newsround

Selected reports edited by Janet Fricker

Cancer survivors less likely to be treated for infertility

■ Lancet Oncology

Although women who survive childhood cancer face increased risks of infertility, nearly two-thirds who had tried unsuccessfully for at least one year to become pregnant eventually conceived, the latest findings from the Childhood Cancer Survivors Study (CCSS) show. However, when compared to siblings, cancer survivors were almost half as likely to be medically treated for infertility.

While substantial improvements in treatment have greatly increased five-year survival for childhood cancers (which now exceed 80% in the USA), the infertility effects of treatment represent a major concern for patients. In the latest CCSS analysis, Sara Barton and colleagues from the Dana Farber Cancer Institute quantified the risk of infertility in survivors of childhood cancers on the basis of clinical definitions of infertility.

CCSS is a collaborative study, conducted at 26 clinical centres in Canada and the US, in which a cohort of five-year cancer survivors, diagnosed before the age of 21 with eligible malignancies (leukaemia, CNS cancer, Hodgkin lymphoma, non-Hodgkin lymphoma, Wilms' tumour, neuroblastoma, soft-tissue sarcoma, and bone tumours), have been assembled.

Survivors were asked to identify all their living siblings, of whom a random sample of closest-aged siblings were asked to participate. Both cancer patients and siblings answered a baseline questionnaire gathering information about demographics, medical care, medical disorders, and reproductive history.

For the current analysis, 3531 female cancer survivors aged 18–39 years, who had enrolled in CCSS between November 1992 and April 2004 and who reported having ever been sexually active, were compared to 1366 female sibling controls. Women with known ovarian failure were excluded from the analysis.

Results show that, in comparison to siblings, survivors had an increased risk of clinical infertility (defined as >1 year of attempts without success; RR=1.48, 95%CI 1.23–1.78, $P<0.001$). Relative risk was most pronounced at early reproductive ages (RR=2.92 for participants <24 years; 1.61 for those aged 25–29 years; and 1.37 for those aged 30–40 years). Altogether 292 survivors with self-reported clinical fertility (64%) achieved a pregnancy. Despite being equally likely to seek treatment for infertility, survivors were less likely than their siblings to be prescribed drugs for infertility (RR=0.57, 95%CI 0.46–0.70, $P<0.0001$).

"We do not have data about why providers did not prescribe infertility drugs, but are concerned about a provider bias against treating cancer survivors for infertility. Perhaps providers assessed the chance of success as poor and therefore decided not to attempt therapy, or perhaps survivors were less motivated to take drugs after previous extensive treatment. Alternatively, reproductive medicine providers might have been uncomfortable with perceived medical comorbidities," write the authors.

In an accompanying editorial, Richard Anderson, from the MRC Centre for Reproductive Health in Edinburgh, writes, "Barton and colleagues' data highlight the risk of infertility in childhood cancer survivors beyond the risk of ovarian failure and the need for this risk to be addressed by oncologists at the time of diagnosis and during follow-up as a key part of long-term care."

■ S Barton, J Najita, E Ginsburg et al. Infertility, infertility treatment, and achievement of pregnancy in female survivors of childhood cancer: a report from the Childhood Cancer Survivor Study cohort. *Lancet Oncol* August 2013, 14:873–881

■ R Anderson. Infertility in women after childhood cancer. *ibid* pp797–798

Colorectal cancer patients do better with adjuvant chemotherapy following metastatic surgery

■ Clinical Colorectal Cancer

Adjuvant chemotherapy following the surgical removal of metastases in patients with colorectal cancer produced significant benefits in disease-free survival (DFS), reports an Italian study.

Approximately 50% of patients with stage III and 20% of patients with stage II colorectal cancer develop metastatic spread, of which the liver is the main target followed by the lung. Surgical resection, where feasible, offers the only hope of long-term survival for patients with liver or lung metastases, resulting in five-year survival rates ranging from 25% to 50%. Two

recent randomised trials, when analysed together, suggested a potential benefit on DFS for patients treated with systemic chemotherapy after radical surgery on metastatic sites, but taken separately, neither study proved conclusive.

In the current study, Giovanni Brandi and colleagues, from the University of Bologna, Italy, evaluated the relative impact of adjuvant systemic chemotherapy and other established prognostic factors on DFS after first resection of liver and lung colorectal cancer metastases.

Between 1997 and 2004 the team retrospectively reviewed data from 181 consecutive unselected patients who underwent R0 resection of colorectal liver (*n*=156) or lung (*n*=25) metastases. Altogether 30 patients were excluded due to factors such as being aged over 75 years and having comorbidities, making them unsuitable for adjuvant chemotherapy following surgery.

This left 151 patients for review (131 with liver metastases, 20 with lung metastases). Due to the lack of conclusive evidence of the benefit of adjuvant chemotherapy, each eligible patient was informed of the possible advantages and disadvantages of each option, and left to choose whether to receive chemotherapy or not. Altogether 78 chose adjuvant treatment and 73 observation. The chemotherapy regimens used in the study varied according to the progress of disease, first-line chemotherapy and the availability of the drugs in clinical practice. Regimens used included 5-FU alone, FOLFIRI (folinic acid, 5-FU, irinotecan hydrochloride [CPT-11]) or FOLFOX (folinic acid, 5-FU, OHP), capecitabine, CAPOX (capecitabine OHP) or CAPIRI (CPT-11, capecitabine).

Results showed that the median DFS of patients who underwent systemic adjuvant chemotherapy was 16 months, versus 9.7 months for patients with observation alone (HR=1.56, *P*=0.014) The overall survival (OS) was 42 months for the adjuvant chemotherapy group versus 39 months for untreated patients (*P*=0.8).

"Our study emphasizes the importance of adjuvant chemotherapy in a postmetastasectomy setting, which showed a significant benefit on DFS, but formal recommendations have yet to be established," write the authors.

A control with surgery alone, they add, is now needed to demonstrate a benefit for adjuvant chemotherapy. This, they caution, may prove an obstacle for accrual. "The clearly established benefit of adjuvant chemotherapy in resected stage III colon cancer had led some authors to consider surgery alone unethical after resection of stage IV disease and that adjuvant chemotherapy should be given even without unquestionable proof of its benefit," they write.

■ G Brandi, E Derenzini, A Falcone et al. Adjuvant systemic chemotherapy after putative curative resection of colorectal liver and lung metastases. *Clin Colorectal Cancer* September 2013, 12:188–194

CT lung screening delivers least benefit for patients at low risk

■ New England Journal of Medicine

Screening with low-dose CT prevented the greatest number of deaths from lung cancer among participants at highest risk and caused the lowest number of false-positives in this group. The study, funded by the US National Cancer Institute, provides 'empirical' support for risk-based targeting of smokers for screening.

Recent results from the National Lung Screening Trial (NLST) showed that screening with low-dose computed tomography (CT) resulted in a 20% reduction in lung-cancer mortality among participants aged between 55 and 74 years with a minimum of 30 pack years of smoking, and no more than 15 years since quitting. Although it is widely agreed that screening should be limited to high-risk persons for whom potential benefits of low-dose CT outweigh potential harms, uncertainty exists as to how high-risk target populations should be defined.

In the current analysis, Stephanie Kovalchik, from the National Institutes of Health in Bethesda, Maryland, and colleagues, used data from the previously completed NLST trial to compare findings from 26,604 NLST participants who underwent low-dose CT and 26,554 who underwent chest radiography, according to the quintile of five-year risk for lung cancer mortality.

The team identified factors known to be associated with death from lung cancer and created an *a priori* prediction model based on such variables. To analyse the efficacy of lung cancer screening they divided the NLST population into five equal quintiles of lung cancer risk (with quintile 1 having the lowest risk) and inserted the NLST outcomes data to analyse efficacy of lung cancer screening. The authors do not share their formula for calculating the *a priori* risk in the paper.

Results show that the number of lung-cancer deaths per 10,000 person-years prevented in the CT-screening group (in comparison to the radiography group) increased according to risk quintile – 0.2 in quintile 1, 3.5 in quintile 2, 5.1 in quintile 3, 11.0 in quintile 4, and 12.0 in quintile 5 (*P*=0.01 for trend).

Furthermore, across risk quintiles, there were significant decreasing trends in the number of participants with false-positive results per screening-prevented lung-cancer death (1648 in quintile 1, 181 in quintile 2, 147 in quintile 3, 64 in quintile 4, and 65 in quintile 5). The 60% of participants at highest risk for lung-cancer death (quintiles 3 through 5) accounted for 88% of the screening-prevented lung-cancer deaths and for 64% of participants with false-positive results. The 20% of participants at lowest risk (quintile 1) accounted for only 1% of prevented lung-cancer deaths.

"Our estimates of the expected benefits and potential harms of such screening across risk groups provide the empirical framework for evaluating the cost-effectiveness of low-dose CT screening, investigating optimal risk cutoffs for screening, and communicating the potential benefits and harms of such screening tailored to each patient's individual risk," write the authors.

■ S Kovalchik, M Tammemagi, C Berg et al. Targeting of low-dose CT screening according to the risk of lung-cancer death. *NEJM* July 18 2013, 369:245–254

Neuropathy persists long term after colorectal cancer treatment

■ Journal of Clinical Oncology

Neuropathy symptoms remain widely reported by patients from 2 to 11 years after diagnosis with colorectal cancer, a Dutch registry study has found. Neuropathy should be screened for and alleviated, the investigators conclude, with more research focused on preventing this condition.

Neuropathy, a common adverse effect of the platinum agent oxaliplatin, has a negative impact on patients' health-related quality of life (HRQOL). Due to the increasing prevalence of colorectal cancer, and increased use of oxalipatin, neuropathy represents a growing issue for cancer survivors. Symptoms for acute neuropathy, often triggered by cold, include distal paraesthesias, dysaesthesias, and mild muscle contractions of hands, feet and perioral regions. A significant proportion of patients experience chronic neuropathy, which is mainly sensory, after oxaliplatin is discontinued.

In the current study, Floortje Mols and colleagues, from the Centre of Research on Psychology in Somatic Diseases, Tilburg University, set out to gain insights into the prevalence and severity of chemotherapy-induced neuropathy and its influence on HRQOL.

All patients diagnosed with colorectal cancer between 2000 and 2009 enrolled in the Dutch population-based Eindhoven Cancer Registry and still alive were eligible. Altogether 83% of patients (n=1643) responded to the request to fill out the EORTC Quality of Life Questionnaire and the EORTC QLQ Chemotherapy-induced Peripheral Neuropathy (CIPN) 20 instrument. Of the respondents, 500 (31%) had been treated with chemotherapy.

The five neuropathy-subscale-related symptoms that bothered patients with colorectal cancer most during the week prior to the survey were erectile problems (42% of men), trouble hearing (11%), trouble opening jars or bottles (11%), tingling toes/feet (10%), and trouble walking stairs or standing up (9%). Additionally, 29% of patients who received oxaliplatin reported tingling versus 8% of those not treated with chemotherapy (P=0.001). Numbness was reported by 17% who were receiving chemotherapy versus 5% who were not (P=0.05), and aching or burning pain by 13% receiving chemotherapy versus 6% not (P=0.03). Those with neuropathy symptoms in the upper 10% reported statistically significant and clinically worse HRQOL scores on all EORTC QLQ-C30 subscales.

"This study is one of the first to show that those with many neuropathy symptoms report a lower HRQOL compared with those with less neuropathy symptoms. Because our results are based on a large population-based study with a high response rate, extrapolating these results to the larger population of CRC survivors seems justified," write the authors.

Future studies, they add, should be prospective in nature, assess neuropathy both objectively and subjectively, and take the dose of oxaliplatin in every cycle and the duration of therapy (cumulative dose) into account. Studies should also focus on possible ways to prevent or alleviate these symptoms, preferably without dose reduction or early cessation of the treatment.

■ F Mols, T Beijers, V Lemmens et al. Chemotherapy-induced neuropathy and its association with quality of life among 2- to 11-year colorectal cancer survivors: results from the population-based PROFILES Registry. *JCO* July 20 2013, 31:2699–2707

Study defines use of neoadjuvant chemotherapy in advanced ovarian cancer

■ European Journal of Cancer

Ovarian cancer patients with stage IIIC disease and less extensive metastatic tumours show higher survival with primary surgery; while patients with stage IV disease and large metastatic tumours have higher survival with neoadjuvant chemotherapy, reports a Dutch study. The analysis of earlier EORTC data found that, in patients who did not meet these criteria, both treatment options showed comparable survival.

The standard treatment for patients with advanced ovarian cancer has been primary debulking surgery followed by chemotherapy. However, in 2010 the EORTC 55971 trial compared outcomes for three cycles of neoadjuvant chemotherapy followed by interval debulking surgery and three cycles of postsurgical chemotherapy (n=334) with primary debulking surgery followed by six cycles of postsurgical chemotherapy (n=336). Results showed that overall survival and progression-free survival were similar for both groups and that there were no significant advantages for either approach in terms of adverse effects, quality of life or postoperative morbidity or mortality. Questions remain whether these conclusions apply to all subgroups of patients presenting with stage IIIC or IV ovarian cancer, and if the selection of the best approach to treatment could be made before the start of therapy.

In the current study Hannah van Meurs, from the Academic Medical Centre in

Amsterdam, and colleagues, set out to investigate whether patient characteristics recorded at baseline in the EORTC trial could help identify subgroups who would benefit more from primary surgery or neoadjuvant chemotherapy. Altogether 10 different baseline clinical and pathological characteristics were identified, and to test the presence of interaction between the biomarkers and treatments the authors undertook Subpopulation Treatment Effect Pattern Plots (STEPP).

The results showed that patients with stage IIIC disease with metastatic tumours less than 45mm benefited more from primary surgery, while patients with stage IV disease with metastatic tumours greater than 45mm benefited more from neoadjuvant therapy. However in stage IIIC patients with larger metastatic tumours and stage IV patients with less extensive metastatic tumours both treatments were equally effective.

Furthermore, the biomarkers, age, WHO performance status, tumour grade, tumour histology, serum CA125 at study entry, pelvic mass, and omental cake showed no statistically significant difference in five-year survival between primary surgery and adjuvant chemotherapy.

"In conclusion... we found that patients with stage IIIC and less extensive metastatic tumours had a better survival after primary surgery while patients with stage IV disease and large metastatic tumours had a better survival after neoadjuvant chemotherapy," write the authors.

This strategy, they add, has the potential to result in an improved five-year survival of more than 6% in certain patient populations. "We suggest that systematic investigations of heterogeneity of treatment effects in randomised trials leading to treatment selection rules, could pave the way towards more individualised patient care."

■ H van Meurs, P Tajik, M Hof et al. Which patients benefit most from primary surgery or neoadjuvant chemotherapy in stage IIIC or IV ovarian cancer? An exploratory analysis of the European Organisation for Research and Treatment of Cancer 55971 randomised trial. *EJC* published online 15 July 2013, doi.org/10.1016/j.ejca.2013.06.013

Two years of trastuzumab shows no more effect than one

■ The Lancet

Two years of adjuvant trastuzumab is no more effective than one year in patients with HER2-positive early breast cancer, reports the latest analysis of the HERA trial. The study also demonstrated prolonged and sustained benefit from one year of trastuzumab compared to observation alone after a median follow-up of eight years.

Trastuzumab is an established treatment for patients with metastatic breast cancer with over-expression or amplification of the *HER2* oncogene. The open-label HERceptin Adjuvant (HERA) trial (*Lancet* 2007, 369:29–36) showed one year of adjuvant trastuzumab after standard neoadjuvant or adjuvant chemotherapy conferred significant overall survival benefits versus observation at a median follow-up of two years in patients with HER2-positive, early-stage, invasive disease. The original HERA trial also included a third randomised group given trastuzumab for two years, which has now been reported by Aron Goldhirsch and colleagues, from the European Institute of Oncology in Milan, for the first time.

In the open-label phase III trial, between December 2001 and June 2005, a total of 5102 patients were randomly allocated to three groups: observation (*n*=1698), trastuzumab for one year (*n*=1703), and trastuzumab for two years (*n*=1701).

Results at a median follow-up of eight years show that disease-free survival occurred in 367 (out of 1552) patients in the one-year treatment group versus 367 (out of 1553) patients in the two-year group (HR=0.99, 95%CI 0.85–1.14; *P*=0.86). Grade 3–4 adverse events, however, occurred in 16.3% in the one-year group versus 20.4% in the two-year group, and decreases in left ventricular ejection fractions were reported in 4.1% of patients in the one-year group versus 7.2% in the two-year group.

Furthermore the hazard ratios for a comparison of one year of trastuzumab treatment versus observation were 0.76 (95%CI 0.67–0.86, *P*<0.0001) for disease-free survival and 0.76 (0.65–0.88; *P*=0.0005) for overall survival, despite crossover of 884 (52%) patients from the observation group to trastuzumab therapy.

"Our results show no such additional benefit and a small but real increase in adverse events, leading to an unfavourable benefit–risk ratio for 2 years of adjuvant trastuzumab," write the authors. Taken together with the high cost of trastuzumab, this finding, they add, supports a standard duration of 12 months adjuvant trastuzumab.

In an accompanying commentary Heikki Joensuu, from Helsinki University Central Hospital, wrote, "The results of the HERA trial are in line with the biology and clinical behaviour of HER2-positive breast cancer. HER2-positive cancers are frequently aggressive tumours that usually recur early, within a few years after detection." This, he added, was in contrast to oestrogen receptor-positive HER2-negative cancers, which have a protracted clinical course, with recurrence that is sometimes detected only after the first decade of follow-up.

■ A Goldhirsch, R Gelber, M Piccart-Gebhart et al. 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label randomised controlled trial. *Lancet*, http://dx.doi.org/10.1016/S0140-6736(13)61094-6

■ H Joensuu. Duration of adjuvant trastuzumab: shorter beats longer. *ibid*. published online 18 July 2013, doi.org/10.1016/S0140-6736(13)61448-8