

**Screening for Breast Cancer:**  
**As the Twentieth Century Begins, How Useful Is It?**

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On January 4, this year, The Lancet published a paper by Peter Gotzsche and Ole Olsen entitled *Is screening for breast cancer with mammography justifiable?* Their conclusion was „Screening for breast cancer with mammography is unjustified.“ Unjustified even for women age 50 and over.

In North America this statement caused a storm of anger. The article was damned on radio, damned in the newspapers and damned on television. The fact that obscure Danish researchers had written the article, researchers no-one had ever heard about before, was sufficient reason to reject their unwelcome conclusion. Moreover, said the critics, Lancet had been irresponsible for allowing the paper to be published at all.

Of major interest to me were 1) the source of the article, 2) its detailed conclusions and 3) the indignant critics in my city of Toronto (population 3 million).

#### **Item 1.**

The source was the Nordic Cochrane Center. In my mind, conclusions from Cochrane researchers are likely to be un-biased. Their business is to evaluate trials. They have no evident conflict of interest as is the case when radiologists defend mammography or when researchers defend their own study or when frightened women demand the miracles of technology.

#### **Item 2.**

In my opinion, their conclusions were quite compelling. After all, they had nice things to say about the Canadian study – that has happened before, but not very often. Gotzsche and Olsen described a number of weaknesses in all the screening trials but they also described the strengths in the Canadian study. All of these points were familiar to me, but were habitually ignored by most of those involved in the promotion of mammography screening. The elements Gotzsche and Olsen chose to examine a priori were valid ones – familiar to anyone interested in evaluating randomized controlled trials. They looked at the quality of randomization, whether trial outcome

assessment had been masked and what numbers of subjects were excluded after randomization. The Canadian study withstands that kind of scrutiny very well. 113 exclusions occurred in the entire study and were equally distributed across both arms of the study. The reasons were documented [2,3]. Whether deaths had been due to breast cancer was assessed by experts masked as to which arm of the study the deceased had been assigned. And, as we had demonstrated in our 1992 publications, randomization had resulted in virtually equal distribution of all important demographic and risk factor variables. We stated age had also been equally distributed as this is demonstrated in table 1.

**Tab. 1 Randomisation: Mean Age at Entry (Median)**

Age at Entry (years)	Allocation	
	MA + CEB	Control
40-44	41.82 (42)	41.82 (42)
45-49	46.96 (47)	46.95 (47)
50-54	51.95 (52)	51.95 (52)
55-59	56.78 (57)	56.80 (57)

**Item 3.**

Many of the Toronto critics of the Lancet paper are my colleagues. I know most of them personally. Not one that I asked knew what a Cochrane Center is. Not one that I asked had actually read the Lancet paper before being interviewed by the media. But they all knew what they believed about screening. They knew the Lancet article was wrong.

What explains the hostile uproar that the Lancet article provoked? People do not like to have their beliefs challenged. In North America, women aged 40-50 years believe their probability of dying of breast cancer in the next ten years is more than 20 times higher than it actually is. The same women magnified the absolute benefit achievable from screening more than 100-fold [4].

Few women in Canada realize that at age 40 they face only a 1 in 200 chance of developing breast cancer in the next five years [5]. Instead they believe their risk to be much higher, and they have been completely convinced that mammography will save them. It is my understanding that the breast cancer incidence is even lower in Europe than in North America.

The exaggerated never-ceasing claims made for mammography which have seduced so many women are well illustrated by the statement of a very prominent US radiologist, Stephen Feig. Mammography screening of women age 40 and older can reduce breast cancer deaths by at least thirty to forty percent [6]. Perhaps some of you believe that. I am convinced that available evidence does not support such a claim.

Understandably, radiologists believe in their technology especially when it is for such a good cause as cancer control. Radiologists also profit from delivering their technology especially now that they have taken over the surgeon's traditional role of performing biopsies. How many people have considered the ramifications of current US guidelines for breast cancer screening in women age 40-49 years? Were they to be implemented fully, the cost for mammography alone would be 1.78 billion USD annually, an amount exceeding the annual budget for the US National Cancer Institute – and that amount does not include the cost of further diagnostic imaging nor does it include the costs of biopsies. Is that really the best way to spend money to improve health? [7] Common sense might question such an expenditure. Breast cancer after all accounts for 5-8% of all female mortality. In North America, lung cancer kills more women than breast cancer does. And cardiovascular deaths kill far, far more. Yet in North America, breast cancer research attracts a degree of support which quite outweighs its actual contribution to overall morbidity and mortality. That is society's priority.

Of course in a capitalistic society, one always looks for increasing revenue and developing new markets. In a recent paper, another prominent US radiologist, Dan Kopans, actually discusses screening with mammography every six months because it might dramatically reduce death rates from breast cancer [8]. Just considering women age 40-49, that would boost revenue in the USA above 3.5 billion annually. As for new markets, one can read in Lancet that mammography is now being 'suggested' in the US for women age 25-35 [9]. Such a policy would yield a windfall for radiologists, pathologists, surgeons and the medico-industrial complex. The direct and indirect costs of false-positive mammograms would be enormous. Women age 40 to 49 receiving 10 annual mammograms, face a 56.2 percent cumulative risk of a false positive mammogram, while for women 50 or older, the cumulative risk is 47.3 percent [10]. For women aged 25-35, that rate would be much in excess of 56.2 percent. I think the fact that radiologists have to deal with conflicts of interest is clearly established.

In that context of public ignorance, public fear and, as The Economist so bluntly stated, professional and corporate greed, what is the status of breast screening in the year 2000? [11]. Up until now reasonable people have agreed that when women over aged 50 were screened competently, one could expect substantial breast cancer mortality reduction. In contrast, reasonable people have agreed that screening women age 40-49 at best produced a minor reduction 10-13 percent - in mortality. They also agreed that this reduction took so long (10-15 years) to become apparent that much of the benefit might be attributable to breast cancer diagnosis actually occurring after women had turned 50 even though they began screening in their forties.

Up until now, a skeptical person could be quietly amazed that the most dramatic mortality reduction had been observed in the New York Health Insurance Plan Study which was using

relatively primitive mammography. A skeptical person would have noticed some design and methodological weaknesses in the trials showing screening benefit for women age 40-49 and some strengths in the trials showing that there was a null effect. For in fact, the Canadian National Breast Screening Study, the one which recruited the largest number of women age 40-49, all of whom signed informed consent and for whom complete information is available for its control population, shows no benefit from screening these women.

At this point let me show you the names of my colleagues in the Canadian study and outline the research questions which it addressed.

In 1992 at seven-year followup, the rate ratio comparing deaths from breast cancer in women age 40-49 years at entry who received annual mammography with those who did not, was 1.36 (0.84-2.21) [2]. In 1997, (10.5 year followup) that ratio had declined to 1.14 (0.83-1.56) [12]. In the year 2000 after 13 years of followup, the rate ratio for cancers diagnosed within seven years of entry is 1.05 (0.78-1.42) [13], a strong indication of a null effect. Including all breast cancer diagnosed up to seven years after entry into the study means that breast cancers are included which were diagnosed three and four years after women had completed their four- or three-year screening program in the study.

Similar null effects have been reported in other screening trials, namely in the Stockholm, Ostergotland, Malmo and Edinburgh trials [14].

What is never addressed is the transient but consistent excess in breast cancer mortality observed in women who are screened compared with controls, a phenomenon occurring in the first few years after screening begins. This has been observed in the HIP study, the Two-County Trial, the Canadian trial and the Edinburgh trial.

In the year 2000, Gotzsche and Olsen are the first to be persuasively skeptical about the value of screening even for women over the age of 50. They seemed to have two reasons. The well conducted Canadian study had shown a null effect. In contrast, those trials reporting positive results for screening had serious methodological flaws. In 1992, with seven-year followup, the Canadian rate ratio comparing women age 50-59 years, who received annual mammography plus clinical breast examinations with women who received only annual breast examinations, was 0.97 (0.62-1.52)[3]. In 2000, with thirteen-year followup, the rate ratio for breast cancers diagnosed in the first seven years after entry was 1.12 (0.83,1.50) [15].

But nothing is ever simple. The Canadian study is unlike all other screening trials in that the control group received annual screening with clinical breast examinations. All the other screening trials compared mammography screening (with or without clinical breast examination) to no screening intervention. Recently it was concluded, that „Screening clinical breast examinations should be conducted for women who are at risk for breast cancer . . . A well conducted CBE can detect at least 50 percent of asymptomatic cancers and may contribute to mortality rate reduction in women screened.“ [16]. It will be no surprise to anyone, that I agree with this conclusion. Furthermore it offers a reason why mortality benefit for women aged 50 to 59 might not be observed in the Canadian study. The incremental benefit of mammography over and above clinical breast examination was that it detected far more breast cancers than clinical breast examination alone, but it did not achieve any breast cancer mortality reduction.

My colleague, Professor AB Miller has suggested here in Bremen, that a trial comparing screening with mammography to screening with skilled clinical breast examination, would remove uncertainty about this issue.

Before I conclude let me make two recommendations. 1. If you want to establish a screening program, why not do it in the context of a randomized controlled trial, as Dr. Miller has outlined? 2. If you have other important health issues, if the expense of mammographic screening will prohibit supporting other health promotion activities with potentially greater opportunities for benefit, why not do as I suggested in my abstract? Establish a public policy which encourages, promotes and supports breast self-examination, which provides routine, expert clinical examination of the breasts by a health professional and which ensures access to high quality diagnostic mammography when there are clinical abnormalities.

### **Conclusions**

As the 20<sup>th</sup> century begins, I am not sure that the question I was assigned by the congress organizers, namely ‘How useful is screening?’ is the right one to ask.

Screening is useful in the sense that women are reassured (sometimes inappropriately) after receiving a normal screen report. Screening is useful in the sense that doctors are gratified by case detection. Screening is useful in the sense that it responds to the demands and expectations of society. Screening is useful for defensive practice – doctors will avoid litigation if they recommend mammograms for all women age 35 and over. And screening may be useful in that women whose breast cancers are diagnosed early may have more treatment options.

However screening is less useful in that the hopes for benefits certainly are not achieved for the majority of women with breast cancer who were screened. It is not useful when you consider the penalty women pay for the high proportion of false positives they must endure – to say nothing of the false-negatives. These disadvantages are too often disregarded and trivialized. The direct and indirect costs of screening programs are huge. You need to screen 2451 women age 50-59 for five years to prevent one death from breast cancer [17]. All is accepted in order to gain a small benefit.

Looking ahead, even for the next decade, is it possible screening will become irrelevant? As I wrote in my recent JNCI editorial, „Just imagine how unimportant early detection could become if breast cancer therapy changed radically in the next decade. Just imagine how controversies relating to early detection would become irrelevant if breast cancer therapy became both relatively non-toxic and generally effective. Is it possible that low-dose, continuous, relatively innocuous chemotherapy combined with the effective use of anti-angiogenesis agents may change everything – and not only for women with breast cancer? Just imagine!“ [18]

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