NEWSROUND

Selected reports edited by Janet Fricker

Exercise found to lower risk of colon cancer

→ British Journal of Cancer

A new meta-analysis adds weight to the claim that exercise lowers the risk of colon cancer. The study, by researchers from Washington University School of Medicine in St Louis and Harvard University, found people who exercised the most were 24% less likely to develop the disease than those exercising the least. Although an inverse association between physical activity and the risk of colon cancer has been well established, this was the first formal estimation of the magnitude of risk reduction that included recent studies.

Kathleen Wolin and colleagues reviewed 24 case-controlled studies and 28 cohort studies, going as far back as 1984. Results showed a 24% reduced risk of colon cancer, giving a relative risk (RR) of 0.76, (95% CI 0.72–0.81), when comparing the most active to the least active individuals across all studies.

Data were provided separately on occupational physical activity in 17 of the 24 case-control studies, and 15 of the 28 cohort studies. For leisure-time physical activity, separate data were provided by 10 and 16 of the studies respectively. Results showed that occupational physical activity was associated with a RR of 0.78 (95% CI 0.74–0.83) for colon cancer, while leisure-time physical activity was associated with a RR of 0.77 (95% CI 0.72–0.82).

This, say the authors, shows that the protective effect of exercise holds for all types of physical activity, whether recreational (such as jogging, biking or swimming) or job related (such as walking, lifting or digging).

Case-control studies demonstrated a higher beneficial effect on average than cohort studies, with a RR of 0.73 for occupational physical activity compared to 0.85 in the cohort studies. For leisure-time physical activity, the RR was 0.69 for case-control studies, compared to 0.82 for cohort studies.

There has been debate about the extent of physical activity required to reduce the risk. Some studies suggest that vigorous physical activity may be necessary, while others have suggested that walking alone may be sufficient. In the current meta-analysis, each of the studies quantified activity differently, limiting the possibilities to draw any conclusions about the amount of physical activity necessary for the 24% reduction. The US Nurse's Health Study, published in 2007, which reported a 23% risk reduction when comparing the most to the least active women, found that the most active women expended more than 21.5 MET (metabolic equivalent) hours per week in leisure-time activity (equivalent to brisk walking for 5–6 hours), while the least active expended less than 2 METs (equivalent to half an hour's brisk walking).

"This meta-analysis provides additional support for the inverse association between physical activity and colon cancer," conclude the authors. "It provides a formal estimate showing that individuals can likely reduce their risk of colon cancer, overall, by 24% through participation in physical activity."

Several mechanisms, they say, have been proposed for the role of physical activity in reducing colon cancer risk, including reduced insulin resistance and hyperinsulinaemia, anti-inflammatory action, direct immune action, decreased intestinal transit time and higher levels of vitamin D.

■ Physical activity and colon cancer prevention: a meta-analysis. KY Wolin, Y Yan, GA Colditz et al. *Br J Can* 17 February 2009, 100:611–616

Alcohol cancer risk defined

→ JNCI

Moderate alcohol consumption in middle-aged women may account for nearly 13% of the cancers of the breast, liver, rectum and upper aerodigestive tract combined, according to the latest data to come out of the UK Million Women Study. The study also found that increased alcohol intake is associated with statistically significant reductions in the risk of thyroid cancer, non-Hodgkin lymphoma and renal cell carcinoma.

Most evidence for an association between alcohol and cancer risk comes from studies of men with high intakes. With the exception of breast cancer, however, little is known about the effect of moderate alcohol intake on women.

Naomi Allen and colleagues from the Cancer Epidemiology Unit at Oxford University, UK, examined the association between alcohol and cancer risk in 1,280,296 middle-aged women. The women, who visited UK breast cancer screening clinics between 1996 and 2001, answered a variety of questions, including the type and frequency of alcohol consumption, smoking, body mass index, exercise and use of oral contraceptives and hormone replacement therapy, allowing the risk estimates to be adjusted for potential confounding factors.

Participants were aged 55 years on average at recruitment. Twenty-five per cent reported they were nondrinkers, 29% reported an average intake of two drinks or fewer per week, 23% reported drinking between three and six drinks, 19% between 7 and 14, and 5% 15 or more drinks per week.

Among drinkers, increasing alcohol consumption was statistically significantly associated with increased risks of cancers of the oral cavity and pharynx (P^{trend}<0.001), oesophagus (P^{trend}=0.002), larynx (P^{trend}=0.008), rectum (P^{trend}=0.02), liver (P^{trend}=0.03), breast (P^{trend}<0.001), and all cancers combined (P^{trend}<0.001). There was also a statistically significant reduction in the risk of thryoid cancer (P^{trend}=0.005), non-Hodgkin lymphoma (P^{trend}=0.001) and renal cell carcinoma (P^{trend}=0.03). For all other cancer sites, there were no statistically significant trends with alcohol intake.

The authors estimated that the excess cancer incidence up to age 75 for each additional drink consumed every day was of the order of 11 per 1000 for breast cancer, 1 per 1000 for cancers of the oral cavity and pharynx and rectum, and 0.7 per 1000 each for cancer of the oesophagus, larynx and liver. Altogether this gave a total excess of about 15 per 1000 women up to age 75 years for these cancers.

"Our risk estimates suggest that about 11% of all breast cancer in women in the United Kingdom, that is, 5000 annually, is attributable to alcohol," write the authors, adding that there is increasing evidence that moderate alcohol consumption increases circulating concentrations of sex hormones, both in premenopausal and postmenopausal women.

In an accompanying editorial, Michael Lauer and Paul Sorlie from the National Heart Lung and Blood Institute, Bethesda, Maryland, write that, although previous epidemiological studies have suggested that there is a cardiovascular benefit associated with moderate alcohol consumption, the excess cancer risk identified in the current study may outweigh these benefits. "From a standpoint of cancer risk, the message of this report could not be clearer. There is no level of alcohol consumption that can be considered safe," they write.

■ Moderate alcohol intake and cancer incidence in women. NE Allen, V Beral, D Casabonne et al. *J Natl Cancer Inst* 4 March 2009, 101:296–305

■ Alcohol, cardiovascular disease, and cancer: treat with caution [editorial]. M Lauer and P Sorlie. *ibid*, pp 282–283

More is not always better

➜ N Engl J Med

Adding cetuximab to capecitabine, oxaliplatin and bevacizumab in previously untreated patients with metastatic colorectal cancer results in significantly shorter progression-free survival and inferior quality of life, concludes a study from the Dutch Colorectal Cancer Group.

"Our results… argue against the combined use of anti-VEGF and anti-EGFR monoclonal antibodies with chemotherapy in cases of metastatic colorectal cancer," write Jolien Tol and colleagues from Radboud University Nijmegen Medical Centre in the Netherlands.

Bevacizumab, a humanised monoclonal antibody against vascular endothelial growth factor (VEGF) combined with fluoropyrimidine chemotherapy (fluorouracil+capecitabine) or capecitabine+oxaliplatin is now standard first-line treatment for metastatic colorectal cancer. Additionally, cetuximab, a chimeric IgGI monoclonal antibody against epidermal growth factor receptor (EGFR), has been shown to have efficacy as a monotherapy and in combination with irinotecan in irinotecan-resistant patients.

In the CAIRO 2 trial, Tol and colleagues set out to study the effect of adding cetuximab to a combination of capecitabine, oxaliplatin and bevacizumab in metastatic colorectal cancer. "Since combining cytotoxic drugs that act through different mechanisms improved outcomes in patients with metastatic colorectal cancer, it seemed logical that further progress would result from combining bevacizumab with either cetuximab or panitumumab and administering these monoclonal antibodies together with chemotherapy," write the authors.

In the open-label, randomised phase III trial, conducted at 79 centres in the Netherlands, 755 patients with previously untreated metastatic colorectal cancer that was not amenable to curative surgery were randomised between June 2005 and December 2006 to capecitabine, oxaliplatin, and bevacizumab (CB regimen, *n*=378 patients) or the same regimen plus weekly cetuximab (CBC regimen, *n*=377 patients).

Results show the addition of cetuximab significantly decreased the median progression-free survival from 10.7 months in the CB group to 9.4 months in the combination CBC group (*P*=0.01). Median overall survival was 20.3 months in the CB group and 19.4 months in the CBC group (*P*=0.16), and the overall response rate in the 649 patients who were evaluated was 50.0% in the CB group and 52.7% in the CBC group (*P*=0.49).

The incidence of any grade 3 or 4 adverse event was 73.2% in the CB group and 81.7% in the CBC group (*P*=0.006).

The reduction in progression-free survival was unexpected, write the authors, since both preclinical and early clinical studies have suggested benefits for the combination of anti-VEGF and anti-EGFR antibodies. However, similar negative results were also observed in

the Panitumumab Advanced Colorectal Cancer Evaluation (PACCE) trial, where the addition of panitumumab to FOLFOX and bevacizumab reduced both median progression-free survival and median overall survival.

The authors speculate that it may be due to negative interactions between cetuximab and bevacizumab. Hypertension, a common side-effect of bevacizumab treatment, was recently shown to correlate with clinical outcome in patients with colorectal cancer.

"Our observation that hypertension was less frequent in the CBC group suggests decreased efficacy of bevacizumab when administered in combination with cetuximab," they say.

In an accompanying editorial, Robert Mayer from the Dana Farber Cancer Institute, Boston, writes that the study serves as a reminder that antitumour activity observed in preclinical and uncontrolled clinical contexts may not be validated when examined in randomised trials. "Furthermore, the data suggest that combining multiple forms of targeted therapies may not be analogous to combining different types of cytotoxic chemotherapy, presumably because of subtle interactions in intracellular signalling," he added.

■ Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. J Tol, M Koopman, A Cats. *N Engl J Med* 5 February 2009, 360:563–572

■ Targeted therapy for advanced colorectal cancer – more is not always better [editorial]. RJ Mayer. *ibid* pp 623–625

Laparoscopic colectomy as good as surgery in colon cancer

→ Lancet Oncology

Laparoscopic colectomy is not an inferior oncological procedure to open colectomy in colon cancer, and should be introduced into daily practice, according to a European study. The level-one data reported in the COLOR (COlon cancer Laparoscopic or Open Resection) trial, suggests that laparoscopic colectomy does not predispose patients to surgical short cuts or unique mechanisms of tumour dissemination.

Laparoscopic colectomy, first reported over a decade ago, is associated with improved convalescence and decreased morbidity compared with open resection. Reports of tumour recurrence at port sites after laparoscopic resection of colon have, however, led to questions over the oncological safety of laparoscopic surgery in patients with colorectal cancer.

Hendrik Bonjer and colleagues from Dalhousie University (Halifax, Canada) recruited 1076 colon cancer patients from 29 European hospitals in order to compare three-year disease-free survival and overall survival after laparoscopic surgery or open surgery for colon cancer. Patients with a solitary cancer of the right or left colon and a BMI up to 30 kg/m² were recruited between March 1997 and March 2003, and randomly assigned to either laparoscopic surgery (n=534) or open surgery (n=542) as a curative treatment.

Results showed three-year disease-free survival was 74.2% for laparoscopic surgery and 76.2% for open surgery (P=0.70), and three-year overall survival was 81.8% for laparoscopic surgery and 84.2% for open surgery (P=0.45). The authors found no difference in positive margins, the number of lymph nodes removed or morbidity between the two groups.

The authors write that the trial could not rule out a difference in disease-free survival at three years in favour of surgery, since the upper limit of the 95% confidence interval for the difference just exceeded the predetermined non-inferiority boundary of 7%. "However, the difference in disease-free survival between groups was small and, we believe, clinically acceptable, justifying the implementation of laparoscopic surgery into daily practice," write the authors, adding that further studies are needed to address whether laparascopic surgery is superior to open surgery in this setting.

Survival data from the first 520 patients recruited in the COLOR trial were included in a meta-analysis of four trials that randomly assigned patients with colon cancer to laparoscopically-assisted surgery or open surgery. The meta-analysis results, with a censored follow-up at three years after primary surgery, showed disease-free survival and overall survival for stages I, II and III, and all three stages combined, did not differ between the two treatment groups.

In an accompanying editorial, Heidi Nelson, from the Mayo Clinic and Foundation (Rochester, Minnesota), wrote, "This is a major step forward for laparoscopic oncological surgery and future patients should benefit from the knowledge gained from this trial."

■ Survival after laparoscopic surgery versus open surgery for colon cancer: long-term outcome of a randomised clinical trial. The Colon Cancer Laparoscopic or Open Resection Study Group. *Lancet Oncol* January 2009, 10:44–52

■ Laparoscopic colectomy: lessons learned and future prospects [editorial]. H Nelson. *ibid* pp 7–8

Prophylactic salpingo-oophorectomy guidance

→ JNCI

Prophylactic salpingo-oophorectomy (removal of the ovaries and fallopian tubes) reduces the relative risk of breast cancer by approximately 50% and of ovarian and fallopian tube cancer by approximately 80% in women with mutations in the BRCA1 or BRCA2 genes, a US meta-analysis has found. The authors, led by Timothy Rebbeck from the University of Pennsylvania School of Medicine in Philadelphia, hope their new risk-reduction estimates will provide useful guidance for women exploring risk-reduction strategies.

Previous research has shown substantial reduction in the risk of breast and ovarian or fallopian tube cancers in BRCA1/2 mutation carriers following salpingo-oophorectomy. But studies examining the extent of risk reduction have used different designs, with some being retrospective case-control studies, and others being prospective. Even among prospective

studies, inclusion criteria and definitions of follow-up time have differed.

To establish a more reliable estimate of the magnitude of benefit, Rebbeck and colleagues analysed reports of risk-reducing salpingo-oophorectomy (RRSO) and breast and/or ovarian or fallopian tube cancer in BRCA1/2 mutation carriers from studies published between 1999 and 2007, identified through a PubMed search. Altogether, 10 studies were identified. Hazard ratios (HR) were identified directly from the original articles, and pooled results were then computed from non-overlapping studies by fixed-effects meta-analysis.

Results show that RRSO was associated with a 51% reduction in the risk of breast cancer in BRCA1/2 mutation carriers (HR 0.49, 95%CI 0.37–0.65). For BRCA1 mutation carriers the associated risk reduction was 53% (HR 0.47, 95% CI 0.35– 0.64) and for BRCA2 it was also 53% (HR 0.47, 95% CI 0.26–0.84). RRSO was also associated with a 79% reduction in the risk of BRCA1/2-associated ovarian or fallopian tube cancer (HR 0.21, 95% CI 0.12–0.39).

"In conclusion, the summary risk reduction estimates presented here confirm that BRCA1/2 mutation carriers who have been treated with RRSO have a substantially reduced risk of both breast and ovarian cancer," write the authors, adding, however, that residual cancer risk remains after surgery. "Therefore, additional cancer risk reduction and screening strategies are required to maximally reduce cancer incidence and mortality in this high-risk population."

In an accompanying editorial, Mark Greene and Phuong Mai, from the National Cancer Institute (Rockville, Maryland), commended the study for its "carefully designed and thoughtfully implemented" meta-analysis, which attempted to "disentangle potential differences between BRCA1 and BRCA2 mutation carriers," and for an improved precision of breast and ovarian/fallopian tube cancer risk reduction estimates. Discussions of the study's limitations provide an excellent outline of future research topics, they add, including optimal age for RRSO, impact of age at RRSO on subsequent cancer risk and the non-oncological risks related to surgical menopause.

The results, they add, should benefit women trying to decide whether to undergo RRSO. "We urge providers of cancer genetics counselling services to adopt the summary risk estimates developed by Rebbeck et al. as those most currently reliable when counselling BRCA mutation carriers," they conclude.

■ Meta-analysis of risk-reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers. TR Rebbeck, ND Kauff and SM Domchek. *J Natl Cancer Inst* 13 January 2009, 101:80–87

■ What have we learned from Risk-reducing Salpingo-oophorectomy? [editorial]. MH Greene, PL Mai. *ibid*, pp 70–71

A new standard of care for locally advanced prostate cancer?

➔ The Lancet

Adding local radiotherapy to endocrine treatment in locally advanced prostate cancer halved the 10-year prostate-cancer-specific mortality, the Scandinavian open-phase III SPCG-7/SFUO-3 study has reported. In an accompanying editorial, Alex Tan from the Noe Valley Clinic (San Francisco, California) and Chris Parker from the Institute of Cancer Research (Sutton, UK) wrote, "SPCG-7 is a pivotal trial, and is the first to show an overall survival advantage for radiotherapy in the primary treatment of prostate cancer. The results should change current practice, making long-term hormonal therapy plus radical radiotherapy the standard of care for men with locally advanced prostate cancer."

While long-term hormonal therapy has long been regarded as the mainstay of treatment for locally advanced prostate cancer (with four key randomised controlled trials showing early use results in improved overall survival), there has been no consensus about whether or not local radiotherapy should be used in addition to hormonal therapy. To assess the benefit of radiotherapy, Anders Widmark and colleagues, from Umeå University (Umeå, Sweden), conducted an open phase III study comparing endocrine therapy with and without local radiotherapy, followed by castration on progression.

In the study, which was conducted between February 1996 and December 2002, 875 men with locally advanced prostate cancer from 47 centres in Norway, Sweden and Denmark, were randomly assigned to endocrine treatment alone (three months of total androgen blockade with the LHRH-agonist leuprorelin, followed by continuous endocrine treatment using flutamide; *n*=439 patients) or to the same endocrine regimen combined with radiotherapy three months after the start of endocrine therapy (*n*=436 patients). A standard 3D conformal radiotherapy technique was applied with a prescribed central dose of 50 Gy to the prostate and seminal vesicles, with a sequential dose of at least 20 Gy.

Results at a median follow-up of 7.6 years show that 79 out of 439 men who received hormone treatment alone died (18%), compared with 37 out of 436 men who received hormone treatment plus radiotherapy (8.5%). After ten years, 23.9% of the men in the hormone therapy-only group had died from prostate cancer compared with 11.9% of the men in the combined treatment group. Furthermore, the researchers found that death from any cause was higher in the hormone therapy-only group (39.4%) than in the combined treatment group (29.6%).

Diarrhoea was the only symptom that differed substantially between the two groups at four years, with moderate or severe diarrhoea reported by 32 of 337 patients (9.5%) in the endocrine only group, and 39 out of 355 (11.6%) in the endocrine plus radiotherapy group (*P*=0.003). At five years, men who were given the combined treatment experienced more side-effects than those on hormone treatment alone. For example, 7% of the combined therapy group reported urinary incontinence versus 3% on hormone therapy alone,

and 9 out of 10 men receiving the dual therapy reported erectile problems, compared with 8 out of 10 men getting drugs alone.

"The present study indicates significant superiority of the endocrine plus radiotherapy treatment compared with endocrine treatment alone in patients with locally advanced prostate cancer," the authors conclude.

In the editorial, Tan and Parker list the study's strengths, which include 100% compliance with treatment allocation, long duration of follow-up and the completeness of the survival data. However, the fact that the trial was "open and not blinded", they suggest, raises the possibility of bias in the use of salvage treatments, assessment of toxic effects and attribution of the cause of death.

■ Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. A Widmark, O Klepp, A Solberg et al. *Lancet* 24 January 2009, 373:301–308

■ Radiotherapy in locally advanced prostate cancer [editorial]. A Tan and C Parker. *ibid* pp 274–276

Tibolone contraindicated in breast cancer

➜ Lancet Oncology

Using tibolone to manage adjuvant systemic treatment side-effects in women with a history of breast cancer increases breast cancer recurrence, a new study has concluded. The LIBERATE study, which was stopped six months prematurely, provides strong evidence against use of tibolone for treating menopausal symptoms in patients with a history of breast cancer.

Vasomotor symptoms and bone loss are complications frequently induced by adjuvant treatment for breast cancer. Tibolone, a synthetic steroid, has been approved in 90 countries for treatment of menopausal symptoms and in 55 countries for the prevention of osteoporosis. Data for the use of tibolone in patients with breast cancer, however, are scarce.

The LIBERATE study group, led by Peter Kenemens of the University Medical Centre, Amsterdam, in the Netherlands, set out to establish whether or not tibolone could be prescribed to women with a history of breast cancer to alleviate their menopausal symptoms, without increasing recurrence. "This is an important question for both doctors and patients, because many patients with breast cancer with bothersome complaints that do not respond sufficiently to nonhormonal treatment seek aid in the form of off-label use of tibolone," write the authors.

In the study, women treated surgically for histologically confirmed breast cancer with vasomotor symptoms, at 245 centres in 31 countries, between July 2002 and December 2004, were randomly assigned to either tibolone (2.5 mg daily) or placebo. At study entry, 66.8% of women were being prescribed tamoxifen and 6.5% aromatase inhibitors.

Results for the intention-to-treat analysis show that, after a median follow-up of 3.1 years, 237 of 1556 women on tibolone (15.2%) had a cancer recurrence, compared with 165 out of 1542 (10.7%) on placebo (HR 1.40, 95%CI 1.14–1.70; *P*=0.001). In the intention-to-treat analysis, 292 of the recurrences were distant metastases, 81 local, 42 contralateral and 13 a recurrence at more than one site.

Results in the per-protocol population were similar: 209 of 1254 women (16.7%) in the tibolone group had a recurrence compared to 138 of 1213 women (11.4%) in the placebo group (HR1.44, 95% CI 1.16–1.79; *P*=0.0009).

Tibolone was comparable to placebo regarding other safety outcomes such as mortality, cardiovascular events and gynaecological malignancies. Furthermore, women with a history of breast cancer who used tibolone had significantly fewer and less-severe vasomotor symptoms, increased bone mineral density of spine and total hip, and a subjective improvement of sex and sleep problems.

"The findings from the LIBERATE trial imply that the use of tibolone for women with a known, past or suspected breast cancer will remain contraindicated," write the authors, adding that the study will prove useful for clinicians counselling patients with breast cancer who experience severe symptoms. "From our study, doctors can also learn from the long lasting symptom relief seen in our placebo population, that personal attention and care for many women are highly successful and sufficient in this respect."

In a subgroup analysis, the investigator found that the interference of tibolone was more severe in women who were using aromatase inhibitors at entry than in tamoxifen users. The most likely explanation, suggest the authors, is that tibolone exerts an oestrogenic effect on dormant breast cancer metastases, and has a greater effect in the oestrogen-depleted tissues of the users of aromatase inhibitors than tamoxifen (where activation of the oestrogen receptor is blocked by the agent).

Limitations of the study, write the authors, include the fact that it was not powered to identify subgroup differences, it did not assess breast cancer risk factors (such as family history) and it did not provide an accurate histopathological classification of the primary tumours. Furthermore, the majority of participants used tamoxifen, while future populations are more likely to use other adjuvant medications, making the generalisability of the study questionable.

In an accompanying editorial, Pamela Goodwin, from the University of Toronto, in Canada, writes, "It is worrying that over 70% of the recurrence events were distant metastases, since these metastases will ultimately lead to death."

Additional research is needed, she adds, to clarify the effects of tibolone on the risk of breast cancer in healthy postmenopausal women (not just those with reduced bone density), with particular emphasis on the effects in women at both high and low risk of breast cancer.

■ Safety and efficacy of tibolone in breast-cancer patients with vasomotor symptoms: a double-blind, randomised, non-inferiority trial. P Kenemans, NJ Bundred, JM Foidart et al. *Lancet Oncol* February 2009, 10:135–146

■ Tibolone: the risk is too high [editorial]. P Goodwin. *ibid* pp 103–104