aspirin (0.79, 0.65 to 0.97). The effect was stronger for people who did not regularly use aspirin before the diagnosis (0.53, 0.33 to 0.86). Importantly, aspirin use after diagnosis reduced mortality from cancer in participants whose primary tumour overexpressed *COX-2* (0.39, 0.20 to 0.76), but not in the rest of the participants (1.22, 0.36 to 4.18).

The linked editorial (p 688) predicts that *COX-2* expression may soon become a stand-

ard predictive biomarker and aspirin standard adjuvant treatment for colorectal cancer.

JAMA 2009;302:649-59

Schizophrenia is linked to violence, but mostly through substance misuse

The stigma attached to mental illness had been fed by the notion that people with psychoses are more violent than other people, but in the 1980s expert opinion suggested this was not the case. Recent observational evidence highlights the topic once more. A systematic review identified 20 studies that included 18 423 people with psychosis and 1 714 904 people without.

The pooled estimates found an excess risk of violence in men (odds ratio 4.0, 95% CI 3.0 to 5.3) and women (7.9, 4.0 to 15.4) with psychosis, compared with the general population. Studies that included both sexes found a five-fold increased risk (5.0, 3.4 to 7.4). However, for people with or without comorbid substance misuse this was 8.9 (5.4 to 14.7) and 2.1 (1.7 to 2.7), respectively, with reduced heterogeneity in the later analysis. Moreover, several studies examined the risk of violence in people with substance misuse and found no excess risk with any comorbid psychoses, including schizophrenia (substance misuse alone 8.9 (5.9 to 13.4) and substance misuse with psychosis 9.8 (5.2 to 18.7)). Finally, the risk of violence in people with psychosis, regardless of substance misuse, was comparable to that in people with substance misuse alone (5.0 (3.9 to 6.4) v 7.4 (4.3 to 12.7)).

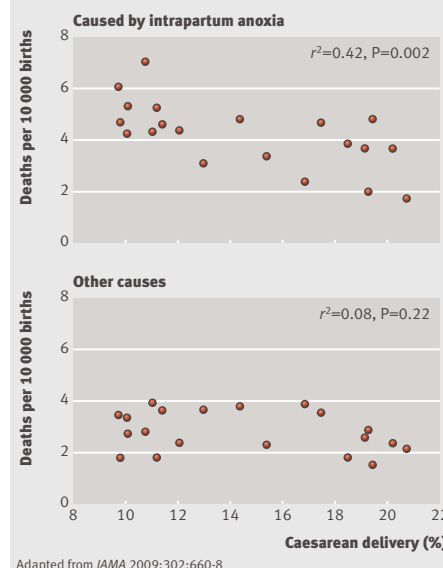
Several studies reported on the risk of homicide, which was found to be 0.3%, 0.2%, and 0.3% in people with psychosis, the general population, and people with substance misuse but no psychosis, respectively.

PLoS Med 2009;6:e1000120; doi:10.1371/journal.pmed.1000120

Do caesarean sections save babies' lives?

Obstetric interventions, including caesarean section, have risen in the past two decades, but studies on whether this has improved perinatal mortality associated with the complications of labour at term have been hampered by the lack of datasets that contain relevant outcomes

CAUSES OF PERINATAL DEATH AND RATES OF CAESAREAN DELIVERY



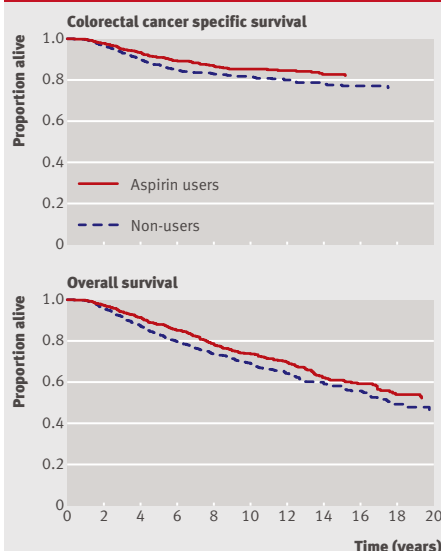
for mother and baby. A national registry linkage study from Scotland helps fill the gap by looking at 1 012 266 singleton births at term between 1988 and 2007. Only deliveries with cephalic presentation were included, and deaths as a result of congenital anomalies or antepartum stillbirth were excluded.

During the study period, the incidence of delivery related perinatal deaths fell by 38%, from 8.8 to 5.5 per 10 000 births. Deaths caused by intrapartum anoxia were nearly halved, whereas reductions in neonatal deaths from any other cause—including antepartum anoxia, birth trauma, intracranial haemorrhage, and infection—did not reach statistical significance. Adjustment for maternal, fetal, and obstetric characteristics did not greatly change these results. Furthermore, the researchers found that the decline in mortality was mainly the result of a decline in the number of severely anoxic infants, rather than improved neonatal interventions.

These changes were paralleled by more than double the proportion of deliveries being carried out by caesarean section, with increases in both planned (2.7% to 7.8%) and emergency (4.7% to 10.4%) caesarean deliveries. Despite the significant interaction between the annual rates of caesarean delivery and deaths as a result of intrapartum anoxia, a causal interpretation is premature.

JAMA 2009;302:660-8

SURVIVAL AND ASPIRIN USE AFTER DIAGNOSIS



Adapted from *JAMA* 2009;302:649-59

Weight lifting is safe for survivors of breast cancer with lymphoedema

Women who have recovered from breast cancer but are left with lymphoedema are usually advised to avoid lifting children, heavy bags, or other heavy objects with the affected arm. A trial tested the effects of twice weekly weight lifting for one year against the control group—in which participants were asked not to change their exercising habits—in 141 survivors of breast cancer with stable lymphoedema of the arm.

At one year, the change in the swelling of the arm and hand (primary outcome) was similar between the groups. The proportion of women who had an increase of 5% or more in limb swelling was 11% with weight lifting and 12% in the control group. Not only was weight lifting safe, it also provided benefits. Women who exercised had fewer exacerbations of lymphoedema (14% *v* 29%), better upper and lower body strength, and reported less severe lymphoedema symptoms. No serious adverse effects of weight lifting were reported.

The exercise programme was supervised for the first 13 weeks and included stretching, cardiovascular warm-up, abdominal and back exercises, and weight lifting exercises. Each woman's programme gradually progressed in intensity, and no upper limit was set for the resistance level to which participants could progress. All women were supplied with custom made compression garments which they wore during exercise. *N Engl J Med* 2009;361:664-73

Percutaneous device matches warfarin for prevention of stroke in atrial fibrillation

In nine out of 10 people with non-valvular atrial fibrillation, thrombi form in the left atrial appendage. Lifelong treatment with warfarin is indicated in many such patients to prevent stroke. However, this treatment is not well tolerated, and the benefits are offset by a high risk of bleeding complications.

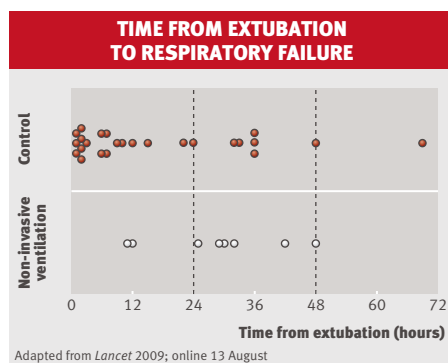
An open label trial tested a procedure in which the left atrial appendage is closed from the rest of the atrium by a parachute-like device, which is brought into the atrium percutaneously through a femoral vein, puncturing the atrial septum on the way. The procedure was non-inferior to treatment with warfarin, with the primary outcome (composite of stroke, cardiovascular death, and systemic embolism) present in 3.0 per 100 patient years with the device and 4.9 per 100

patient years with warfarin (rate ratio 0.62, 95% credible interval 0.35 to 1.25) during 1065 patient years of follow-up.

Serious adverse events were more common with the procedure and included pericardial effusion serious enough to need percutaneous or surgical drainage (22/463 (4.8%) patients), bleeding requiring at least two units of packed red blood cells or surgery to correct (16/463 (3.5%)), and ischaemic stroke as a result of the procedure (5/463 (1.1%)). The commentators (p 504) explain why warfarin is still the treatment of choice for patients with non-valvular atrial fibrillation who have indications for, and who are suitable for, treatment with long term oral anticoagulation.

This week's print issue of the *Lancet* is devoted to cardiovascular medicine. *Lancet* 2009;374:534-42

Non-mechanical ventilation may benefit people with hypercapnia after extubation



A trial compared non-invasive ventilation for 24 hours with conventional oxygen treatment in 106 people who had been intubated for 48 hours or more and who tolerated a spontaneous breathing trial after recovery from their disease and extubation, but who had hypercapnia (partial pressure of arterial carbon dioxide >45 mm Hg) and a history of chronic respiratory disorders, such as chronic obstructive pulmonary disease, tuberculosis, or asthma.

At 72 hours, fewer people assigned to ventilation developed respiratory failure, compared with usual oxygenation (8 (15%) *v* 25 (48%), respectively; odds ratio 5.32, 95% CI 2.11 to 13.46). As rescue treatment for people who did develop respiratory failure, non-invasive ventilation avoided reintubation in 17 of 27 patients, averting possible complications such as nosocomial pneumonia or extended hospital stay. No difference was seen between the groups in in-hospital mortality, but mortality

at 90 days favoured the intervention group (odds ratio 3.56, 1.27 to 10.0)

The authors call for routine use of early 24 hour non-invasive ventilation in people with chronic respiratory disorders who develop hypercapnia during weaning from invasive mechanical ventilation.

Lancet 2009; online 13 Aug; doi:10.1016/S0140-6736(09)61038-2

Denosumab prevents fractures due to bone loss

Compared with placebo, subcutaneous injections of denosumab given once every six months over three years reduced the risk of vertebral, non-vertebral, and hip fractures in postmenopausal women with osteoporosis. At three years, 2.3% of women randomly allocated to denosumab had experienced a new vertebral fracture, compared with 7.2% of women who received placebo (risk ratio 0.32, 95% CI 0.26 to 0.41). The cumulative incidence of hip fractures and any non-vertebral fractures was 0.7% and 6.5% with denosumab and 1.2% and 8.0% with placebo, respectively (hazard ratios 0.60 (0.37 to 0.97) for hip fractures and 0.80 (0.67 to 0.95) for non-vertebral fractures). The trial found no excess risk of adverse events with denosumab, including cancer, infection, and cardiovascular disease, although rates of eczema and hospital admission for cellulitis were higher with denosumab.

In another trial, denosumab improved bone mineral density and prevented fractures in men receiving androgen deprivation treatment for non-metastatic prostate cancer. At two years, bone mineral density of the lumbar spine had increased by 5.6% with denosumab, compared with a loss of 1.0% with placebo. Differences were seen as early as one month after treatment began and were sustained at three years. The three year incidence of new vertebral fractures was 1.5% and 3.9% for denosumab and placebo, respectively, with a relative risk 0.38 (98% CI 0.19 to 0.78).

Denosumab is a fully human monoclonal antibody to RANKL (receptor activator of nuclear factor- κ B ligand)—the key molecule in the development, activity, and survival of osteoclasts. The editorial (doi:10.1056/nejme0905480) compares denosumab with other available antiresorptive drugs, but says that new anabolic drugs are what we really need for treatment of bone loss.

N Engl J Med 2009; online first doi:10.1056/NEJMoa0809493

N Engl J Med 2009; online first doi:10.1056/NEJMoa0809003

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