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Selected reports edited by Janet Fricker

Cancer family histories found to be inaccurate

→ JNCI

General population reports on their family history for lung, colorectal, breast and prostate cancer were not found to be highly accurate, the 2001 Connecticut Family Health study has reported. Accuracy was greater for reports on first-degree relatives (FDR) than second-degree relatives (SDR).

It is well recognised that knowledge of a patient's family cancer history is essential for estimating their individual cancer risk and making clinical recommendations regarding screening and referral to cancer genetics clinics. It has not been clear, however, whether reported family cancer history is sufficiently accurate for this purpose.

In the current study, Phuong Mai and colleagues, from the National Cancer Institute (Bethesda, Maryland), undertook a random-digit dial survey involving 1019 participants. In the telephone interviews respondents were asked to list all biological FDRs (parents, siblings and children) and SDRs (grandparents, uncles, aunts, nieces, and nephews) who had suffered from cancer. Altogether the participants reported 20,578 FDRs and SDRs, of which 2605 were sampled for confirmation of cancer reports on breast, colorectal, prostate and lung cancer using state cancer registries, Medicare databases, the National Death Index, death certificates and heathcare facility records. The state of Connecticut was chosen for the study because it has the oldest population-based cancer registry in the US, with records dating back to 1935, thereby facilitating the process of confirming cancer reports.

Results showed that, for lung cancer, the sensitivity value was 60.2% and positive predictive value was 40%; that for colorectal cancer the sensitivity value was 27.3% and the positive predictive value was 53.5%; for breast cancer the sensitivity value was 61.1% and the positive predictive value was 61.3% and for prostate cancer the sensitivity value was 32.0% and the positive predictive value was 53.4%. Overall, cancer history reports on FDR were more accurate than reports on SDR. For prostate cancer, FDR had 58.9% sensitivity versus 21.5% for SDR (P=0.002); for lung cancer FDR had 78.1% sensitivity versus 31.7% for SDR (P<0.001); for colorectal cancer FDR had 85.8% sensitivity versus 43.5% for SDR (P=0.004); and for breast cancer FDR had 79.9% sensitivity versus 53.6% for SDR (P=0.02).

"In summary, the sensitivity and PPV (positive predictive value) of a reported family history of lung, colorectal, breast, and prostate cancers in this population-based survey were low to moderate, especially among SDR, but the specificity and NPV (negative predictive value) were high," write the authors, adding that there is a need to promote family history awareness and to find better tools to capture it accurately to ensure that appropriate risk assessment and clinical care recommendations can be made. "Improved knowledge about cancer might encourage people to be more willing to communicate about it with others, either when sharing information about their own diagnoses or when asking for information about their relatives' diagnoses," they write.

In an accompanying commentary, Rachel Freedman and Judy Garber, from the Dana Farber Cancer Institute (Boston, Massachusetts), said that although for the foreseeable future detailed family cancer histories will continue to provide the basis for identification of susceptibility genes, ultimately genomic analyses will become a routine part of cancer with predispositions to cancer identified at a young age.

■ PL Mai, AO Garceau, BI Graubard, et al. Confirmation of family cancer history reported in a population based survey. *JNCI* 18 May 2011, 103:788–797

■ R Feedman, J Garber. Family cancer history: healthy scepticism required. *ibid* pp 776–777

FOLFIRINOX improves survival in metastatic pancreatic cancer

➜ NEJM

In comparison with single-agent gemcitabine, FOLFIRINOX was associated with a survival advantage as a first-line treatment in patients with metastatic pancreatic cancer, a phase II-III trial has found. However, the FOLFIRINOX regimen (oxaliplatin, irinotecan, fluorouracil and leucovorin) showed increased toxicity.

In 2010 pancreatic adenocarcinoma was the fourth leading cause of death from cancer in the US, with five-year survival rates of 6% in Europe and the US. Since a randomised trial showed significant improvements in median overall survival for gemcitabine compared with fluorouracil, gemcitabine has been the reference treatment regimen. However the combination of gemcitabine with a variety of cytotoxic and targeted agents has generally shown no significant survival advantage as compared with gemcitabine alone. Data are lacking on the efficacy and safety of the combination chemotherapy regimen FOLFIRINOX compared with gemcitabine as a first-line therapy in metastatic pancreatic cancer.

Between December 2005 and October 2009, Thierry Conroy from Nancy University (France) and colleagues from 48 French centres randomised 342 patients in a ratio of 1:1 to receive FOLFIRINOX (n=171) or gemcitabine (n=171). Inclusion criteria included an Eastern Cooperative Oncology Group performance status score of 0–1 (on a scale of 0–5, with higher scores indicating greater severity of illness). Six months of chemotherapy was recommended in both groups for patients who had a response.

Results show that the overall survival at a median duration of follow-up of 26.6 months was 11.1 months in the FOLFIRINOX group compared with 6.8 months in the gemcitabine group (HR=0.57, 95%CI 0.45–0.73; P<0.001). The median progression-free survival was 6.4 months in the FOLFIRINOX group compared with 3.3 months in the gemcitabine group (HR=0.47, 95%CI 0.37–0.59; P<0.001). The safety profile of FOLFIRINOX was less favourable than that for gemcitabine, with FOLFIRINOX associated with a higher incidence of grade 3 or 4 neutropenia, febrile neutropenia, thrombocytopenia, diarrhoea, and sensory neuropathy, as well as grade 2 alopecia. Despite this higher incidence of adverse events, however, a significant increase in the time to definitive deterioration in the quality of life was observed in the FOLFIRINOX group. At six months, 31% of the patients in the FOLFIRINOX group had a definitive degradation of the quality of life versus 66% in the gemcitabine group (HR=0.47, 95%CI, 0.30–0.70; P<0.001).

"Our findings suggest that FOLFIRINOX is a first-line option for patients with metastatic pancreatic cancer who are younger than 76 years and who have a good performance status (ECOG 0 or 1), no cardiac ischemia, and normal or nearly normal bilirubin levels," write the authors. The success of the trial over previous studies, they suggest, may be due to the fact that the selection criteria were more rigorous.

■ T Conroy, F Desseigne, M Ychou, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *NEJM* 12 May 2011, 364:1817–25

15 years follow-up: radical prostatectomy beats watchful waiting

➜ NEJM

After 15 years of follow-up, radical prostatectomy continues to be associated with a reduction in the rate of death from prostate cancer as compared to watchful waiting, the latest results of the Scandinavian Prostate Cancer Group 4 (SPCG-4) study have shown. Subgroup analyses also showed that the risk of death from prostate cancer after radical prostatectomy was increased by a factor of seven for men who had tumours with extra-capsular growth, and that the benefits of prostatectomy were confined to men under 65 years old.

In 2008 the SPCG-4 study group reported that radical prostatectomy, as compared with watchful waiting, reduced the rate of death from prostate cancer. The current study, which presents an additional three years of follow-up, represents the only randomised investigation thus far to demonstrate that surgery reduces the risk of mortality from prostate cancer.

Between October 1989 and December 1999, Anna Bill Axelson and colleagues, from Uppsala University Hospital (Uppsala, Sweden), randomly assigned 695 men with newly diagnosed localised prostate cancer to radical prostatectomy (n=347) or watchful waiting (n=348).

Results at a median follow-up of 12.8 years show that 166 of the 347 men in the radical prostatectomy group and 201 of the 348 in the watchful waiting group died (P=0.007). Death was due to prostate cancer in the case of 55 of the men assigned to surgery and 81 assigned to watchful waiting. At 15 years the cumulative incidence of death from prostate cancer was 14.6% for the surgical groups versus 20.7% for the watchful waiting group (P=0.01).

Subgroup analysis showed that the survival benefit was limited to men under 65 years of age, and that the risk of death from prostate cancer for men with extra-capsular tumour growth who underwent radical prostatectomy was seven times that for men without extra-capsular tumour growth undergoing the same procedure.

Gleason scores were also highly predictive of the risk of death from prostate cancer: among 129 men who had tumours with Gleason scores of 2 to 6, only 5 died from prostate cancer. The current analysis showed that the number needed to treat with surgery to avert one death was 15 overall and seven for men younger than 65 years of age. This compared with 19 in the earlier analysis.

"Although extra capsular growth is not a perfect predictor of lethal disease, our findings indicate that these men could be a group for which adjuvant local or systemic therapy

would be beneficial," write the authors, adding that continued follow-up data from the SPCG-4 study might allow them to identify prognostic markers in men assigned to watchful waiting that can serve as trigger points for active treatment.

In an accompanying commentary, Matthew Smith from Massachusetts General Hospital Cancer Center (Boston, Massachusetts) writes, "The survival benefit with prostatectomy in men with low-risk disease is the most important new finding of the SPCG-4." He adds, however, that the findings may not be relevant for men today who have early-stage low-risk prostate cancers identified by prostate-specific antigen screening.

■ A Bill-Axelson, L Holmberg, M Ruutu et al. Radical prostatectomy versus watchful waiting in early prostate cancer. *NEJM* 5 May 2011, 364:1708–17

■ MR Smith. Effective treatment for early-stage prostate cancer – possible, necessary or both? *ibid* pp 1770–72

Sunitinib improves PFS in pancreatic neuroendocrine tumours

➔ NEJM

Continuous daily administration of sunitinib doubled progression-free survival (PFS) in patients with advanced pancreatic neuroendocrine tumours (NETs) in comparison to patients receiving placebo, a phase III trial has concluded. The trial also showed objective response rates and overall survival data that consistently favoured the sunitinib arm. The trial was terminated early by the data monitoring committee due to the risk of serious adverse events, disease progression and death among patients receiving placebo.

The incidence of pancreatic NETs, which arise from endocrine cells in the pancreas, is increasing, but five-year survival rates are still below 43%. Surgery has been the mainstay of treatment, with somatostatin analogues used to relieve symptoms resulting from hormone hypersecretion. The only approved chemotherapeutic agents remain streptozocin alone or in combination with doxorubicin. In both preclinical models and phase I and II trials the multitargeted tyrosine kinase inhibitor sunitinib, which was rationally designed to inhibit VEGFR and PDGFR, showed activity against pancreatic NET tumours.

In the current study, conducted between June 2007 and April 2009, Eric Raymond from Hôpital Beaujon, (Clichy, France) and colleagues from 42 centres in 11 different countries randomly assigned 171 patients in a 1:1 ratio, to receive best supportive care with either sunitinib at a dose of 37.5 mg per day (n=86) or placebo (n=85). Eligible patients had pathologically confirmed, well-differentiated pancreatic endocrine tumours that were advanced, metastatic, or both, and were not candidates for surgery.

In February 2009 the data and safety monitoring committee recommended discontinuation of the trial because of the greater number of deaths and serious adverse events in the placebo group, and differences in PFS. Results show that median PFS was 11.4 months in the sunitinib group versus 5.5 months in the placebo group (HR for progression or death = 0.42, 95%CI 0.26–0.66; P<0.001). The objective response rate was 9.3% in the sunitinib group versus 0% in the placebo group. At the data cut-off point, nine deaths (10%) were reported in the sunitinib group versus 21 deaths (25%) in the placebo group (HR=0.41, 95%CI 0.19–0.89; P=0.02). The most frequent adverse events in the sunitinib group were diarrhoea, nausea, vomiting, asthenia, and fatigue. Most sunitinib-related adverse events, report the authors, were manageable through dose interruption or modification.

"The improvement in progression-free survival observed among patients who received sunitinib provides support for previous preclinical and clinical data suggesting that neuroendocrine tumors may be particularly sensitive to combined inhibition of VEGFRs and PDGFR," write the authors, adding that the improvements were achieved without adversely affecting quality of life.

Although early termination of clinical trials may result in overestimation of treatment effects, the magnitude of the observed treatment effect, the consistency of the hazard ratio for disease progression or death and the favourable survival data provide strong evidence of a clinically meaningful benefit for sunitinib, say the authors.

■ E Raymond, L Dahan and JL Raoul. Sunitinib malate for the treatment of pancreatic neuroendocrine tumours. *NEJM* 10 February 2011, 364:501–513

Opportunities found for improving colorectal cancer patients' quality of life

➔ British Journal of Cancer

Most factors that adversely affect quality of life in patients with colorectal cancer (CRC) can be modified, a UK study has suggested.

Advances in treatment for CRC, which represents the third most common cancer in western countries, is resulting in more people being cured and also surviving longer with the disease. The adverse effects of both the disease and treatment can be longterm and include lack of energy, bowel problems, poor body image and emotional problems, as well as difficulties with sleep, fear of recurrence, anxiety, depression, sensory neuropathy, gastrointestinal problems, urinary incontinence and sexual dysfunction. As many people with CRC are more elderly, they often have additional functional limitations and comorbidities such as geriatric syndromes, heart disease, chronic obstructive pulmonary disease or other cancers.

To tackle the challenge of improving quality of life in patients with CRC, Nicola Gray and colleagues from the Centre of Academic

Primary Care at the University of Aberdeen (Scotland), set out to identify the potentially modifiable and fixed factors most associated with better or worse quality of life.

In the study 496 people diagnosed with CRC completed the EORTC-QLQ-C30 quality of life questionnaire, which comprises five functional scales (physical, role, cognitive, emotional and social) and three symptom scales (fatigue, pain, nausea and vomiting). Additional symptoms commonly reported by people with cancer (dyspnoea, loss of appetite, insomnia, constipation and diarrhoea) and the perceived financial impact of the disease were also assessed. The mean age of participants in the study was 66 years, with 70% being over the age of 60.

Results show that, of the unmodifiable factors, female sex ($P<0.001$), more self-reported comorbidities ($P=0.006$) and having metastases at diagnosis ($P=0.036$) significantly predicted poorer quality of life, but explained little of the variability of the model, giving a correlation coefficient of $R^2=0.064$ (1 = perfect correlation and 0 = no correlation). However, when the modifiable risk factors poorer role ($P<0.001$) and poorer social functioning ($P=0.003$), together with fatigue ($P=0.001$), dyspnoea ($P=0.001$), anorexia ($P<0.001$), depression ($P<0.001$) and worse perceived consequences ($P=0.013$), were introduced, the model fit improved considerably ($R^2=0.574$).

"We found that physical, psychological and social factors were all significantly and independently associated with overall QoL. Most predictors were modifiable, with symptoms, depression and limitations to usual activities being most important," write the authors, adding that the influence of unmodifiable factors was small, with the remaining independent predictors offering the potential for intervention.

Fatigue, for example, has been shown to respond in a variety of diseases to programmes of graded activity, say the authors, while depression and anxiety have improved with nurse led interventions, exercise and antidepressants, and difficulties with travelling may be helped by interventions to reduce the need for it, such as providing more locally based follow-up.

"If we wish to improve QoL in people with colorectal cancer, then we need first to identify those most at risk, and second to intervene to address factors which are modifiable," conclude the authors, adding that any future interventions will require rigorous evaluation.

■ NM Gray, SJ Hall and S Browne. Modifiable and fixed factors predicting quality of life in people with colorectal cancer. *Br J Cancer* 24 May 2011, 104:1697–1703

Short-term radiotherapy added to surgery delivers long-term gains in rectal cancer

➜ Lancet Oncology

For patients with resectable rectal cancer, preoperative short-term radiotherapy reduced local recurrence by more than 50% compared to surgery alone, reports the Dutch Colorectal Cancer Group. In the long term follow-up of the total mesorectal excision (TME) trial, investigators found that a reduction in local recurrence was maintained, and that overall survival was improved in a subset of patients.

The TME trial, undertaken by Cornelis van de Velde and colleagues at Leiden University Medical Centre (Leiden, Netherlands), was the first study to suggest that, in combination with TME, short-term preoperative radiotherapy delivered added value. Results at two years showed a decreased risk of local recurrence for irradiated patients (2% vs 8%, $P<0.001$); while results at six years again showed a decreased risk of local recurrence for irradiated patients (6% vs 11 %, $P<0.0001$). In both cases no difference was found in overall survival. However, the possibility that radiotherapy might not prevent, but merely postpone, local recurrence could not be excluded. The current publication reports on the long-term results after a median of 11.6 years follow-up.

In the TME trial between January 1996 and December 1999, 1861 patients with resectable rectal cancer without evidence of distant disease were randomly assigned, in a 1:1 ratio, to TME preceded by 5x5 Gy radiotherapy ($n=897$) or TME alone ($n=908$). The patients were recruited from 118 European centres and one Canadian centre.

Results show that the 10-year cumulative incidence of local recurrence was 5% in the group assigned to the short-course preoperative radiotherapy plus TME versus 11% for the TME alone group ($P<0.0001$). Again overall survival did not differ between the two groups. However, in the subset of patients with TME stage III and negative circumferential margins, survival was 40% in patients receiving just TME versus 50% in patients receiving TME plus radiotherapy ($P=0.031$).

In an accompanying editorial, Rob Glynne-Jones, from Mount Vernon Cancer Centre (Northwood, London, UK), comments that the fact that the results do not show a difference in survival implies that some subgroups may be being disadvantaged by radiotherapy in terms of survival. Indeed, he adds, the results showed that death from a second malignancy was more frequent in the radiotherapy group than in the TME-alone group (14% vs 9%).

"Preoperative short-term radiotherapy significantly improved 10-year survival in patients with a negative circumferential margin and TNM stage III," conclude the authors, adding that future staging techniques should offer possibilities to select patient groups for which the balance between benefits and side-effects will result in sufficiently large gains.

■ W van Gijn, C Marignen, I Nagtegaal et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *Lancet Oncol* June 2011, 12:575–582

■ R Glynne-Jones. …and a two-edged sword in their hands. *ibid* pp 519–520