NEWSROUND

Selected reports edited by Hannah Brown

CT screening may not decrease lung cancer mortality

→ JAMA

Screening current or former smokers with computed tomography (CT) may increase the rate of diagnosis and treatment of lung cancer, but may not necessarily reduce the numbers of advanced lung cancers or deaths from lung cancer, according to a recent study.

Randomised controlled trials have shown that although chest X-ray is effective at identifying small tumours in the lung that could be removed, doing so did not reduce the likelihood that patients would be diagnosed with new cases of lung cancer or would die of lung cancer. Some researchers believe that lung cancer screening with CT might be more effective than chest X-ray at reducing deaths from lung cancer, since it can detect very small nodules; randomised controlled trials to test this idea are underway.

In the meantime, researchers from Memorial Sloan-Kettering Cancer Center, New York, compared the frequency of lung cancer cases, lung cancer resection, advanced lung cancer cases, and deaths using data from three completed single-arm studies with a set of validated prediction models. They included data from 3,246 asymptomatic current or former smokers who had been screened for lung cancer with a median follow-up of 3.9 years. Participants received annual CT scans with comprehensive evaluation and treatment of detected nodules.

The researchers found that individuals screened with CT were three times more likely than validated controls to be diagnosed with lung cancer (144 diagnosed cases compared with 45 expected cases), and ten times more likely to undergo lung cancer surgery (109 individuals with lung surgery compared with 11 expected cases). However, CT screening did not reduce the number of advanced lung cancer diagnoses (42 individuals compared with 33 expected cases) or deaths from lung cancer (38 actual deaths compared with 39 expected deaths).

"Our finding of a ten-fold increase in lung cancer surgeries resulting from screening underscores one of the potential public health consequences of CT screening," say the authors. "Until more conclusive data are available, asymptomatic individuals should not be screened outside of clinical research studies that have a reasonable likelihood of further clarifying the potential benefits and risks," they say.

■ Computed tomography screening and lung cancer outcomes. PB Bach, JJ Jett, U Pastorino et al. *JAMA* 7 March 2007, 297:953–961

Breast radiotherapy increases heart disease risk

→ JNCI

Breast cancer patients treated with radiation therapy during the 1970s have been shown to have an increased risk of cardiovascular disease. The treatment protocols in use at that time are now considered obsolete. However, a new study suggests that women who were treated with radiation for breast cancer during the 1980s may also be at an increased risk for heart disease compared with the general population.

The researchers compared radiation treatment options, looking for differences in heart disease incidence among 4,414 ten-year survivors of breast cancer who were treated in two Dutch hospitals between 1970 and 1986. Approximately half of the patients were treated for breast cancer between 1970 and 1980 with the other half being treated after 1980.

After a median follow-up of 18 years, the researchers identified 942 cases of cardiovascular disease, with heart failure accounting for 41% of cases. The breast cancer patients had an increased risk of heart attack, angina, and congestive heart failure, compared with the general female population.

To examine the effects of changes in radiation therapy techniques over time, the researchers compared cardiovascular disease incidence in patients who were treated before and after 1980, when a new therapy to conserve breast tissue was introduced in the two hospitals. Radiotherapy was associated with increased risk of cardiovascular disease among women who were treated from 1970 through 1979. Among women treated with radiotherapy between 1980 and 1986, the risk of myocardial infarction declined with time; however, risks of valve dysfunction and congestive heart failure remained increased.

The researchers were surprised to find that smoking had an unexpectedly large effect on the risk of heart disease. "We found that the joint associations between radiotherapy and smoking and [heart attack] risk were greater than expected when individual risks were summed. Consequently, the

advice to stop smoking appears to be even more important for irradiated patients and should be given at the time of treatment," the authors suggest.

■ Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. MJ Hooning, A Botma, BMP Aleman et al. *JNCI* 7 March 2007, 99:365–375

European cancer deaths decline again

➛ Annals of Oncology

Cancer deaths in the EU are declining, although death from lung cancer in women is on the increase, according to a recent study.

The researchers obtained official death certification numbers and population estimates for 24 EU countries from the World Health Organization database during the period 1980–2002 and recoded all cancer deaths according to the *10th Revision of the International Classification of Diseases.*

In men, total cancer mortality declined from 191 to 167 per 100,000 between 1987 and 2002. In women the pattern was similar, with total cancer mortality declining from 108 to 95 per 100,000 over the same period. The largest contributions to the fall in cancer mortality in women came from declines in breast and colorectal cancer death rates, which the authors suggest is down to improved diagnosis of both diseases as well as better treatment of breast cancer.

However, although lung cancer mortality decreased in men, it rose by 8% in women between 1997 and 2002. Indeed, in 2002 lung cancer overtook intestinal cancer to become the second leading cause of cancer deaths in European women after breast cancer. In men, about 40% of the overall decline in mortality is due to falling lung cancer mortality rates, with at least an additional 10% caused by other tobacco-related cancers, following the decreased prevalence of tobacco smoking in European men over the last decades.

"Despite the persisting rises in female lung cancer, the recent trends in cancer mortality in the EU are encouraging and indicate that an 11% reduction in total cancer mortality from 2000 to 2015 is realistic and possible," the authors conclude.

■ Continuing declines in cancer mortality in the European Union. F Levi, F Lucchini, E Negri et al. *Ann Oncol* March 2007, 18:593–595

Childhood cancer survivors are at increased risk of sarcoma

➛ JNCI

A report from the Childhood Cancer Survivor Study reveals that survivors of childhood cancers are nine times more likely to develop a secondary sarcoma – cancers of connective or supportive tissue such as bone, fat, or muscle – than the general population. The findings, say the authors, suggest a need for careful follow up in this growing population group.

"As the childhood cancer survivor population ages and expands in number, clinicians and researchers must carefully identify patients who are at risk for secondary morbidities, particularly for secondary cancers," the authors write. "Diagnosis of a sarcoma can sometimes be elusive because symptoms are often non-specific," they add.

The researchers examined the incidence of secondary sarcomas and the associated risk factors among the 14,372 participants in the Childhood Cancer Survivor Study. Overall, there were 751 second cancers diagnosed among the participants, of which 108 were secondary sarcomas. These sarcomas were diagnosed a median of 11 years after patients were diagnosed with their primary cancer.

Patients with secondary sarcomas were more likely to have received primary radiation therapy, to have received higher doses of anthracyclines or alkylators, to have had a primary diagnosis of soft tissue sarcoma, bone tumour, or Hodgkin's lymphoma, to have a family history of cancer or to have a history of other second cancers. The authors calculated that the excess number of cases of secondary sarcomas among childhood cancer survivors over those in the general population is 32.5 cases per 100,000 person-years of follow up.

■ Secondary sarcomas in childhood cancer survivors: a report from the Childhood Cancer Survivor Study. TO Henderson, J Whitton, M Stovall et al. *JNCI* 21 February 2007, 99: 300–308

Endotoxin exposure cuts lung cancer risk

➛ JNCI

Long-term exposure to high doses of endotoxins – substances present in the cell walls of Gram-negative bacteria and common in raw cotton fibre and cotton dust – reduced the risk of lung cancer by around 40% in a cohort of female textile workers from Shanghai, China.

The study analysed endotoxin exposure among 628 women who had developed lung cancer between 1 January 1989 and 31 December 1998, and among 3,184 matched control workers. All of the women in this nested case-cohort study had originally been enrolled in a randomised trial of 267,400 women to test the efficacy of breast self-examination on reducing breast cancer mortality, which involved collection of data on site-specific cancer incidence rates.

Previous investigations have suggested that cotton-factory work offers a protective effect, but this study is the first to quantify the associations between lung cancer risk and endotoxin levels. The authors found that exposure to endotoxin was associated with a decreased risk of lung cancer, amounting to a drop in incidence of 7.6 per 100,000 in Shanghai, and that the magnitude of the effect increased with cumulative exposure and with increasing duration. When recent exposures to endotoxin were discounted, the protective effect became even stronger. This observation led the authors to suggest

that endotoxin may exert its influence at an early stage during lung carcinogenesis. The mechanism for the protection is unclear, but it is likely to result from the interplay between Th-1 (neutrophil-induced) and Th-2 inflammation in the immune system.

Study limitations include the fact that long-term workers may represent a pool of survivors resistant to the acute effects of endotoxin exposure; sensitive individuals may have switched jobs to avoid excessive contact with cotton dust. However, low job mobility among both cases and controls led the authors to conclude this was probably not a significant biasing factor. Another possible problem with the study stems from the inherent uncertainties associated with estimating historic endotoxin exposure due to the fact that workplace concentrations of endotoxin can vary depending on the source of cotton, humidity, and handling procedures.

■ Lung cancer risk among female textile workers exposed to endotoxin. G Astrakianakis, NS Seixas, R Ray et al. *JNCI* 7 March 2007, 99:357–364

Research reveals more cancer genes than expected

➛ Nature

Several genes with previously unknown roles in driving cancer development have been identified by researchers who systematically searched the genomes of 210 human cancer samples.

The researchers screened samples from several different cancer types, including breast, lung, colorectal, gastric, testis, ovarian, kidney, melanoma, glioma and acute lymphoblastic leukaemia for somatic mutations in the 518 genes encoding protein kinases – the structure most commonly found among known cancer genes.

A total of 274Mb of cancer genome was systematically analysed and the search identified 1,007 somatic mutations, only around one-third of which had been previously reported. Of the mutations found by the team, 921 were single-base substitutions, 78 were small insertions or deletions and 8 were complex changes. Numbers of mutations differed between the cancer types. Lung carcinomas had the highest prevalence of somatic mutations, followed by gastric cancers, ovarian cancers, colorectal cancers, and kidney cancers. Testis cancers and most breast cancers had a far lower mutation prevalence. A possible explanation for the different mutation rates could be the fact that high-mutation-prevalence tumours originate from epithelial tissue, which is frequently exposed to mutagens.

Starting from the premise that some mutations are likely to be 'drivers', responsible for the tumour's malignant characteristics, and some 'passenger' mutations, not causally implicated in cancer development, the researchers also attempted to ascertain which mutations fell into which category. Of the 921 identified single-base substitutions, 763 were estimated to be passenger mutations, meaning that the large majority of mutations are not implicated in cancer development. Most of the 158 estimated driver mutations were not previously known to be involved in oncogenesis.

The researchers concluded that around 120 of the 518 genes screened in the study carried a driver mutation enabling them to function as cancer genes – a larger number than previously anticipated. They suggest that systematic sequencing studies of other tumour samples will yield further insights.

■ Patterns of somatic mutation in human cancer genomes. C Greenman, P Stephens, R Smith et al. *Nature* 8 March 2007, 446:153–158

Gene-expression biomarker for early lung cancer

➛ Nature Medicine

A gene-expression biomarker that can detect lung cancer in smokers or former smokers without the need for invasive screening techniques has been developed. The biomarker was around 90% sensitive for identifying stage I lung cancer, a potentially curable stage of disease. However, when the researchers combined the biomarker with cytopathology of lower airway cells obtained at bronchoscopy, the sensitivity increased to 95%, with a 95% negative predictive value. "A lung cancer diagnostic using this approach might eliminate the need for additional diagnostic tests that are costly, incur risk and prolong the diagnostic evaluation of suspect lung cancer patients," the authors wrote.

Physicians often use flexible bronchoscopy as an initial diagnostic test in a smoker or former smoker who presents with suspected lung cancer. However, the sensitivity of bronchoscopy for lung cancer ranges from 30% for small peripheral lesions to 80% for centrally located endobronchial disease. As a result, most patients require further invasive diagnostic tests, which delay treatment and generate additional costs and risks for complications.

Since cigarette smoke injures the airway, the researchers hypothesised that gene-expression profiling of large-airway epithelial cells could detect smokers in whom the mutagenic effects of cigarette smoke have resulted in lung cancer. The researchers used microarray analysis to identify an 80-gene biomarker profile that could distinguish between smokers with and without lung cancer.

They tested the biomarker on samples taken from an additional 52 patients and found that it had a sensitivity of 80% and a specificity of 84%. Similar results were obtained when they validated the test on a prospective series of 35 patients, independently obtained from five medical centres.

"Our study has identified an airway gene-expression biomarker that will impact the diagnostic evaluation of smokers with suspect lung cancer," said lead author Avrum Spira, an assistant professor of medicine and pathology at Boston University. "Our data also suggests that combining cytopathology

of lower airway cells with the gene expression biomarker improves the diagnostic sensitivity of the overall bronchoscopy procedure from 53 to 95%," he said.

■ Airway epithelial gene expression in the diagnostic evaluation of smokers with suspect lung cancer. A Spira, JE Beane, V Shah et al. *Nat Med* 4 March 2007, 13:361–366

PET scans identify aggressive kidney cancers

➛ The Lancet Oncology

Positron Emission Tomography (PET) using a radiolabelled antibody called G250 can accurately identify whether a patient has clear-cell renal carcinoma – the most common and aggressive type of renal tumour – before surgery, according to a recent study.

G250 reacts against an enzyme that is over-expressed in clear-cell renal carcinoma. Previous studies have shown that, of all solid tumours, renal carcinoma has the highest recorded tumour uptake of the antibody, making it ideal for use with PET imaging for this disease.

In the study, 25 patients scheduled to have surgery to remove a renal mass received intravenous 124I-cG250. All patients were monitored for toxicity and the antibody infusion was well tolerated with no side-effects or other adverse events related to the agent. PET images obtained before surgery were graded as positive or negative for antibody uptake. A pathologist unaware of the PET scan results assessed whether the resected-tumour specimens were indicative of clear-cell renal carcinoma.

The researchers were able to identify correctly 15 out of 16 clear-cell renal carcinomas – a sensitivity of 94%. The tumours of all nine patients with non-clear-cell renal masses were graded negative on the PET scan. According to the authors, G250 PET may ultimately be used not only to determine the aggressiveness and extent of a patient's disease prior to surgical intervention, but also to measure the therapeutic effects of a particular treatment and to predict the likelihood of recurrence.

"Antibody PET could end up changing the standard of care for patients with kidney cancer," said the study's senior author, Paul Russo, a urologic cancer surgeon at Memorial Sloan-Kettering Cancer Center, New York, USA. "The excellent sensitivity and specificity of this tool supports the utility of G250 PET imaging in the work-up and management strategies for clinically localised renal masses and as an alternative to biopsy for distinguishing renal lesions."

■ Preoperative characterisation of clear-cell renal carcinoma using iodine-124-labelled antibody chimeric G250 (124I-cG250) and PET in patients with renal masses: a phase I trial. CR Divgi, N Pandit-Taskar, AA Jungbluth et al. *Lancet Oncol*, published online 7 March 2007, doi:10.1016/S1470-2045(07)70044-X

IGF-IR implicated in resistance to trastuzumab

➛ Clinical Cancer Research

A new study provides additional evidence that resistance to treatment with trastuzumab – a monoclonal antibody that targets the HER2 receptor which is frequently overexpressed in breast cancers – is mediated by the insulin-like growth factor receptor (IGF-IR) rather than by a loss of HER2 receptor expression as had previously been suggested.

Researchers examined tissue samples from 48 patients with stage II or III HER2-positive breast cancers who had enrolled in the study between June 2001 and May 2003 and had been treated with a combination of trastuzumab and vinorelbine before undergoing surgery and postoperative chemotherapy.

By use of surgical samples from these patients, the investigators analysed a series of biomarkers and did RNA expression studies in an attempt to identify potential genes or expression profiles that predict response or resistance to therapy. Immunohistochemistry was used to ascertain the patients' HER2 status and expression of receptors for oestrogen (ER), progesterone (PgR), epidermal growth factor (EGFR), and IGF-IR before treatment and after surgery. They also used RNA amplification and microarray analysis to find gene-expression profiles that differentiate between good and poor responders.

The clinical response rate (complete plus partial responders) to preoperative trastuzumab and vinorelbine was 42 of 48 (88%), but only eight patients achieved a pathological complete response. No correlation was found between biological markers and pathological or clinical response. To explore gene-expression patterns associated with response to treatment, the researchers compared nonresponding tumours with the others. Resistant tumours showed a significantly different expression pattern from the remaining tumours, with higher expression of several growth factors and growth factor receptors among the differences.

The researchers also investigated changes in receptor expression over time in patients who did not achieve complete response (22 patients). In most of these patients, HER2 score did not change with therapy and there was no evidence that the number of HER2 gene copies improved response. Neither were there changes in hormone receptor number or localisation during treatment. However, in a separate analysis of 46 of the cases, those patients staining positive for IGF-IR showed a lower likelihood of response to the preoperative treatment than those staining negative for IGF-IR.

Furthermore, tumours with membrane IGF-IR expression were significantly less likely to respond to trastuzumab and vinorelbine than tumours with mainly cytoplasmic IGF-IR.

■ Predictors of resistance to preoperative trastuzumab and vinorelbine for HER2-positive early breast cancer. LN Harris, F You, SJ Schnitt et al. *Clin Cancer Res* 15 February 2007, 13:1198–1207