NEWSROUND

Selected reports edited by Hannah Brown

HRT increases risk of ovarian cancer

→ The Lancet

Women who use hormone replacement therapy (HRT) face a small but increased risk of ovarian cancer, in addition to an increased risk of breast cancer, according to a new analysis of data from the Million Women Study. The results suggest that around 1,000 extra women in the UK died from ovarian cancer between 1991 and 2005 because they were using HRT.

Researchers from the Cancer Research UK Epidemiology Unit, Oxford, UK, studied nearly one million postmenopausal women, none of whom had a history of cancer or surgery to remove their ovaries. Around 30% of the women were current HRT users and 20% were past users. During follow-up, 2,273 women developed ovarian cancer and 1,591 died from the malignancy.

Current users of HRT were more likely to develop and die from ovarian cancer than never users; for every 1,000 women using HRT, 2.6 developed ovarian cancer over five years, compared with 2.2 per 1,000 in women who had never used HRT. In other words, there was one extra ovarian cancer in roughly 2,500 users and one extra ovarian cancer death in roughly 3,300 users.

For current users of HRT, incidence of ovarian cancer increased with increasing duration of use, but did not differ significantly by type of preparation used, its constituents, or mode of administration. Past users of HRT were not at an increased risk of ovarian cancer. The researchers also reported that after women stop taking HRT, their risk of ovarian cancer returned to that found in never users of HRT.

"The effect of HRT on ovarian cancer should not be viewed in isolation, especially since use of HRT also affects the risk of breast and endometrial cancer," say the authors. "The total incidence of these three cancers in the study population is 63% higher in current users of HRT than never users. Thus when ovarian, endometrial and breast cancer are taken together, use of HRT results in a material increase in these common cancers."

■ Ovarian cancer and hormone replacement therapy in the Million Women Study. Million Women Study Collaborators. *Lancet* 19 May 2007, 369:1703–1710

Undertreatment common in ovarian cancer patients

→ Cancer

Previous research has shown that women who are treated by gynaecologic oncologists at a hospital that performs a high volume of ovarian cancer surgeries or at a teaching hospital have significantly better short-term and long-term outcomes. However, according to a new study, only two-thirds of US patients receive the recommended surgical treatment.

Researchers from the University of Washington, Seattle, USA, analysed hospital data from nine US states over a three-year period to identify factors that were associated with comprehensive surgical care among 10,432 women. They assessed the comprehensiveness of surgery by using diagnostic and procedural ICD-9-CM (international classification of diseases) codes and comparing them with the US National Institutes of Health Ovarian Cancer Consensus Guidelines. Women who had both a lymph node dissection and omentectomy/cytoreduction, or who had a diagnosis of a secondary malignancy of a specified organ/site and underwent an omentectomy/cytoreduction, were classified as having comprehensive surgery.

The researchers found that only 67% of the women whose cases they reviewed had received comprehensive surgery. Women who were older than 70 years, of African-American or Hispanic origin, or insured by Medicaid, were at greatest risk for undertreatment. Almost half of the women were treated by physicians who performed fewer than 10 procedures per year and 25% were cared for by surgeons who performed only one ovarian cancer surgery annually.

"Because optimal surgery with cytoreduction is associated with improved survival, efforts should be made to ensure that all women with ovarian cancer, especially those who are vulnerable because of age, race, or socioeconomic status, are referred to centers or surgeons from whom they are more likely to get optimal surgery," suggest the authors. "Our study findings suggest that the referral of women with suspected ovarian cancer to expert centers for primary surgery would be an effective strategy to improve overall outcomes for women with ovarian cancer."

■ Predictors of comprehensive surgical treatment in patients with ovarian cancer. B Goff, BJ Matthews, EH Larson et al. *Cancer* 15 May 2007, 109:2031–2042

Intensive chemotherapy offers no survival benefit in gastric cancer

→ JNCI

A more intensive postoperative chemotherapy regimen for high-risk gastric cancer patients does not improve their survival, according to the results of a randomised controlled trial.

Four hundred patients with gastric cancer who were at high risk of recurrence after complete resection of the tumour were enrolled in the trial, which aimed to compare the PELFw regimen with a combination of fluorouracil and leucovorin.

A total of 201 patients were randomly assigned to the PELFw regimen, which consisted of eight weekly treatments of five chemotherapy drugs (cisplatin, leucovorin, epirubicin, fluorouracil, and glutathione with the support of filgrastim). Another 196 patients received six monthly cycles of a five-day course of fluorouracil and leucovorin. After their treatment, the patients were followed for a median of 54 months.

The researchers found no significant difference in survival between the two groups. The five-drug regimen did not reduce the risk of death or relapse and both groups had a five-year survival rate of around 50%, which is much higher than previous studies have reported and which the authors attributed to the high quality of surgery in the trial.

In an accompanying editorial, Susan Ellenberg and Weijing Sun (University of Pennsylvania School of Medicine, Philadelphia) discuss the lessons to be learned from this negative result. "Unfortunately, some legislators, pushed by patient advocacy groups, seem willing to ignore the lessons of the past and are pushing for an extensive rollback of regulatory policy such that drugs for cancer and other life-threatening diseases could be marketed without being shown to be beneficial in a rigorously designed and conducted trial such as this study's authors have described," they write. "This trial provides an important reminder of how much patients have to lose should such efforts prevail."

■ Adjuvant treatment of high-risk, radically resected gastric cancer patients with 5-fluorouracil, leucovorin, cisplatin, and epidoxorubicin in a randomized controlled trial. S Cascinu, R Labianca, C Barone et al. *J Natl Cancer Inst* 18 April 2007, 99:601–607

Allografts for newly diagnosed myeloma

→ New England Journal of Medicine

Patients with newly diagnosed myeloma who receive a haematopoietic stem-cell autograft followed by an allograft from an HLA- (human leucocyte antigen)-identical sibling are more likely to survive than patients who receive a protocol of tandem autografts.

Patients with newly diagnosed myeloma who are younger than 65 years of age are often treated with high-dose chemotherapy followed by rescue of the bone marrow by an autologous haematopoietic-cell transplant. However, few patients who undergo the procedure are free of the disease for more than 10 years, with recurrences often due to the failure of the chemotherapy to eradicate all myeloma cells.

Lower relapse rates and longer remissions have been reported in patients receiving allogeneic stem-cell transplants, presumably because of the graft-versus-myeloma effects of the graft. However, the high risk of transplant-related mortality – which is 30–60% among young, medically fit patients – has limited the use of allogeneic transplants.

Now, a team of Italian researchers has investigated whether a protocol in which a haematopoietic stem-cell autograft is followed by an allograft from an HLA-identical sibling can improve overall survival.

The researchers enrolled 162 consecutive patients with newly diagnosed myeloma who were younger than 65 years and who had at least one sibling. All siblings and patients underwent HLA typing. The 80 patients who had an HLA-identical sibling then received non-myeloablative total-body irradiation and stem cells from the sibling. By contrast, the 82 patients without an HLA-identical sibling received two consecutive myeloablative doses of melphalan, each of which was followed by autologous stem-cell rescue.

The researchers followed up the patients for between 21 and 90 months. Seventy-three percent of patients completed the autograft–allograft treatment and 56% of patients completed the double-autologous transplant treatment; "19% of the eligible patients refused the autograft–allograft protocol, mostly because of concerns about the high transplant-related mortality previously reported for myeloablative conditioning," said the authors.

The researchers found that the median overall survival was longer in patients who received the autograft–allograft treatment than in those who had the double-autologous-transplant treatment (80 months vs 54 months). In addition, the rate of complete remission was significantly higher in the autograft–allograft group than the double-autologous-transplant group (55% vs 26%).

■ A comparison of allografting with autografting for newly diagnosed myeloma. B Bruno, M Rotta, F Patriarca et al. *N Engl J Med* 15 March 2007, 356:1110–1120

Hearing loss can be detected in children treated with platinum chemotherapy

→ Journal of Clinical Oncology

Children who are treated with platinum chemotherapy sometimes develop permanent sensorineural hearing loss, although it is impossible to predict which children will be affected based on the drug dose or its plasma concentration. However, researchers from Oregon Health and Science University think that there are some audiologic tests that are sensitive enough to detect changes

in auditory function before ototoxicity affects hearing at frequencies important for speech recognition.

Changes in hearing due to platinum ototoxicity are usually first detected in the highest audible frequencies. Yet, the standard method for monitoring ototoxicity is to measure pure-tone hearing thresholds within the conventional frequency range 0.25–8 kHz. Therefore, the researchers investigated whether two other measurement techniques – extended high-frequency audiometry and distortion product otoacoustic emissions – can detect ototoxic changes before hearing loss is detected by conventional audiometry.

The researchers did baseline and serial measurement of conventional pure-tone audiometry and distortion product otoacoustic emissions (DPOAE) for 32 patients, aged 8 months to 20 years, who were treated with cisplatin and/or carboplatin chemotherapy. Twenty of the 32 children (63%) acquired bilateral ototoxicity in the conventional frequency range during chemotherapy treatment, and 26 (81%) had bilateral decreases in DPOAE amplitudes and dynamic range.

The team also did baseline and serial measurement of extended high-frequency (EHF) audiometry (9–16 kHz) in 17 of the children, and found that 16 of them had bilateral ototoxicity in the EHF range. "The trend is that ototoxic changes occurred first in EHF thresholds, then in DPOAEs, and last in the conventional audiologic thresholds," write the authors, who also point out that EHF testing was feasible and reliable in children who were five years and older. "Unfortunately, it is difficult to obtain EHF results in very young children, a population for whom hearing loss is a particular concern as they are in the process of speech and language acquisition and are at greatest risk for platinum-induced hearing loss," they say.

■ Early changes in auditory function as a result of platinum chemotherapy: use of extended high-frequency audiometry and evoked distortion product otoacoustic emissions. KR Knight, DF Kraemer, C Winter, and EA Neuwelt. *J Clin Oncol* 1 April 2007, 25:1417–1422

Predicting pancreatic cancer

→ Journal of Clinical Oncology

Newly diagnosed patients with pancreatic cancer have a short life expectancy, because most are not diagnosed until the disease is advanced. A newly developed Mendelian risk prediction tool for pancreatic cancer, PancPRO, that can provide accurate risk assessment for patients with a family history of pancreatic cancer, may therefore be especially important.

PancPRO uses a patient's family history of pancreatic cancer to estimate the probability that the individual carries a pancreatic cancer susceptibility gene and to determine probability that an asymptomatic individual will develop pancreatic cancer in the future. It was built by a group of researchers based at the Johns Hopkins Bloomberg School of Public Health and the Johns Hopkins School of Medicine.

"Although clinical genetic testing for pancreatic cancer is currently limited, genetic counselling can still be of value," say the authors of the study. "PancPRO can form the basis for cancer risk counselling and can guide the design of screening trials for early pancreatic cancer detection in asymptomatic individuals," they suggest.

The model was validated by use of prospective data on 961 families enrolled into the National Familial Pancreas Tumor Registry. The sample included 26 individuals who developed incident pancreatic cancer during follow up. The researchers found that PancPRO calibration yielded an overall observed to expected ratio of 0.83.

"PancPRO is the first risk prediction model for familial pancreatic cancer and provides mutation-carrier probability and absolute risk for a specified age interval," write the authors. "Our validation indicated that PancPRO provided accurate risk assessment, discriminating between individuals with and without incident pancreatic cancers," they say. PancPRO is currently distributed free of charge for research and counselling use through BayesMendel or CaGene (http://astor.som.jhmi.edu/BayesMendel/pancpro.html).

■ PancPRO: risk assessment for individuals with a family history of pancreatic cancer. W Wang, S Chen, KA Brune et al. *J Clin Oncol* 10 April 2007, 25:1417–1422

Temozolomide is active in primary brain lymphomas

→ British Journal of Cancer

Temozolomide, an alkylating agent licensed to treat several types of malignant brain tumour, may also be active in patients with recurrent primary brain lymphoma, for whom there is currently no recommended second-line chemotherapy.

The standard treatment for this type of cancer is high-dose methotrexate, which was first described as a successful approach in 1980. However, even with this treatment, five-year survival rates for primary central nervous system (CNS) lymphomas remain low, and for most patients this is an incurable disease. Efforts to combine methotrexate regimens with other chemotherapeutic agents to enhance survival have so far failed to yield convincing results, and there are few agents with demonstrable activity in these tumours.

After reporting a single case in which temozolomide had induced a rapid and complete response in a patient with recurrent primary brain lymphoma in 2000, a team of Italian and Canadian researchers set up a phase II trial to assess the activity of temozolomide monotherapy in 36 immunocompetent patients with recurrent primary brain lymphomas – the first phase II trial to assess salvage monochemotherapy in patients with primary CNS lymphomas. All participants had been previously treated with high-dose methotrexate-containing chemotherapy and/or radiotherapy.

The researchers administered temozolomide at 150 mg/m^2/day for five days every four weeks up to a maximum of six cycles, stopping only if the disease progressed, there

was unacceptable toxicity, or the patient refused to continue. Of the 36 patients, nine achieved complete responses, 2 recorded partial responses, 5 had stable disease, 14 had disease progression, and 6 died before the response could be evaluated. Median progression-free survival was 2.8 months, median overall survival was 3.9 months and one-year overall survival was 31% (95% CI 16–46%). Toxicity was negligible.

Because the need is so great for new chemotherapeutic agents with clear activity in brain lymphoma, the researchers believe that temozolomide is an excellent candidate agent for further development. "It is well tolerated, even in elderly patients; it exhibits additive cytotoxic activity with radiotherapy; and its noncumulative and modest toxicity makes it potentially useful as an agent for induction, consolidation and maintenance therapy," they conclude.

■ Temozolomide as salvage treatment in primary brain lymphomas. M Reni, F Zaja, W Mason et al. *Br J Cancer* 26 March 2007, 96:864–867

Care for elderly cancer patients based on stereotypes

➜ Annals of Oncology

Current practice of care for elderly cancer patients is based more on stereotypes than evidence, according to a position paper by the International Society of Geriatric Oncology (SIOG). The paper suggests that ageing populations in many developed countries are forcing a re-evaluation of the way society can support older people. Noting that many older adults with cancer tend to be underserved and receive poorer care than their younger counterparts, the SIOG authors identify several areas where treatment of elderly cancer patients needs to be improved.

After reviewing available literature on cultural competence in elderly cancer patients, the researchers identified a need for more sophisticated and redesigned systems of care as well as improved education and training of professionals working in geriatric oncology. They conclude that knowledge about how older people understand, perceive, and experience their illness is essential to the planning and delivering of effective cancer care.

Many clinicians underestimate the willingness and capacity of elderly patients to face cancer and undergo aggressive treatment, but patients and their families are also sometimes unaware of the extent to which cancer can be treated in elderly people, and may not understand the benefits of treatment, say the authors.

They suggest that clinicians should learn to understand the social and cultural aspects of ageing to provide culturally competent cancer care. "Clinicians, researchers, educators, legislators, and policy makers need to address the change in demographics and look at innovative ways to address aging and cancer," the researchers conclude.

■ The illness trajectory of elderly cancer patients across cultures: SIOG position paper. A Surbone, M Kagawa-Singer, C Terret and L Baider, on behalf of the SIOG Task Force on Cultural Competence in the Elderly. *Ann Oncol* April 2007, 18:633–638

Lymph node ratio may beat TNM

➜ Annals of Surgery

Calculating the ratio of lymph nodes positive for metastatic disease to all lymph nodes examined when patients undergo lymphadenectomy – the so-called N ratio – may be a more reliable method of staging patients than the TNM system, through which patients are classified according to characteristics of their primary tumour and the number of metastatic lymph nodes, according to a study by the Italian Research Group for Gastric Cancer.

The notion of the N ratio was first proposed in 1998 as a novel method to identify prognostic subgroups among patients with N1 and N2 disease and to reduce the phenomenon of 'stage migration', since N stage can be affected by the extent of lymphadenectomy – i.e., how many lymph nodes are examined. After initial studies suggesting that this calculation was a simple and effective prognostic indicator in patients in whom at least 15 nodes had been removed at lymphadenectomy, the researchers set out to test whether the N ratio could also stratify patients by different clinical outcome when D1 lymphadenectomy, in which fewer than 15 lymph nodes are removed, was used.

In a retrospective multicentre study, the researchers collected data from the medical records of 1,853 patients who underwent radical resection for histologically confirmed gastric carcinoma between January 1988 and December 2001 at one of six centres in Italy. For each patient, the extent of lymphadenectomy was classified as either D1, D2, or D3; node status was assessed according to the UICC/AJCC guidelines, and N ratios were calculated and subdivided into groups.

Multivariate analysis showed that a high N ratio has prognostic value independent of both traditional prognostic factors – such as age older than 70 years, T stage, and site of tumour – and the extent of lymphadenectomy, leading the researchers to conclude that the N ratio "is a simple, convenient and reproducible system that can be used to better identify a subgroup of gastric cancers with similar prognosis."

As the first study to look at patients who have undergone lymph node dissection that removes fewer than 15 nodes, the authors said this work raises the question of what is the lower limit of node dissection for which the N ratio still works.

They conclude that their study should draw attention to the need for improving the prognostic power of current staging systems, "which would profoundly impact on the selection of patients who may most benefit from adjuvant treatment."

■ The ratio between metastatic and examined lymph nodes (N ratio) is an independent prognostic factor in gastric cancer regardless of the type of lymphadenectomy. A Marchet, S Mocellin, A Ambrosi et al. on behalf of the Italian Research Group for Gastric Cancer. *Ann Surg* April 2007, 245:543–552