Comment

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Comments on "'Screening' for Breast Cancer: Misguided Research Misinforming Public Policies" by O. S. Miettinen

DOI 10.1515/em-2015-0021

Abstract: From the writings in medical journals and newspapers, for many decades already, it has seemed uncertain whether programs of mammographic screening reduce mortality from breast cancer. Reviewers of the evidence, in the Cochrane Collaboration in particular, have repeatedly concluded that there is no clear evidence supporting such screening. But their results and conclusions have not impressed the advocates who continue to believe that it does reduce mortality from the cancer.

Keywords: screening, breast cancer, case-fatality rate, mortality rate

From the writings in medical journals and newspapers, for many decades already, it has seemed uncertain whether programs of mammographic screening reduce mortality from breast cancer. Reviewers of the evidence, in the Cochrane Collaboration in particular, have repeatedly concluded that there is no clear evidence supporting such screening. But their results and conclusions have not impressed the advocates who continue to believe that it does reduce mortality from the cancer.

Switzerland is illustrative of this uncertainty. Each of the country's cantons ($N = 26$) have, in some respects, a unique health-care system, and each of them can decide whether to recommend screening and pay for it or not. So, e.g., in the Canton of St. Gallen and Vaudoise mammographic screening is officially recommended and the government as well as the health insurers pay for it, while in the Canton of Zurich and Aarau this is not the case. The findings of the Swiss Medical Board published in December 2013 (Swiss Medical Board, 2013), noted in the article at issue here (Miettinen, 2015), have so far had no impact on the screening policies in the various cantons of the country.

Over a decade ago, an article by Miettinen et al. (2002) on the benefit from mammographic screening was published. From it I learned two critically important elementary things: what the centrally-relevant mortality-related measure of this is, and what the evidence about the magnitude of this is from the trials that have repeatedly been reviewed. To me it is astonishing that in the most recent Cochrane review on the topic (Gotzsche and Jorgensen, 2013), the thinking and evidence put forward by Miettinen et al. a decade earlier were left without any comment, as though obviously irrelevant or worthless.

In his article in this issue of *Epidemiologic Methods* (Miettinen, 2015) Prof. Miettinen delineates some of the theoretical fundamentals of community-level screening for a cancer, and of the research to produce the scientific knowledge-base for the quantification of the mortality benefits from programs of such screening. Clearly, the topic is quite complex and understanding of the issues quite demanding.

To facilitate the readers' understanding of his article, I put some questions to him, and he swiftly answered. These were the questions and answers:

Q1: What is "normal science"?

A1: Thomas Kuhn, in his highly influential *The Structure of Scientific Revolutions*, describes the common pattern of progress in science. Problems and their solutions are, for a time, patterned after prevailing paradigms for these. This is "normal science," prone to ultimately come to a "crisis" such that a 'paradigm shift' takes place. I take the prevailing orthodox cancer-screening research to be an eminent example of Kuhnian normal science.

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Q2: What is a "parameter of Nature"?

A2: It is a constant of Nature akin to entities such as the speed of light and Planck's constant. Here it is the proportional reduction in the case-fatality rate of breast cancer resulting from its being diagnosed and treated in a given way (early) relative to another way (late). In the prevailing normal science on "screening" for a cancer, the object of study is taken to be the proportional reduction in mortality from the cancer at issue in a meaning such that its magnitude is (highly) dependent on the study's design parameters, notably the duration of the screening and that of the follow-up. The object in each of these studies has been determined by the methodology of it, while the converse ought to have been the case. Thus, remarkably, quantified in those trials has not been a parameter of Nature but something whose magnitude has a melange of major determinants beyond a parameter of Nature.

Q3: Is the "certain quantitative equivalence" at issue here that between case-fatality rate and mortality rate?

A3: No. Case-fatality rate of a cancer is a mortality rate, just as is a population's incidence density of death from the cancer. These are the mortality concerns regarding a particular species of cancer in clinical medicine and epidemiology (i.e., community medicine), respectively. In my article I explicate the nature of the equivalence of the two treatment-based reductions in these two.

Q4: As the "screening"-based proportional reduction in a population's mortality from a cancer depends on the pattern of the people's histories regarding early clinical care for the cancer, are these histories about whether the cancer actually was diagnosed under the "screening" and treated without delay?

A4: That is the nature of the histories among those who actually have a positive history of the cancer having been diagnosed, among them only. Among the others, the counterpart of this is about whether the cancer would have been thus diagnosed and treated had it occurred.

Q5: Is the policy-relevant effectiveness measure – proportional reduction in mortality – about incidence density of death from the cancer (in a defined stratum of the population in question), and a matter of explanation of the level of mortality in this meaning?

A5: Yes indeed.

Q6: What, exactly, are the survival-optimal histories in this context?

A6: This is a subtle matter. At issue is the explanation in Q5, with specificity to a particular point in time. So in Switzerland, at present, some particular proportion of women 60–80 years of age have an optimal history in respect to early care for breast cancer – as to the cancer's potential early diagnosis and treatment per optimal protocols for these – in reference to the relevant period of the past: the entire period in which the care at issue had bearing on preventing death from the cancer at present, at the very time at issue. The relevant histories may have to do with the time period 5–15 years ago (cf. ref. 5 in my piece), and they are optimal in reference to this period if they imply maximal reduction in the mortality rate à la Q5: insofar as a case of the cancer was going to be diagnosed, it was going to be diagnosed under the "screening" (though not necessarily because of it).

Q7: What is "submission" to early clinical care directed to breast cancer?

A7: To say it in Arabic, it is "islam" to such care. (A Muslim submits to the will of Allah, expressed in the Qur'an). A woman submits to the care at issue here if she "complies" with a doctor's "prescription" of that care – or, in more reasonable medicine, if she is "doctored" (taught by her doctor) about the implications of the care in question and if she, thus informed, elects to "undergo" it. The former meaning is strictly in accord with my esteemed American Heritage Dictionary of the English Language; and here in Quebec, for example, the government is almost ordering women to submit to screening for breast cancer (in regularly repeated personal messages – in the spirit of "doctor's orders").

Q8: Are those concepts of dynamic or open population and cohort or closed population well-established among epidemiologists and epidemiological researchers?

A8: They aren't, alas. Emblematic of this is the amalgamation of this logical duality into the now-common concept of "dynamic cohort," which is a contradiction in terms (akin to "clinical epidemiology"). Logically, a population is either open or closed (for exit), leaving no place for such an amalgam of these two. Among epidemiologists it still isn't generally understood that a dynamic population is one for which membership is defined by a state of being for the duration of that state (at the end of which each member

leaves – exists – the population. Swiss women aged 60–69 years – and alive – constitute a dynamic population, open to exit by losing one of these characteristics). And it still isn't generally understood that a cohort is a population for which entry into membership is defined by an event and in which the membership, once established, lasts forever.

Q9: Is the distinction between source population and study population well-established in etiologic/etiogenetic research?

A9: It isn't, far from it. Even the very concept of such a study commonly tends to remain quite muddled, starting from the misunderstanding that an etiogenetic study is either a "cohort study" or a "case-control study," the earlier terms for which were "prospective study" and "retrospective study," respectively. In my article here I outlined the singular essence of etiogenetic studies, inherently retrospective (per the essence – retrospective – of etiogenesis). For a study on the etiogenesis of death from breast cancer in lack of early diagnosis-and-treatment of the disease, the domain (abstract) could be women aged at least 60 years. The study population naturally would be one of people from this domain, and more specifically it could be one of such persons who also have been long-term residents in a particular geographic region, one in which "screening" for breast cancer has been rather common for 15 years at least. This is a subpopulation (dynamic) of the resident population of that region, the latter serving as the source population for the study. The first-stage case and base series would derive from the source population-time – this source base – while narrowing these series down to instances (person-moments) from the study domain (by gender and age, most notably) and with the requisite history of residence, leads to the actual study series (from the study result's actual referent, the actual study base).

Even upon these clarifications, comprehension of that article of Prof. Miettinen requires mental exertion, except perhaps by those to whom it is directly addressed, namely epidemiological researchers. This is because the topic – one of utmost relevance – is quite complex and hence quite challenging to understand, and it also is because Miettinen's writing here, as could be expected, has its usual dense quality. But he himself, here just as elsewhere, is anything but dense, and the text of that article I find to be not only tidy but also coherent and elegant in its train of thought.

In the first section of his article, Miettinen explains something fundamental that in this context has not been generally appreciated and which, I find, goes a long way to explain the confusion of the various "expert panels," "task forces," and "clinical experts" that have been advising policy makers on screening for a cancer. His fundamental point is that public policies on screening for a cancer, while they are epidemiological – concerned with community medicine – in their motivation, are clinical in their operational, direct implications. Lack of appreciation of the (profound) difference between the epidemiological and clinical concepts of mortality from a cancer is, so I have come to understand, at the root of the confusion.

The confusion is further explained by Miettinen's point about the fundamental nature of the requisite research for the scientific input to the mortality-related estimate on the epidemiological level, which policy makers need. While clinical in nature, the relevant measure is not meaningfully quantified by such "clinical" trials as thus far have been conducted and reviewed for inputs to policies on the screening. And what is more, the relevant measure really is not subject to quantification by any practicable clinical trials; realistic assessment of its magnitude requires epidemiological research, addressing the clinical-level etiology of community-level deaths from the cancer – providing for quantification of the proportional reduction in the cancer's case-fatality rate resulting from its being diagnosed and treated when it still is preclinical in its development (rather than in its already overt stage).

Miettinen, in that article, is proposing a major "paradigm shift" in a very important area of health research; and this journal, I understand and much appreciate, is arranging quite extensive a discussion of that article. I very much hope that the result of this discussion will be not only an end to the confusion now surrounding this topic but also progress in the research relevant not only to policy makers' decisions but also to doctors' teaching the "worried well" about their individual risks of dying from the cancer of their concern and the potential for reduction in these risks by clinical care directed to early stages of this disease.

References

Gotzsche, P. C., and Jorgensen, K. J. (2013). Screening for breast cancer with mammography. Cochrane Database of Systematic Reviews, 6:CD001877–CD001877.

Miettinen, O. S. (2015). 'Screening' for breast cancer: Misguided research misinforming public policies. Epidemiologic Methods, 4(1).

Miettinen, O. S., Henschke, C. I., Pasmantier, M. W., Smith, J. P., Libby, D. M., and Yankelevitz, D. F. (2002). Mammographic screening: No reliable supporting evidence?. Lancet, 359:404–405.

Swiss Medical Board. (2013). Systematisches Mammographie-Screening. Report Dec. 15th, 2013, available at http://www.medical-board.ch/fileadmin/docs/public/mb/Fachberichte/2013-12-15_Bericht_Mammographie_Final_rev.pdf.