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Answers concerning the criticisms raised by Cancer Rose and 3 other collectives (Healthwatch-UK, Gras-Belgium, NoGrazzie-Italy) concerning MyPeBS

1. Lack of a "no screening" arm

MyPeBS is a “comparative effectiveness” study funded by the European Commission in a dynamic that aims to challenge and improve public health practices in Europe.

MyPeBS therefore compares a new individualized screening strategy to the current standard.

Breast cancer screening by mammography is today the standard recognized by the vast majority of health authorities, medical societies, and public health organizations in Western countries, as well as a large number of emerging countries.
The latest European publications remain very clear regarding the benefits of mammographic screening (Zielonke N, Gini A, Jansen EEL, et al. Evidence for reducing cancer-specific mortality due to screening for breast cancer in Europe: A systematic review. Eur J Cancer. 2020 ; 127: 191–206. Doi: 10.1016 / j.ejca.2019.12.010)

All, including us, however acknowledge that the current mammographic screening strategy is imperfect, and that it must be improved.

An arm without screening would be completely non-standard and even unethical: not only does this screening save lives (cft Zielonke et al for updated data), but also a group without screening in Western countries is currently not feasible, because it would mean individual screening based on socio-economic status and not “no screening”.

Overdiagnosis: MyPeBS unfortunately cannot answer all questions. This study will primarily answer the question of the effectiveness of individualized screening based on the personal risk of breast cancer. This is a major question, considering the remaining lethality of this disease, despite 40 years of treatment improvements. It is illusory to think that even the best treatments can solve this problem. There is an urgent need for better screening and better prevention. MyPeBS follows this logic.

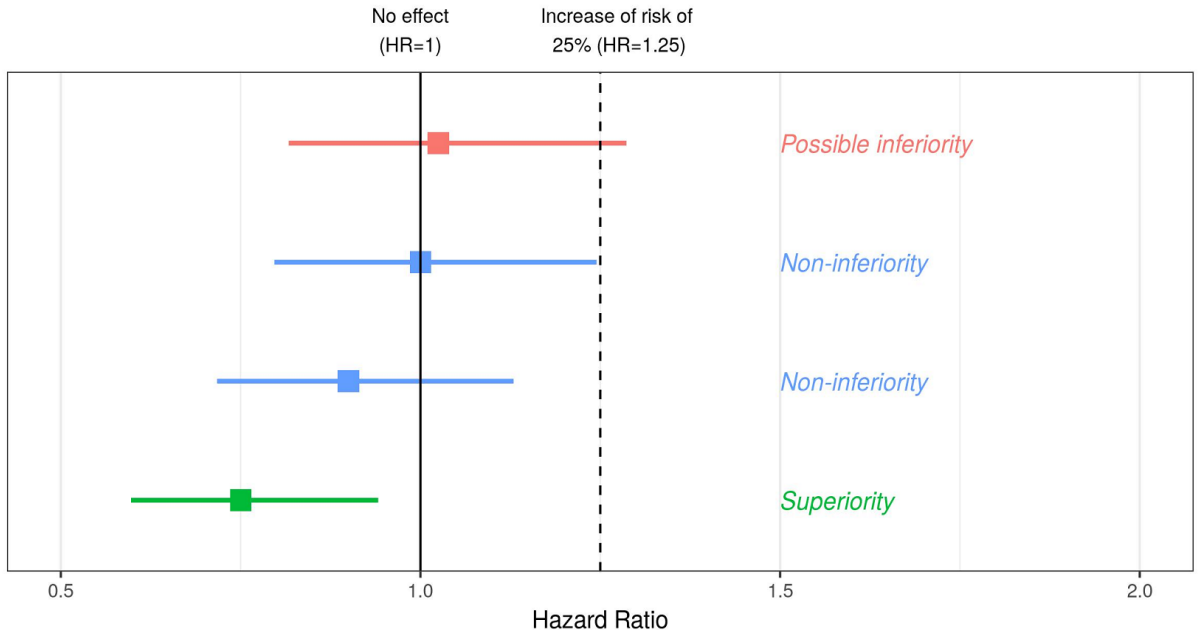
The design of MyPeBS can indeed not help resolving the problem of overdiagnosis in general, but will allow advances on this question, especially among women at low risk. Other studies tackle this problem of overdiagnosis and gradually install a therapeutic de-escalation of these cancers.

2. The chosen non-inferiority methodology

It is heavier and more difficult to conduct a non-inferiority study. However, we chose this design because MyPeBS is partly a “de-escalation” study. Some women will indeed have less mammograms than the current standard. It is therefore essential to demonstrate that this strategy is not

deleterious ("primum non nocere"). We have therefore chosen non-inferiority in the first intention. But this screening strategy could only become a standard if a superiority is demonstrated; superiority is therefore our first secondary objective.

The criticisms formulated on a potential 25% increase in the rates of advanced cancers in the women participating in the study are totally wrong: the statistical plan set the upper bar of the confidence interval to judge non-inferiority at 1.25 (25% increase in the incidence of stage 2 and above cancers). This is the upper bar of a confidence interval!!! Even if a few more cases were observed, this limit would be reached (see the red bar on the diagram below).
Our strong assumption, given the proposed screening strategy, is that we will be in the superiority zone (green), with a decrease in the incidence of stage 2 and higher cancers.



3. Risk levels

The basic question of MyPeBS is to assess whether screening based on the individual risk of breast cancer is at least as, or more effective than a standard screening where only age is taken into account for mammography or not. 25% of breast cancers occur before the age of 50 (and much more in other less advantaged countries) with higher rates of advanced cancer than in older women. Today, for women aged 40 to 50, whether or not a screening mammography is performed depends on the country, region, sometimes the doctor, and very much on the socio-economic level. Our study therefore has a particular interest in the youngest women.

Most of women aged less than 50 (60%) will be classified as low risk, which will allow them to avoid unnecessary mammograms currently being performed! On the contrary, women who really need mammograms should be identified, while many of them are not currently.

The evaluation of the individual risk of breast cancer by clinical risk scores associated with a polymorphism score has today a good level of retrospective validation in large international studies including many recent ones. MyPeBS is one of three major international prospective studies (a Canadian study (PERSPECTIVE) and an American one of the same design as MyPeBS (WISDOM) are in

progress) aiming to validate prospectively a screening based on these software for assessing the individual risk of breast cancer.

4. Information of participants

The women's information form for this study gives them an objective and balanced view of all the data regarding cancer screening. A whole paragraph is dedicated to the disadvantages of screening (page 3), including overdiagnosis which is clearly explained. A glossary contains all the terms where overdiagnosis also appears and is explained again.
Of note, this form has been reviewed and validated by several hundred stakeholders including many doctors and scientists, more than twenty international ethics committees, and several patient associations.

The non-inferiority design of the trial is clearly explained in the informed consent in all countries but UK, where it has been shortened due to local requirements. We will amend this point and thank the collectives for pointing it out.
Potential conflicts of interest of the investigators are never mentioned in informed consent forms. They are however absolutely public and available (among others) on the project's webplatform. We remind all readers that this project is totally academic and independent.

5. Economic issues

MyPeBS cannot do everything, and funding this study is a choice of the European Commission, where this project was one of 6 selected from 200 submitted. The European Commission requests that this project, after analyzing all the results and all the components, provide the EU with recommendations for the future of breast cancer screening in Europe.

Beyond that, a demonstration of the interest of an individual risk assessment of cancer in the general population has, of course, other impacts than personalized screening, and this is a major potential fallout from this project.

MyPeBS is a step in a 4P prevention of breast cancer, in progress and which, we are convinced, will contribute in a major way to reduce this disease's burden.