to prevent one breast-cancer death).[15,16] Therefore the decision of whether to recommend screening mammography crucially depends on estimates of harm, which will never be zero. Although the best estimates of harms from screening mammography seem to be less than the benefits, they remain too uncertain to conclude with a high level of confidence that screening mammography in this age-group is associated with a net benefit.[5,7] Every woman, with her physician's guidance, should decide whether regret will be greater if she develops breast cancer that could have been detected earlier by screening mammography, or if she develops breast cancer later in life as a result of screening mammography itself.

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A third episode of transfusion-derived vCJD

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To date, there have been two cases of transfusion-derived variant Creutzfeldt-Jakob disease (vCJD) infection.[1,2] In today's *Lancet*, Stephen Wroe and colleagues[3] report a third case of autopsy-confirmed vCJD infection (and a second case of clinical vCJD) from a cohort of recipients who received transfused blood products derived from individuals who were subsequently diagnosed with vCJD.

Wroe and colleagues' report is important and concerning. Evidence that vCJD is transmitted by transfusion has accumulated, first from animal models and then from human cases.[1,2,4,5] This third incidence considerably strengthens the inference that transfusion transmission is possible, and suggests that the causative prion can be efficiently transmitted via this route. The inefficiency of oral transmission and the species barrier between cows and human beings has been credited with protection of human populations from a larger vCJD epidemic.[6] By contrast, the evidence now suggests that the within-species transmission of the prion through transfusion is efficient and, unmanaged, could pose a serious risk of propagating the vCJD epidemic.

The UK's Transfusion Medicine Epidemiology Review (TMER) has been following up 66 recipients of blood products from individuals who subsequently developed vCJD.[7,8] 34 of these individuals died within 5 years of the transfusion, and their deaths are not attributed to exposure because the incubation period of vCJD is probably longer than 5 years. Of the other 32, 24 are alive and are at risk of developing vCJD. Of the eight who have died, three were infected with the prion and two developed the disease (figure). These numbers suggest that a transfusion risk is more than remote. The potential efficiency of transmission by transfusion

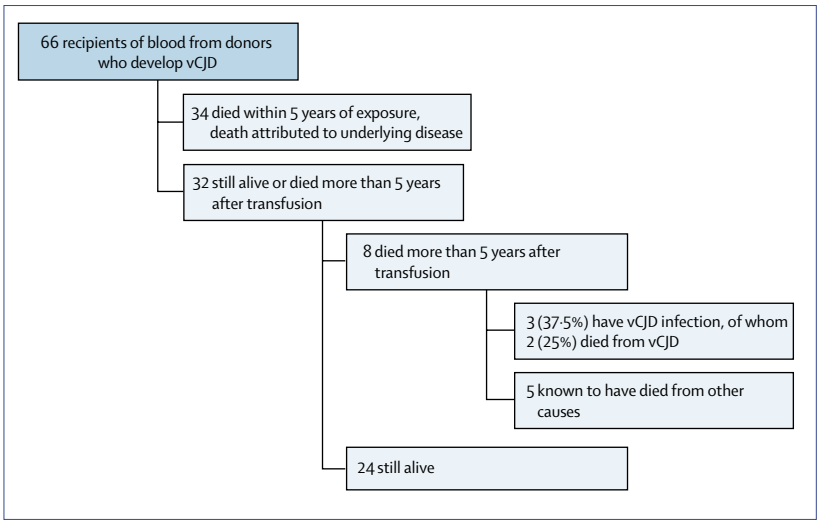

***Figure*: Fate of recipients of blood products from donors who went on to develop vCJD**
Until Aug 8, 2006 from reference 8.

further increases when one notes that the recipients susceptible to developing clinical vCJD probably only consists of those with the *MM* genotype in the prion protein gene.[6]

It is important to recognise that the numbers on which to base estimates of efficiency of transmission are small, and extended follow-up of all recipients of blood from vCJD-infected donors will be necessary before we can comment on the level of risk posed by transfusion. We also do not know whether leucoreduction reduces the likelihood of transmission of the prion by transfusion. Nevertheless, other findings from Wroe and colleagues' report and the overall review of transfusion recipients emphasise the implications for blood supplies. First, individuals with vCJD tend to be young and therefore are more likely to be eligible blood donors. In the TMER study,[7] 12% of all patients with vCJD who were eligible donors were confirmed to have donated blood. Second, in this third case, the infected donor developed vCJD 20 months after blood donation; in another, the donor developed vCJD 40 months after donation.[1] Therefore we must recognise that an extended preclinical stage can exist, during which an individual's blood products can be infectious. Without a blood test for vCJD, we cannot easily identify these preclinical infections. Third, we have learned from another episode of transfusion-transmitted vCJD infection that subclinical infection is possible when individuals harbour the prion but do not have clinical disease.[2] Their blood might be able to transmit infection to a susceptible recipient, although this suggestion remains uncertain.

In light of this new evidence about the efficiency of transfusion transmission, the recent UK policy to refuse donations from individuals who have previously received a transfusion, a policy that reduced the number of eligible blood donors by 5–10%, appears especially prudent.[9] This policy effectively prevents transfusion from propagating the vCJD epidemic. Other countries will also have to reassess their policies designed to reduce the threat of vCJD to their blood supplies.[10] This third transmission of vCJD creates an even greater urgency to identify techniques to reduce prion infectivity in the blood and to develop a test to identify potentially infected blood.[11,12] Finally, the findings raise important ethical and legal concerns, including the need to communicate the risk of vCJD to potential recipients of blood, especially in countries with cases of bovine spongiform encephalopathy.

That transmission of vCJD by transfusion is manifest and could have led to propagation of the epidemic is becoming increasingly apparent. Iterative approaches that amended policy rapidly in view of new evidence have served blood safety well.[13]

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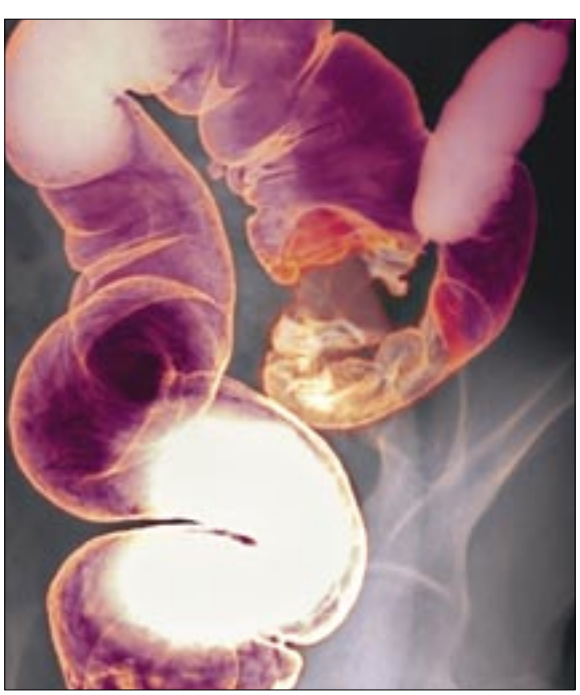
Optimum chemotherapy for metastatic colorectal cancer

In the past 10 years, several new agents have increased median survival for patients with metastatic colorectal cancer from about 12 months with fluorouracil alone to 24 months or higher.[1] Despite these new treatments, we are still learning how to maximise survival benefit while keeping toxic effects to a minimum. In a recent randomised North American Intergroup trial, Goldberg and colleagues[2] studied patients with untreated metastatic colorectal cancer given two chemotherapy regimens: bolus fluorouracil, leucovorin, and irinotecan (a topoisomerase I inhibitor) and infusional fluorouracil, leucovorin, and oxaliplatin (a platinum drug; this regimen is also called FOLFOX4).

The North Central Cancer Treatment Group trial 9741 previously[3] compared the efficacy of irinotecan-based and oxaliplatin-based regimens for first-line treatment of metastatic colorectal cancer. In this trial, patients were randomly assigned: FOLFOX4; bolus fluorouracil, leucovorin, and irinotecan; or irinotecan and oxaliplatin. About 1 year into the trial, real-time monitoring of toxic effects[4] identified an imbalance in the number of deaths within 60 days of enrolment in the group assigned fluorouracil, leucovorin, and irinotecan (4·5%) compared with the FOLFOX4 group (2·5%). Thus accrual to this part of the trial stopped, and the trial was amended to a two-group study of FOLFOX4 versus fluorouracil, leucovorin, and irinotecan, with the doses of fluorouracil and irinotecan reduced by 20% and leucovorin held at full dose for this study group.

Data from the North Central Cancer Treatment Group trial[3] showed that patients allocated FOLFOX4 had a higher response rate than did those allocated fluorouracil, leucovorin, and irinotecan (45% *vs* 31%), longer time to disease progression (8·7 *vs* 6·9 months), and higher overall survival (19·5 *vs* 15·0 months). The results of this study were controversial because oxaliplatin was not widely available when the study was done. 60% of patients who received oxaliplatin were given irinotecan as second-line treatment, whereas only 24% of those who received fluorouracil, leucovorin, and irinotecan were given oxaliplatin as second-line treatment. Furthermore, there was discussion about comparison of infusional fluorouracil with that of bolus fluorouracil because previous data[5] suggested infusional fluorouracil was associated with higher responses and survival than was bolus administration.

Goldberg and colleagues[2] report data for patients entered on the amended two-group trial. The number of deaths occurring within 60 days of treatment and the frequency and severity of toxic effects for patients assigned reduced-dose fluorouracil, leucovorin, and irinotecan were similar to those assigned FOLFOX4; however, paraesthesia and non-febrile neutropenia were more frequent with FOLFOX4. Moreover, the efficacy of the reduced-dose regimen was similar to the fluorouracil, leucovorin, and irinotecan regimen of the original trial. However, patients assigned FOLFOX4 had a higher response rate than those assigned reduced-dose fluorouracil, leucovorin,



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Cancer of sigmoid colon shown