**What's new and why does it matter?**

Bear with me… this is a long post, but addresses some reasons for the divergence in breast screening recommendations.

I have to admit I love my gadgets. The latest mobile device or home network gizmo and especially kitchen gadgets… if it's new, I have a hard time resisting. And that's a risk when new technology appears in medicine, including imaging.

**Does it change performance benchmarks?**

Just because a technology is new, doesn't mean it's better; however, there are some material benefits to improved technology in mammographic screening, particularly when they result in improved audit benchmarks.

As with all screening programs, mammographic screening is heavily audited with long established benchmarks. Commonly used measures include cancer detection rate, recall rate, false negative rate and positive predictive value.

Quality assurance and quality improvement are intrinsic to all areas of medicine, particularly screening. Improving the image quality, such as contrast and resolution, of the mammogram has been an ongoing challenge since the earliest mammograms and there have been ongoing improvements in image quality, from the old xeromammographic technique and gridless detectors to current day tomosynthesis and beyond. These improvements have materially improved audit outcomes with, for example, digitally reconstructed "3D" tomosynthesis showing improved cancer detection and positive predictive value without significant radiation dose increase [FIGURE 1]. [https://www.cadth.ca/tomosynthesis-3d-mammography-breast-cancer-screening]

The ability to find small cancers on mammography hinges on image quality, so rigorous ongoing standardized QA monitoring is encouraged. In Canada this is audited through the Canadian Association of Radiologists Mammography Accreditation Program (CAR MAP). This was started in 1992. The American Mammography Quality Standards Act (MQSA) became effective in 1994.

**Tech and QA advances lead to Obsolescence**

Conversely, the ongoing improvements in technology and QA result in significant attrition in the value of old research. The original RCTs, largely run from the 60s to the 80s, were performed on now obsolete mammographic units and used variable positioning and even a variable number of views (some only used one mammographic view per breast, missing approx. 20% of cancers) as they were performed prior to standardized legislated QA. These studies, performed during the infancy of mammography, were useful in their day. Unlike a medication, such as aspirin, which remains the same molecule no

matter what era the study, technology-based research becomes “stale” with time. The early to mid-80s, when many of the currently quoted RCTs were performed, was the era of the Delorean car and the Commodore 64 computer (and I know some of you youngsters will have to look those up!). As revolutionary as those technologies were for the day, they are long since obsolete and we would not dream of heavily relying on research performed on them to inform current automobile safety standards or computer security policy. Technology attrition is a significant concern in mammographic screening recommendations.

**Additional RCT problems**

There will likely never be another RCT on screening mammography because it would violate equipoise. Knowing what we know about the benefits of mammographic screening, it would not be ethical to randomize some women to a non-screening limb. So, all the RCTs are frozen in time. While they showed enough evidence to initiate the mammographic screening programs by the mid-80s, they have limited value informing modern practice.

Even within the 8-10 RCTs that are available to us, there was a very variable quality of implementation. At least one set of RCTs, the Canadian National Breast Screening Study (CNBSS), was an outlier, demonstrating a higher relative risk of death in the screening limbs, probably attributable to problematic recruitment and randomization as well as poor quality mammography. Additionally, many RCTs were contaminated by women in the non-screening limb receiving screening mammography. Calculations were made using number invited instead of number screened, which further diminished the evidence of benefits. For these and many more reasons, the benefits of mammography were somewhat suppressed in these old trials. There is more to evidence quality than study design and unfortunately, the quality of some of the RCTs was poor, although this may not be readily apparent without content expert review. [1,2][FIGURE 3, Table 1]

**Better options in modern evidence**

We do, however, have some very large and well performed observational studies, including a multi-decade Swedish study and a 19-year study of Canadian provincial screening programs, demonstrating a large (40-60%) mortality benefit when screening mammography is used in practice [3,4]. Long term follow-up demonstrates increasing benefits over time with diverging survival curves in the screened versus non-screened populations [5]. This is consistent with what we know about the biology of breast cancer, and late development of metastatic disease.

When weighing the evidence, it should be noted that while RCTs are considered optimal design, they can be downgraded in certainty by the very implementation problems we see among some of the trials, particularly CNBSS, which was rejected in the 2002 WHO review. The technological attrition also downgrades their value in comparison with modern mammography. Observational studies can be upgraded in certainty of evidence when they are well performed and show a large magnitude of benefit, as we see in the Pan Canadian and Swedish studies. [6]

**A Final Word**

Yes, screening is imperfect and all screening comes at a cost, financial and otherwise. All women considering screening should understand that about 8% of screening mammograms might be recalled for a second look and 1.5% of those screened may experience anxiety and discomfort associated with biopsy with 30-40% of biopsies being malignant. Most biopsies, however, are minimal access and most patients describe them as less uncomfortable than a dental filling. Beware of false equivalencies between transient anxiety and discomfort and avoidable early death. Patients considering screening mammography should be informed that they have a 1-10% chance of being treated for a cancer that might never have caused them problems in their lifetime, although that is more likely with older women than younger women, since older women are more likely to die of other causes [7]. For all women, non-mortality benefits, including lower mastectomy and axillary dissection rates, should be considered. While a smaller number of younger women are saved by screening overall, the life years gained are substantially greater when screening younger rather than older women [8] and as we target younger, denser and high-risk women with personalized supplemental screening, we aim to improve outcomes in these groups, albeit at the cost of increased recalls and biopsies. Women should also be informed that, somewhat counterintuitively, lethal breast cancer is more common in younger women [9, FIGURE 2] and that half of fatal breast cancers are diagnosed by age 49 with more than half of younger women with breast cancer (40-49) having no known risk factors [9]. For truly informed consent, the woman must be told that her biggest risk for dying of breast cancer, if she gets it, is not screening [9].

Thanks for joining me this week. I hope I answered some questions and provided some food for thought. Thank you for your questions and interest.

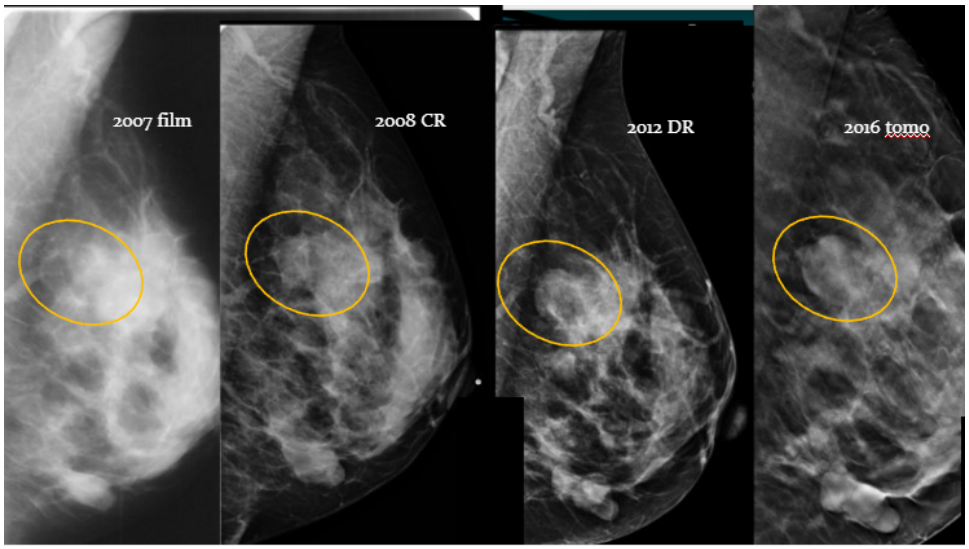

FIGURE 1. The improvements in technology and what they look like. All of these mammograms, performed between, 2007 and 2016, are relatively recent in comparison to the RCTs, the latest of which was performed in 1991. The 2007 mammogram was screen-film technology, 2008 was CR (an early digital format), 2009 was DR (a current 2D format) and 2016 is a tomosynthesis mammogram. There's a large benign mass in the lower half of the image, which becomes better circumscribed over time, demonstrating increased specificity. In the upper half of the image there is a more subtle mass, which was present at all these mammograms (documented sonographically), but became mammographically visible with the improvements in technology, demonstrating increased sensitivity.

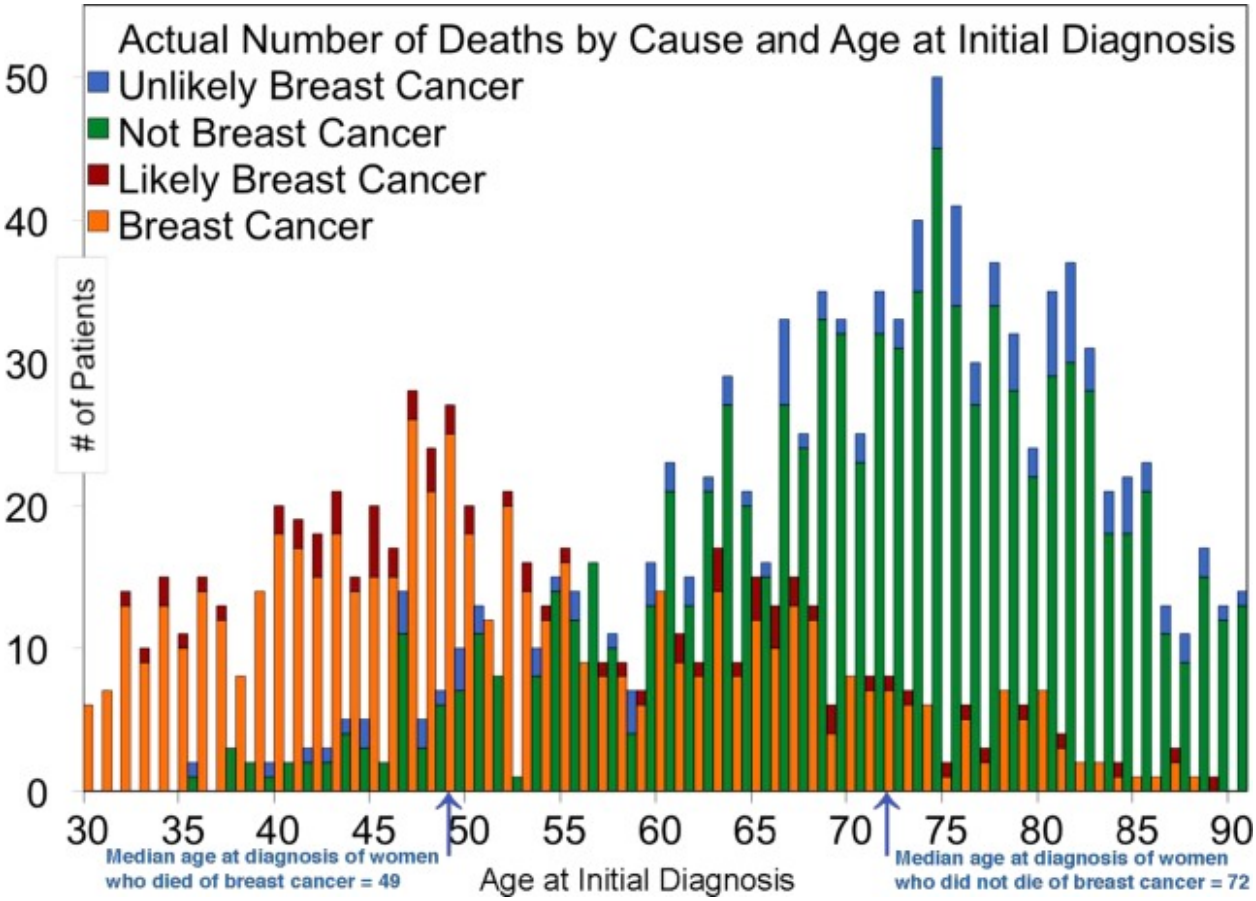


FIGURE 2. Graph demonstrating distribution of age versus death from breast cancer.

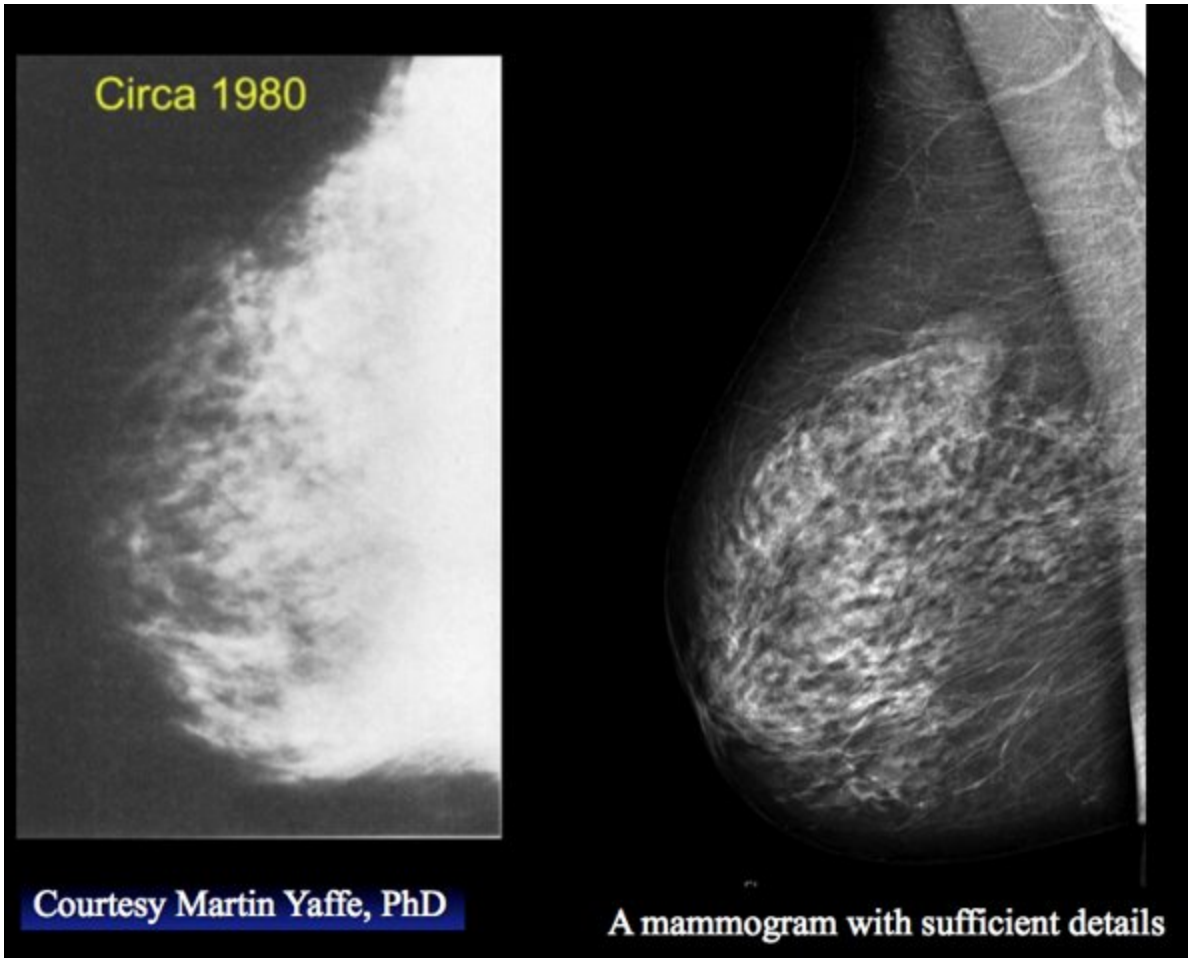


FIGURE 3

A 1980 mammogram from the CNBSS study compared to a 1982 mammogram from the Swedish Two County study. Although these were roughly contemporaneous, you can see that there were large differences in image quality, which result in differences in study quality which may not be obvious to non-experts judging the study by design alone. The responsible physicist for this study rated the image quality as “far below state of the art of that time”.

TABLE 1

| Trial | RR | 95% CI |
|---|---|---|
| | | |
| HIP | 0.77 | 0.63, 0.93 |
| Malmo 1 | 0.82 | 0.67, 1.00 |
| Malmo 2 | 0.64 | 0.39, 1.06 |

| | | |
|---|---|---|
| Two-County | 0.69 | 0.56, 0.84 |
| Edinburgh | 0.71 | 0.53, 0.95 |
| CNBSS 1 | 1.06 | 0.80, 1.40 |
| CNBSS 2 | 1.02 | 0.78, 1.33 |
| Stockholm | 0.74 | 0.51, 1.08 |
| Gothenburg | 0.76 | 0.56, 1.04 |
| Age | 0.75 | 0.58, 0.97 |


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