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VIEWS & REVIEWS

PERSONAL VIEW

Harms from breast cancer screening outweigh benefits if death caused by treatment is included

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Each new intake of medical students to my surgical "firm" started off with a tutorial where I posed a rhetorical question: "Why do we screen for cancer?" To which the inevitable answer would be, "To catch it early, sir." Wrong. The question should be reframed, as "Does screening for cancer improve length or quality of life?" All other outcomes are surrogates.

The clinical trials of screening for breast cancer that informed the recent Marmot review[1] made no attempt to measure quality of life, but a surrogate for that might be mastectomy rate in screened compared with unscreened populations. On that measure alone, screening fails: the hazard ratio for mastectomy of 1.2 favours the unscreened population.[2]

So, does screening improve length of life? Sadly, the Marmot committee chose to duck that one and rely on another surrogate outcome measure, cause specific mortality, with the rather lame excuse that the trials weren't powered to detect any impact on all cause mortality. Well shame on them, I say. The ProtecT trial of prostate specific antigen screening for prostate cancer gives equal weight to cause specific and all cause mortality by accepting that overdiagnosis and overtreatment might lead to an increase in all cause mortality.[3] Here I estimate the additional non-breast cancer deaths that might be the consequence of screening for breast cancer.

The CRC1 trial was published in the *BMJ* in 1989.[4] Patients were randomised to mastectomy with or without radiotherapy. This cohort of 2800 women was recruited contemporaneously with those in the old randomised trials of screening by mammography. Note in figure 1 of this paper that the 10 year survival was about 55%. Also, after about eight years of follow-up the curves for deaths other than breast cancer begin to separate, favouring those women who avoided radiotherapy.

In 2008, nearly 20 years later, I coauthored a paper in the *Lancet* reporting an update of the ATAC trial, which compared adjuvant tamoxifen with adjuvant anastrozole for postmenopausal women with early breast cancer.[5] The 10 year survival in that cohort was 80% (five year survival was approximately 90%).

The two key points are that, as systemic therapy improves, the window for the impact of screening narrows substantially,[6] and as overdiagnosis 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, as adjuvant systemic therapy developed over 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 (box 1). This estimate is much lower than in the Marmot report, which dismissed the impact of improvements in treatment.

Now consider overdiagnosis. The most important and comprehensive examination to date was recently published, a few weeks after the Marmot report.[7] Bleyer and Welch estimate that about 30% of all cancers, or 50% of those detected by screening, are overdiagnosed each year in the United States. This is similar to that reported by the Nordic Cochrane Centre.[2] In absolute terms this is 70 000 cases a year of women 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 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.[8] 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.[9] This can have devastating long term consequences on cardiopulmonary function among breast cancer survivors.[10] As recently as October 2012 the British Institute of Radiology organised a conference on this topic.

For these reasons, any estimates of benefits and harms based on trials reported 20 to 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

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women invited for screening, three to four deaths from breast cancer are avoided (see box 1).

If each of those were translated into total lives saved from all causes then I would remain content but, unfortunately, when 10 000 are screened along the way about 120 to 140 cases will be overdiagnosed with the current age group invited.[7] 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 (box 2) and multiplying these by the factors 1.27 and 1.78 gives us increases of 2% for lung cancer and 1.33% for myocardial infarction. Adding that to all cause mortality rates I crudely estimate that an additional one to three deaths might be expected from other causes for every breast cancer death avoided.[14]

Competing interests: MB has been an outspoken critic of mammographic screening for some years.

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1 Independent UK Panel on Breast Cancer Screening. The benefits and harms of breast cancer screening: an independent review. *Lancet* 2012;380:1778-86.
2 Gøtzsche PC, Nielsen M. Screening for breast cancer with mammography. *Cochrane Database Syst Rev* 2011;(1):CD001877.
3 Lane JA, Hamdy FC, Martin RM, Turner EL, Neal DE, Donovan JL. Latest results from the UK trials evaluating prostate cancer screening and treatment: the CAP and ProtecT studies. *Eur J Cancer* 2010;46:3095-101.
4 Haybittle JL, Brinkley D, Houghton J, A'Hern RP, Baum M. Postoperative radiotherapy and late mortality: evidence from the Cancer Research Campaign trial for early breast cancer. *BMJ* 1989;298:1611-14.
5 Arimidex, Tamoxifen, Alone or in Combination (ATAC) Trialist's Group, Forbes JF, Cuzick J, Buzdar A, Howell A, Tobias JS, Baum M. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial. *Lancet Oncol* 2008;9:45-53.
6 Burton RC, Bell RJ, Thiagarajah G, Stevenson C. Adjuvant therapy, not mammographic screening, accounts for most of the observed breast cancer specific mortality reductions in Australian women since the national screening program began in 1991. *Breast Cancer Res Treat* 2012;131:949-55.
7 Bleyer A, Welch HG, Effect of three decades of screening mammography on breast-cancer incidence. *N Eng J Med* 2012;367:1998-2005.
8 Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans E, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;366:2087-106.
9 Lind PA, Paganelli R, Marks LB, Borges-Neto S, Hu C, Zhou SM, et al. Myocardial perfusion changes in patients irradiated for left-sided breast cancer and correlation with coronary artery distribution. *Int J Radiat Oncol Biol Phys* 2003;55:914-20.
10 Jones LW, Courneya KS, Mackey JR, Muss HB, Pituskin EN, Scott JM, et al. Cardiopulmonary function and age-related decline across the breast cancer survivorship continuum. *J Clin Oncol* 2012;30:2530-7.
11 Cancer Research UK. CancerStats: cancer statistics for the UK. 2011. http://info.cancerresearchuk.org/cancerstats.
12 Law M, Wald N, Morris J. Lowering blood pressure to prevent myocardial infarction and stroke: a new preventive strategy. *Health Technol Assess* 2003;7:1-94.
13 Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al. Executive summary: heart disease and stroke statistics--2012 update: a report from the American Heart Association. *Circulation* 2012;125:188-97.
14 All cause mortality rates: Mortality rates for England and Wales for 2008 (ONS).
15 NHS Breast Screening Programme and Association of Breast Surgery. An audit of screen detected breast cancers for the year of screening April 2009 to March 2010. 16 May 2011.

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Box 1: Benefit in reduction of cause specific mortality

For 10 000 women aged 50-70 the incidence of breast cancer is 2 per 1000 per year, or 200 for 10 000 women over 10 years observation

Median period at risk = 5 years

Treated with modern systemic therapy, 90% survival = 20 deaths[5]

If screening risk reduction is constant at 20% then breast cancer deaths avoided = 4 (Marmot estimate[1]) or 15% reduction = 3 (Nordic Cochrane Centre estimate[2])

That is, 2500 to 3300 women screened for 10 years to avoid one breast cancer death.

Box 2: Harms caused by overdiagnosis

Best case scenario

I estimate overdiagnosis is 129 per 10 000 women screened, or 4000 every year in the UK (as in Marmot review[1]).

Therefore:

Cumulative mortality = 3.28% (lung cancer) and 6.16% (myocardial infarction)

Radiotherapy relative risk = 1.78 and 1.27

Excess deaths per 10 000 screened = 1.65 and 1.07

Total excess deaths = 2.72

I used 2008 age and sex specific lung cancer mortality rates from Cancer Research UK to calculate cumulative mortality.[11] I used 1998 age and sex specific myocardial infarction mortality from the Health Technology Assessment report[12] adjusted downwards by 30% to reflect declining mortality from myocardial infarction to estimate rates in 2008, based on trends in the US[13] and UK. I calculated cumulative lung cancer and myocardial infarction mortality (adjusted for intercurrent mortality[14]) for a 30 year period (similar to Marmot review); 100 women aged 50, followed for the next 30 years. Radiotherapy is used as adjuvant treatment in 50% of these overdiagnosed cases. Detrimental effects of radiotherapy have been assumed to start immediately (without any lag) and last for the entire 30 year period. This will not inflate the excess deaths caused by radiotherapy because the effect is applied only to the overdiagnosed cases and not the entire population. I used point estimates from the Early Breast Cancer Trialists' Collaborative Group overview to estimate detrimental effects of radiotherapy.

Worst case scenario

Excess deaths per 10000 screened = 5.60 (lung cancer) and 1.07 (myocardial infarction)

Total excess deaths = 9.25

This scenario differs from the best case scenario in these assumptions:

Estimate of overdiagnosis is 274 per 10 000 women screened, or 8500 every year in the UK. These figures are estimated by applying rates from Bleyer and Welch[2] to NHSBSP figures. Bleyer and Welch estimate that 31% all breast cancers in the US (60% of which are screen detected) are overdiagnosed—that is, 50% all screen detected cancers are overdiagnosed. From 1 April 2009 to 31 March 2010, UK NHSBSP (England, Wales, Northern Ireland and Scotland) diagnosed 17013 cases.[15] Radiotherapy is used as adjuvant treatment in 80% of these overdiagnosed cases.

Balance of benefit versus harm (best and worst case scenarios)

For every 10 000 women invited for screening, 3 to 4 breast cancer deaths are avoided at the cost of 2.72 to 9.25 deaths from the long term toxicity of radiotherapy.