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NEWS

Health groups criticise EU funded breast cancer screening study as a "missed opportunity"

Ingrid Torjesen

London, UK

Critics have branded an EU funded trial looking at the potential for personalised breast cancer screening "a missed opportunity" for failing to fully evaluate the benefits and harms of screening.

Four groups concerned about women's health and human rights in research—the UK charity Healthwatch, Belgium's Group de Recherche et d'Action pour la Santé, the Italian epidemiologists and scientists of No Grazie, and the French group Cancer Rose—identified problems with the EU funded My Personal Breast Screening (MyPeBS) trial, which aims to show non-inferiority to current national screening. Their criticisms are outlined in a letter in the *Journal International de Médicine*.[1]

MyPeBS involves 85 000 women aged 40 to 70 in Belgium, France, Israel, Italy, and the UK randomised to breast screening according to their personalised risk or to their national standard screening programme.

In the intervention group, women's personal risk is estimated using factors such as breast density, genetic profile, personal and family history, and age. Those deemed low risk will receive a mammogram at the end of the study after four years while average risk women will receive mammograms every two years. Women at high risk, likely to be those with a personal history of the disease, will receive mammograms annually, and very high risk women (such as BRCA 1, BRCA 2, or PALB2 carriers) will receive an annual mammogram plus an annual magnetic resonance imaging scan until age 60. The primary outcome measure will be incidence of stage 2 and higher primary breast cancers after four years.

The groups criticise the trial for assuming that breast screening is beneficial and for failing to compare stratified screening with a "no screening" group.

"MyPeBS represents a missed opportunity to provide the answer, with current data, to the question: Should planned screening tests be continued, be changed to risk based screening, or stopped?" they wrote.

They also raise concerns about the trial's "lax approach to non-inferiority" and point out that the two groups will be statistically compared with a threshold of "non-inferiority" arbitrarily set at 25%.

They go on to explain, "This comparison is obscure and conceals disconcerting information. According to the sponsors of MyPeBS, in the standard screening group, 480 new cases of severe tumours per 100 000 women are expected to be diagnosed. If the same rate does not exceed 600 per 100 000 women in the new personalised risk based group, both groups will be declared equivalent. This means that if the rate of serious cancers is increased by less than 25% (for example 18% or 24%), then the study will be considered a success and the researchers conclude that the new screening methods are 'as efficient' as the former ones. In other words, +25% of serious cancers equals zero."

Karsten Juhl Jørgensen, acting director of the Nordic Cochrane Centre and an author of the Cochrane review on breast screening, said that screening trial data were old, women below the screening age had experienced far greater reductions in breast cancer mortality than those invited, and new treatments have a far more important role than screening.

Jørgensen told *The BMJ*, "We desperately need a new trial of screening that can inform us about its role today. Whether personal screening strategies can optimise benefits and reduce harms is an important and relevant question. But screening trials need to be done extremely well to be informative, part of which means not relying on surrogate outcomes such as stage at detection, which we know can be misleading. The design of the new trial seems to raise more ethical questions than it answers."

Suzette Delaloge, lead investigator of MyPeBS, said, "The basis of this study is to demonstrate whether risk based screening is better, which has never been demonstrated in a prospective study."

While there were clear benefits from breast cancer screening in terms of reduced breast cancer specific mortality, she said, "we need to improve on what currently exists, but we cannot have an arm in which screening would disappear. That would not be ethical at all."

The study is not advocating four yearly mammography for low risk women, all women were receiving a mammography at the end of the four year follow-up period because that is how long the study is funded, Delaloge said. Longer intervals might be appropriate, she added.

It was difficult to design a study aiming to target screening at women who most need it and gain approval from some ethics committees, which were "very frightened" about decreasing the frequency of mammograms in low risk women, she explained. For example, the French ethics committee insisted that yearly breast cancer awareness reminders should be sent to all such women, and this has been added to the study protocol.

Around 60% of women aged 40 to 50 and 25% of women aged 50 to 60 are expected to be classified low risk, she said, and will receive less screening than they do currently in most

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countries, but not in the UK where the national screening programme does not start until 50.

Delaloge pointed out that the investigators expected to see a decline in cancer cases, not a 25% increase, as "that would be totally crazy." She said that the non-inferiority figure quoted was actually the top of the confidence interval for non-inferiority, which was wide because of the size of the study.

1 Group de Recherche et d'Action pour le Santé, No Grazie, Cancer Rose, HealthWatch. Interrogations sur l'étude MyPEBS pour un dépistage personalisé du cancer du sein. *J Intern Med* 2020. www.jim.fr/e-docs/interrogations_sur_l_etude_mypebs_pour_un_depistage_personnalise_du_cancer_du_sein_181909/document_edito.phtml.