EDITORIAL

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The Marmot report: accepting the poisoned chalice

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'The pellet with the poison's in the vessel with the pestle; the chalice from the palace has the brew that is true!'

That catchy little verse came from a film I remember called *The Court Jester*, a musical comedy starring Danny Kaye and Glynis Johns that was screened in 1955. I think the members of Marmot's panel must have been alerted that the chalice from the palace (of Westminster) carried the true brew. Unlike Marmot *et al* (Independent UK Panel on Breast Cancer Screening, 2012), I chose to commit professional suicide by taking the hemlock in the manner of Socrates (May *et al*, 2010).

On re-reading the full report (Marmot *et al*, 2013) on the 'true brew', I'm astonished to see the level of uncertainty expressed in many sections of the report.

For example, there are nine expressions of uncertainty in the executive summary. These include estimates of the extent of over-diagnosis after 20 years of screening varying from 0% to 50% and estimates of benefits varying between 1 : 250 to 1 : 2000 breast cancer deaths avoided after 10 years of screening. They even go so far as to state, 'Given the uncertainties around the estimates, the figures quoted give a spurious impression of accuracy' (Marmot *et al*, 2013). These wide ranges of estimates are based on calculations from equal numbers of 'distinguished professors' on each side of the debate, and we are not talking confidence intervals here. What we are observing is either a clash of ideologies or so much uncertainty as to suggest that the profession is in a state of perfect equipoise. If the former is true then one has to ask which side of the debate has the greatest conflict of interest, if the latter, then we can only resolve the differences by launching a new set of randomized controlled trials that involve modern diagnostic techniques, state of the art of adjuvant systemic therapy and 'safer' ways of delivering radiotherapy. Failing that, we will forever be stuck in a time warp based on trials conducted 20–30 years ago.

I strongly advocate the recognition of uncertainty in the noble pursuit of evidence-based medicine and by way of encouraging this healthy state of mind recently published a paper in the *BMJ*, wherein I tried my best to calculate the range of possible outcomes for breast cancer deaths avoided balanced against deaths resulting from the over-diagnosis and overtreatment of women gratuitously being subjected to surgery, radiotherapy and adjuvant systemic therapy (Baum, 2013). Central to these calculations is the recognition that as systemic therapy improves the window for the impact of screening narrows substantially (Burton *et al*, 2012), and as over-diagnosis rates increase, then the importance of the relatively rare lethal toxicities of treatment increase. If we accept the Marmot estimate of reduction in cause-specific mortality of 20%, then, factoring in the role of adjuvant systemic therapy that was adopted in the years since the data accumulated to provide this estimate, we would now have to screen 2500 women for 10 years to avoid one breast cancer death.

Next considering the toxic effects of over-diagnosis, I made use of the most comprehensive examination of rates in the USA that was recently published in the *New England Journal of Medicine*, and appeared a few weeks after the Marmot report (Bleyer and Welch, 2012). In this paper, Bleyer and Welch estimate that about 30% of all cancers or 50% of those detected by screening are over-diagnosed each year in the USA. This is a similar number to that reported by the Nordic Cochrane Centre (Gøtzsche and Nielsen, 2011). In absolute terms this means that 70 000 women each year in the USA are told that they have breast cancer, yet their pathology will not become life threatening. The UK has a fifth of the population of the US, and if the NHS breast screening programme (NHSBSP) widens its age limits to match the US, 14 000 more women a year would be exposed to the risks of treatment with no hope of benefit.

The Early Breast Cancer Trialists' Collaborative Group, 2005 overview of trials involving radiation estimated a relative risk of 1.78 for deaths from lung cancer and 1.27 for deaths from myocardial infarction in the irradiated group (Clarke *et al*, 2005). These data were relevant when women were recruited into the old screening trials, and despite reassurances that they don't apply today, I remain concerned. The left anterior descending coronary artery is in the field of treatment and remains at risk despite recent advances (Lind *et al*, 2003). For these reasons, any estimates of

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benefits and harms based on trials reported 20–25 years ago, as described in the Marmot report, are irrelevant to the modern practice of medicine. It is exceptionally difficult to calculate the benefit-to-harm ratios based on all the developments in the past 25 years since the NHSBSP started, but my crude estimate is that for every 10 000 women invited for screening, 3–4 breast cancer deaths are avoided, but along the way ~120 to 140 cases will be over-diagnosed. Four-fifths of these women would receive radiotherapy and would be at an increased risk of dying of ischaemic heart disease and lung cancer. Knowing the background risks and multiplying these by the factors 1.27 and 1.78 gives us increases of 2.0% for lung cancer and 1.33% for myocardial infarction. Adding that to all-cause mortality rates, I crudely estimate that an additional 1–3 deaths might be expected from other causes for every breast cancer death avoided (Baum, 2013). Given the uncertainties around the estimates, the figures quoted might give a spurious impression of accuracy. It is even possible that my worst estimate is too optimistic because of two papers I overlooked in the past that describe the risk of stroke following radiotherapy to the breast (Nilsson *et al*, 2005; 2009) and one very recent letter to the *N Engl J Med* on the early risk of cardiovascular deaths from the act of surgery alone, amongst patients with cancer (Voskoboynik *et al*, 2012).

Finally, it is worthy of comment that the remit of the Marmot commission excluded health economics, and the silence on this matter is deafening.

If we consider opportunity costs alone, I can think of many better ways of spending £100 000 000 a year on women's health. Yet when I consider distributive justice, my blood boils over. I'm writing this piece on 'Red Nose Day' and have just calculated that the sums of money spent on mammographic screening in the UK and USA alone could save 500 000 innocent children in Africa dying from malaria, each year (Comic Relief, 2013).

I accept that the conclusions of the Marmot committee are the first step in the right direction, but not the last word on the subject and I feel sure they would agree.

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