The controversy of breast cancer screening

Sir,

The debate about the benefits of breast screening in the population continues with the publication of the Cochrane review (Olsen and Gotzsche, 2001). The issues raised by the authors have been challenged by Stephen Duffy in his editorial (vol 63(12), 2002, p. 708). Each issue has been debated and rejected based on convincing argument. There can be little doubt that breast screening improves mortality in breast cancer. This is believed to be a result of earlier diagnosis of invasive and pre-invasive lesions. In combination with better treatment strategies, this has led to a substantial reduction in mortality in women with breast cancer (Peto et al, 2000).

The Cochrane review distracts from the real issues that face clinicians and patients. Some of these issues, outlined below, need to be addressed further:

1. Age and frequency of screening
2. Screening in women at high risk of breast cancer
3. Natural history and biological behaviour of pre-invasive lesions – which lesions will progress and over what period of time?
4. Molecular genetics of pre-invasive disease
5. Therapeutic interventions in pre-invasive disease
6. The role of chemoprevention.

While it is important to debate issues in health care, in particular ones that require substantial resource, it is also important to recognize that it is time to move on and focus our attention on more important issues such as those highlighted above.

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Acute interstitial nephritis and COX-2 inhibition

Sir,

An 18-year-old woman presented with nausea and bilateral loin pain for 3 days. She had recently had an upper respiratory tract viral infection, which resolved after symptomatic therapy with paracetamol and rofecoxib. She did not notice dysuria but reported urinary frequency.

Examination found mild dehydration and left loin tenderness. Urinalysis showed increased white cells, markedly increased albumin levels and trace amount of red blood cells. She had a normal full blood count and differential count. Serum creatinine was raised (217 μmol/litre) as was blood urea (9.7 mmol/litre). Urine culture was sterile and antistreptolysin O titre was normal. Abdominal ultrasound showed normal kidneys, but the left one was comparatively bulky. Renal biopsy showed intense interstitial oedema with cellular infiltrate by eosinophils. Glomeruli were normal.

Her serum creatinine level rose to 367 μmol/litre 2 days after hospitalization, by which time all medication had been stopped. Acute interstitial nephritis (AIN) was diagnosed, and systemic corticosteroid therapy was initiated. Loin pain and pyuria quickly resolved together with recovery of renal function.

Conventional non-steroidal anti-inflammatory drugs (NSAIDs) can cause AIN (Rossert, 2001). An acute rise in serum creatinine levels is accompanied by urine sediments including leukocytes, red cells and white cell casts, and occasionally heavy proteinuria. Fever, rash, eosinophilia and eosinophiluria occur in most cases of AIN, except disease induced by NSAIDs (Rossert, 2001). The same might apply to cyclooxygenase-2 (COX-2) inhibitor-induced AIN, as seen in this case. Flank pain is a common but less often quoted complaint of AIN. This reflects renal capsule distension and has been seen in about 50% of cases (Eknoyan, 2001).

COX-2 inhibitors target the inducible enzyme isoform which is thought to mediate inflammation, but constitutive COX-2 expression has been demonstrated in human kidneys. It appears that use of COX-2 selective inhibitors does not necessarily protect the kidneys (Dunn, 2000).

Celecoxib-induced AIN has been reported (Henao et al, 2002; Markowitz et al, 2003), and meloxicam (Martin et al, 2000) and rofecoxib (Rocha and Fernández-Alonso, 2001) have been implicated. COX-2 inhibitor-induced AIN presents as acute renal failure with or without associated nephrotic syndrome. Patients prescribed COX-2 inhibitors should be assessed for nephrotoxicity.

Patients can present with AIN long after they have taken COX-2 inhibitors. Such delayed hypersensitivity is probably attenuated by the anti-inflammatory properties of the drug. Recurrence or exacerbation can occur with a second exposure of the same or a related drug. Cell-mediated delayed hypersensitivity against tubular cells is also implicated (Eknoyan, 2001). AIN is likely to be a class effect of COX-2 inhibitors.

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