

Some Remarks and Deliberations about Methodology, animated by the cohort study “Breast cancer mortality in Copenhagen after introduction of mammography screening” (BMJ 2005)

**by Karlheinz Bayer
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When you face mammography-screening without bias it becomes clear that its methodology cannot solely be used to reduce breast cancer mortality just as the EKG is not able to solely reduce heart mortality rates. The question at issue is whether one can detect more cancers and whether women really derive a benefit from mammography screening more than from regular mammograms or other examinations. The possible screening benefit is highly overrated in interested political and industrial circles, especially in Germany, where the introduction of the national disease management for breast cancer was justified by a non-proven allegation of great numbers of wrong diagnoses in mammography and ultrasounds.

The complexity of the problem is addressed by an article about breast cancer prevention in Copenhagen ¹⁾ and a very critical look into this article in the *Ärztezeitung* of January 27th of 2005 ²⁾. The rate of false positive diagnoses of breast cancers in mammography screenings, according to all known studies, is approximately 10 %. Unfortunately, this means that an equal estimate of 10% false negatives also has to be granted (allowed). On one hand, mammography screening creates unjustified anxieties in every tenth women examined, and on the other hand, every tenth women with cancer is unjustifiedly calmed and sent home without proper treatment.

As with all methods concerning relatively rare diseases - breast cancer affects 0.4 % of women between the ages of 50 to 70 years of age - a statistically relevant reduction of death rates is only possible when there is a virtual 100 % participation in screening. Every method concerning with rare diseases reach their furthestmost benefit statistically only if the participation is next to 100. Voluntary participation by 100 % of the women themselves is neither to be expected, nor is it possible to be approved by political action. These kinds of preventative measures would exceed 170 million Euro each year in Germany, following the *Ärztezeitung*. Moreover, in any case, if a government was willing to extend such funding and if all the women were to participate in screening, the mortality rate would decrease by 25 % at the most. Even the greatest possible use of mammography could not prevent 75 % of those with breast cancer dying from the disease. In absolute numbers, in Copenhagen, 0.4 % of the 40,000 women examined represent about 160 cases of newly detectet cancers. 40 of these women could be saved, an average of 4 women each year. But 120 women or 12 each year would not be saved, even though they were correctly diagnosed. And what is more relevant, 39,840 women needed to be screened to detect 4 additional cases of breast cancer each year. The pros and contras of radiation induced damage shall not even be mentioned here.

These considerations imply that based on numbers alone 25 % of cancer mortality could be avoided through the use of massive mammography screening alone. The past studies, most from Scandinavian countries ³⁻⁹⁾, are able to create a doubt in this assumption. Maybe individual behavior and regional anomalies are statistically as important or even more important than participation in a screening program ^{10,11)}. All further conclusions drawn from the Copenhagen study include unproven, that the follow-up cancer-treatment was successful and

that it was statistically equivalent in all cases. No consideration was given to the idea that differing rates of cancer mortality in different parts of the country might be the result of superior or inferior treatment methods or institutions, as well as where treatment takes place. Maybe there also is a bias in the fundamental and individual agreement or disagreement towards different treatments and institutions. None of those parameters are discussed as part of the reason for a possible and assumed mortality reduction.

There is evidence of biased calculation in the Copenhagen study. The title "...after introducing mammography screening" itself uncovers that an assumption was the foundation of the reasoning.

The authors elaborated in their subsection "statistical analysis" that it was impossible to adjust the data for items such as local differences and time trends from the effects of mammography as determinants for the reduction of breast cancer rates. Therefore they felt compelled to use a correction factor, expecting it to eliminate bias errors arithmetically. This approach is not without pitfalls as it is an attempt to calculate bias which cannot be mathematically assessed.

It is without doubt wrong and unscientific to describe the risk reduction in fractions of percents and call it the "*reduction of the relative risk*"¹²). The authors of the Copenhagen study stress that the numeral shift is within the range of the statistical error, which is pitched at the mark of 5 %, and they declare that the numerals are also spread over a large range. But they seem to forget that the range of errors does not decrease and change its validity if only a so-called relative risk is determined. A relative risk reduction of 25 % is basically (in reality) only a risk reduction of 0.1 %. Undoubtedly 25 % sound much better than 0.1 %, but the risk of including errors and biases exceeds the true and mathematically proven benefit by about fifty times. These kinds of calculations belong to the tricks of prestidigitators¹³).

The Copenhagen study amplifies many biases and errors. One of its chief problems is how the samples are selected. As a whole, every third woman was excluded from the study. The result of having no information about a third of the sample is that the likelihood of having more errors embedded in the data increases. The results of the study being allowed to be transferred to all women or at least to the whole female Danish population can therefore not be supported. One consequence may have been to exclude women in whom breast cancer had already been detected, because it would be obvious to screen them. Nonetheless, the number of these women increases the share of those who certainly have no benefit from mammography screening. So, in sum total, three quarters of the women with cancers, although correctly detected by the mammography screening, plus at least 10 % of all false positive and false negative diagnosis, plus every non-participant and plus every pre-diagnosed breast cancer are comprising the group of the women not benefiting. Also added to this group is the unidentified grey area of all excluded women.

Open to critique also is the manner of building the cohorts . It makes the study artificial.

The cohorts are not really chosen at random. Copenhagen is a) urban and b) as Denmark's capital has a different than the rural samples. The authors of the Copenhagen study were confronted by those differences, which they described as local and time trend differences. These were so severe that they were forced to use a correction factor, but that is not the solution to the problem. Another conundrum is indicated because initially the cancer mortality rate in Copenhagen

was significantly higher than in the rest of Denmark. The question arises as to whether this data is based on an underlying, undetected error or whether it is the results of medical care in the Danish capital being below average. If the second theory is the correct then the reversal of the mortality rates in Copenhagen and the other cohorts may only show that Copenhagen reached the high standard of the rest of the country by initiating mammography screening. And this would also show that high standards in cancer prevention are to be obtained by other means as well.

Thus, if many methods lead so similar results, it is fair to assess their advantages and disadvantages and costs. Mammography, used as a screening tool, is very expensive. In order to show positive effects at all, participation must be close to 100 %. However, the more women participate, the greater the number of false positives and false negatives. Before declaring the mammography screening to be the gold-standard method, one has to consider other methods, such as ultrasound and palpation. It is a fact that the palpation of the mammary glands has caused the largest advance in the fight against cancer; and it is true also, that until today most of the breast cancers are detected by women themselves.

Ultrasounds, especially as practiced by less experienced health care professionals, results in twice as many errors in diagnosis than mammography. But the statistical effects are not as obvious as presumed. Let us assume that mammography detects 90 % of all breast cancers and ultrasound 80 %; and let us then translate these assumption into the statistics underlying the Copenhagen study. Mammography there has prevented 40 out of 160 cases of death, and it has missed 4 more cases of undetected cancer. If it were not mammography but ultrasound screening, the statistics would show 32 cases prevented and 8 cases not detected. Mammography is more effective, but the benefit is very small and far beyond estimated benefits. The question remains whether the high effort and expense of mammography used as a method of screening is really justified, all the more as all the calculations have to be adjusted by the described statistical deficiencies.

What is the best advice for a woman between 50 and 70 years old?

First of all to accept that breast cancer is one of the relatively rare diseases. But it is a cancer with best conditions for detection. Every woman ought to be guided and instructed in the methods of the palpation of the own breast's glands. Ultrasounds shall not be considered as a second rate quality method, because it is unerring enough for a screening method and has no negative collateral effects like induced cancers. Mammography remains a high-quality method, especially when used as indicated and individually, but definitely not as a screening method.

In all cases of pre-existing suspicious results from whatever kind of examination used, the 10 % errors of mammography are less important in both directions. If the result is false positive and more invasive examinations are made, it is justified by the pre-existing suspicion. And if it is false negative, the pre-existing suspicion demands for closely coordinated follow-up examinations in any case. Both aspects differ fundamentally to which we are accustomed in a screening-area.

The reasonable use of all existing methods combined in a logical system is supposed to be more effective than the preference of one method especially when it is used in screening.

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¹¹⁾ Olsen O, Gøtzsche PC. Cochrane review on screening for breast cancer with mammography. **Lancet 2001;358: 1340-2**

¹²⁾ R Kürzi, Evidenzbasierte Mißverständnisse beim Mammakarzinom **Deutsches Ärzteblatt (Heft 36-2004) Jg.101: A2387-2390**

¹²⁾ W Krämer **So lügt man mit Statistik Campus Verlag 1992**