

MENOPAUSE MATTERS

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Views on mammography

No matter your opinion of the usefulness or otherwise of routine mammography screening – it is a topic about which we should all be informed.

One of the issues receiving attention is why have breast cancer mortality rates declined in recent years in the face of increasing rates of breast cancer presentation? More specifically the debate could be divided into two schools of thought:

1. Is screening mammography “paying off” and are more cancers being detected early – thus leading to smaller, more confined lesions being treated with better outcomes?
2. Is treatment improving to such an extent with more accurate surgery, radiotherapy and especially adjuvant therapy (chemo and hormonal) that improved outcomes are being achieved at all stages of presentation and screening is irrelevant?

Logic would suggest – why not embrace both concepts? But two articles published recently give opposing views. One says mammography is the key with “truly substantial” benefits, while the other suggests screening exposes women “to unnecessary morbidity and mortality” and “should be terminated.” Both start from near identical standpoints which are –

“It is of paramount importance to evaluate the impact of participation in organised mammography service screening independently from changes in breast cancer treatment” ([Duffy et al *Am Can Soc* 2020 doi:10.1002/cncr.32859](#)). This is a quote from a study in Sweden which found in favour of mammography making the major difference.

“measurement of breast cancer [outcomes using] all-cause mortality, and adjuvant therapy uptake should be mandatory in monitoring and evaluating mammographic screening programs.” ([Burton & Stevenson *JAMA Netw Open* 2020;3:e208249](#)). This quote comes from an Australian study that found in favour of modern therapy making the major difference.

The first study looked at 2 groups of Swedish women – those participating in the public screening programme – and those choosing not to attend for screening. The researchers took mortality from breast cancer within 10 years of the diagnosis as their endpoint, thus hoping to eliminate changes in therapy as the variable, and therefore comparing mammography versus no mammography as the determining factor in survival. It did not matter if the woman’s cancer was diagnosed by screening or clinically, as they had the same treatments under the national health system.

Their conclusions were impressive in that they found “a 40% reduction in their risk of dying of breast cancer within 10 years” and a 25% “reduction in the rate of advanced breast cancers.” They write that “the body of evidence supports a reduction in advanced stage disease with screening” and that “Detection at an earlier stage through participation in mammography screening confers a significant reduction in the risk of death”.

The second study takes a longer-term view but posed the same question; is it screening or treatment that has reduced breast cancer death rates? Death rates have decreased by about a third since

modern treatments were introduced in the mid-1990s. This reduction in mortality occurred while the actual number of breast cancer cases was increasing. They showed that after screening was initiated (in the region of Australia under review) the number of advanced cases remained unchanged but the number of early cases increased – suggesting more slow-growing lesions were being identified and treated (including those over-diagnosed or false positives). They also showed that the biggest changes in outcomes followed improvements in adjunct therapy. The implication is that screening is missing the cases that matter – the fast-appearing, aggressive lesions – and better treatment is responsible for the better outcomes at all stages of presentation – not screening.

So there are two opposing points of view about what has been responsible for the reduction in death rates and whether mammography has reduced advanced cancer presentations or not.

It is difficult to reconcile these different findings and opposing points of reasoning. I am happy to offer a brief critique but, for the sake of transparency, I have frequently declared my misgivings and scepticism about the value and benign nature (both medically and economically) of routine mammographic screening in low-risk women. My views do not necessarily reflect the stance of SAMS or its office bearers.

The Swedish observational study compares attenders with non-attenders – but are these two groups comparable? Those who reject invitations for screening are generally of lower socio-economic status than those who accept and have more risk factors for breast cancer such as obesity, smoking, sedentary habits and lower educational levels.

The harms of overdiagnosis with its morbidity and potential mortality are not addressed in this paper. By confining their investigation to a 10 year time-frame they ignore the deaths that occur as the result of breast cancer treatment from cardiovascular disease and other causes that happen many years later. The only true question about any screening test for me is “Does the test improve the duration and quality of the person’s life?” Using a decade as the end-point and not including all-cause mortality weakens the study in my view.

For me the important controversy is around the “advanced” cancers.

These are lesions that do not follow the traditional concept that cancers start small, grow slowly, then spread to local lymph nodes and eventually metastasise. This model (the Halstedian paradigm of steady progression) is no longer accepted as the sequence of events as how lethal or aggressive tumours behave ([Welch et al *NEJM* 2015; 373:1685-7](#)).

These advanced tumours **may** serendipitously be identified by screening when they arise just prior to a woman’s mammography appointment but more commonly they appear as symptomatic tumours between screenings and are called “interval cancers”.

If these can be “caught early” by mammography or any means, this would be a major advantage that could be claimed for screening. With this in mind, investigators involved in the WHI study decided to relook at their data and address the issue ([Irwin et al *JAMA Netw Open* 2020;3:e207227](#)). You will recall that all the women in the WHI study, whether on hormones or placebo, had mammograms. They were diligently followed up for the occurrence of breast cancer and their findings are significant. They found that screening mammography missed “20% to 30% of breast cancers” and these interval cancers present with “a larger tumour size, more lymph node involvement, a more lobular histologic type, and higher breast cancer-specific mortality than cancers detected by screening”.

So, according to them mammography not only misses a quarter of breast cancers, but it misses the advanced, aggressive lesions. The WHI group of authors appeal for “novel approaches to detect life-threatening cancers currently missed by mammographic screening”.

I side with the WHI group and with the countries that have published their data on the changes in advanced breast cancer numbers (Australia, United States, Norway and the Netherlands) who all “reported that advanced breast cancer incidence either remained stable or increased after mammographic screening began, so no downstaging to early breast cancer was detected.” ([Burton & Stevenson JAMA Netw Open](#) 2020;3:e208249 and [Welch et al NEJM](#) 2016;375:1438-47).

I shall keep reading and reporting on the literature about mammography and will approach each article with the most equipoise I can muster.

My hopes lie with genetic advances

We know of the familial genetic predisposition to breast cancer but details are sketchy as to where on the human genome the likelihood of variants reside. Perhaps it is a combination of sites that are triggered by chemicals, activities or behaviours that allows their expression as clinical malignancies. Progress down this pathway is being made and 3 types of variants are known; with surely more to come ([Gallagher et al JAMA Netw Open](#) 2020;3:e208501).

The first set of genetic variants discovered and their sites in the genome identified were the BRCA1 and BRCA2 pathogenic mutations. This group account for 20% of the familial traced cancers and led geneticists to the second set of susceptibility genes at various specific sites on the genome with names such as PALB2, CHEK2, ATM etc. These are rarer groups of genes but have a “pattern” to their locations. The third group are a large number of individual variations called single-nucleotide variants (SNVs) scattered at various places on the genome. There are 88 of these single variants at present that geneticists use to quantify any woman’s risk of breast cancer but there is a long way to go yet.

Put together these 88 SNVs are called a woman’s polygenic risk score which can be calculated irrespective of her family history. There are polygenic risk scores for a number of conditions but the accuracy of their predictive value is still questionable ([Elliot et al JAMA](#) 2020;323:636-45).

I am convinced there will be many more single or combination variants identified and that tumours either biopsied or removed will be genetically “typed” to give more precise prognoses which in turn will lead to more precision medicine therapies.

Stepping out

The theoretical goal of 10 000 steps per day has little scientific provenance and now two articles bring more rigour to the situation.

Firstly, in middle-aged Americans 8 000 steps per day reduces mortality rates by half compared to those recording 4 000 steps per day ([Saint-Maurice et al JAMA](#) 2020;323:1151-60).

Secondly, in women with a mean age of 72 years, those who took 4 000 steps per day had significantly lower mortality rates than their sisters who accrued 2 700 steps per day, irrespective of stepping intensity ([Lee et al JAMA Intern Med](#) 2019;179:1105-12).

Drinking & thinking

It is established that drinking alcohol in moderation has cardiovascular benefits but what are the effects on older adult brains? In an attempt to gauge benefits or harms, researchers followed 20 000 retired US citizens for a decade and measured their cognitive scores serially ([Zhang et al JAMA Netw Open](#) 2020;3:e207922). They showed that low to moderate drinking defined as less than 8 drinks a week for women and 15 drinks a week for men, was consistently associated with higher cognitive scores, better trajectories over time and lower rates of cognitive decline than never-drinkers. There was a U shaped relationship between cerebral functioning and drinks per week that was consistent for women and men.

Again we find that wisdom points to moderation in all things. In the UK “moderate” alcohol consumption is accepted as 14 units per week for women and 21 units per week for men. While on the topic, alcohol induced cancers can be reduced by regular exercise – for women and men ([Feng et al Intern J Cancer](#) 2020 doi. 10/1002/ijc.33052).

Does aspirin affect cerebral function?

Low-dose aspirin is a popular preventative measure taken by older adults who believe it affords protection against cardiovascular disease and possibly colo-rectal malignancies. However, the range of potential benefits has been enlarged by some to include improved cerebral function, so a placebo controlled trial was initiated in Australia and the US to investigate this possibility ([Berk et al JAMA Psych](#) 2020 doi. 10.1001/jamapsychiatry.2020.1214).

There were 20 000 women and men with a mean age of 75 years who were followed up for 5 years, but no benefits were apparent in terms of less depression, dementia, mild cognitive impairments or lesser decline in general cerebral functioning (ASPREE Trial [Ryan et al Neurology](#) 2020 doi: 10.1212/WNL.0000000000009277) but there was an increased risk of haemorrhage. I should admit to taking low-dose aspirin for 2 decades without mishap. Maybe I should reconsider?

A possible ovarian cancer screening test

There is no clinically reliable screening test for ovarian cancer and late presentations with poor prognoses remain the rule. Recent work suggests that cellular proliferations in the Fallopian tube may be precursors to cancer in the ovary which is a slow process, taking years to develop.

Early intra-epithelial Fallopian tube neoplastic changes and progression to high-grade serous epithelial ovarian cancer, seems to be associated with a pathogenic genetic variant located in the TP53 gene. The TP53 variants could be markers of future malignancy predisposition. In established gynaecological cancers, DNA variants have been recovered in cytological samples obtained from the genital tract, raising the possibility of screening for molecular variants in cells that are exfoliated.

Researchers selected 17 patients with ovarian cancer and looked for TP53 variants in cytology specimens taken years earlier as part of these women’s routine Pap smear testing ([Paracchini et al JAMA Netw Open](#) 2020;3:e207566). In 11 women they found DNA with TP53 variants – in some cases 6 years prior to the ovarian malignancy appearing clinically.

The authors are extremely cautious about the hypothesis they are raising – namely the possibility of using Pap smear molecular testing as a screening test for future ovarian cancer risk. They make the case for large, long, prospective studies to guide investigations. They conclude their article with

“Our results hint at a promising prospect to significantly improve the future diagnosis” of ovarian cancer. I find the report very exciting.

Athol Kent

Menopause Matters is a monthly review of matters menopausal that have recently appeared in the journals. It is produced for the South African Menopause Society and the summaries concentrate on clinical issues although some underlying patho-physiology will be included to ensure a scientific basis for the work. These summaries and opinions do not necessarily reflect the views of the S A Menopause Society.

The idea is derived from the Journal Article Summary Service (JASS) which summarises general O&G articles. Information about this service can be obtained from Athol Kent (atholkent@mweb.co.za) or from the JASS website www.getjass.com