The review of randomization in the Canadian National Breast Screening Study

Editorial

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What does the verdict mean for clinicians?

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Abstract

WHAT IS THE PRACTISING CLINICIAN to make of the review by Drs. John C. Bailar III and Brian MacMahon (see pages 193 to 199 of this issue) of the randomization procedure used in the Canadian National Breast Screening Study? Their conclusion that any flaws in randomization would not have affected the published data is reassuring. Nevertheless, the review has not resolved the controversy surrounding the recommendations for screening mammography for women aged 40–49. Recommendations must be based on strong evidence that the benefits of population-based testing outweigh the harms. The absence of such evidence for women aged 40–49 should not, however, preclude the use of mammography as a diagnostic test for women in their 40s whose clinical signs require follow-up. Mammography could also be considered for women whose family history or other factors suggest an increased risk for breast cancer, provided that the limitations and potential disadvantages of testing are explained.

Résumé

QUE DOIVENT PENSER LES CLINICIENS ACTIFS de l'examen effectué par les D[rs] John C. Bailar III et Brian MacMahon (voir pages 193 à 199 du présent numéro) de la méthode de randomisation utilisée dans le cadre de l'étude nationale sur le dépistage du cancer du sein au Canada? Les auteurs concluent qu'aucune lacune de la randomisation n'aurait modifié les données publiées, ce qui est rassurant. L'éxamen n'a néanmoins pas dissipé la controverse relative aux recommandations pour la mammographie de dépistage chez les femmes âgées de 40 à 49 ans. Les recommandations doivent être fondées sur des données probantes solides démontrant que les avantages d'un dépistage généralisé l'emportent sur les inconvénients. L'absence de telles données probantes chez les femmes âgées de 40 à 49 ans ne devrait toutefois pas empêcher d'utiliser la mammographie comme test de diagnostic chez les femmes dans la quarantaine dont il faut suivre les signes cliniques. On pourrait aussi envisager la mammographie chez les femmes dont les antécédents familiaux ou d'autres facteurs indiquent un risque accru de cancer du sein, à condition toutefois de leur expliquer les limites et les inconvénients possibles des tests.

For years people have debated the potential of screening mammography to reduce the considerable death toll from breast cancer. For women aged 50–69 years, at least, a firm consensus has been reached; most groups now recommend population-based screening.[1,2] However, there is still a lack of consensus on whether screening women aged 40–49 is effective.[1–3]

The Canadian National Breast Screening Study (NBSS) was designed, in part, to contribute evidence that could help settle this debate. As part of the study, women in their 40s were enrolled and randomly assigned to receive either annual mammography and physical examination for 5 years or an initial physical examination followed by no specific screening intervention. The first follow-up data, published in 1992, failed to detect any advantage for screening mammography in

this age group.[4] In fact, the point estimate showed a non-statistically significant detrimental effect.

The NBSS results generated considerable controversy. One persistent criticism related to the study's randomization procedure. The review by Drs. John C. Bailar III and Brian MacMahon (see pages 193 to 199 of this issue) was carried out to provide an independent assessment of the randomization issues of the study. Bailar and MacMahon did not find any substantial cause for concern. Furthermore, although a small number of names in the "allocation books" were found to have been altered, Bailar and MacMahon conclude that these would have had a minimal effect on the data published in 1992.

No doubt these findings are reassuring. The open and positive approach to dealing with the persistent criticisms of the NBSS, which is demonstrated by the involvement of such a review team, is to be applauded. By effectively ruling out the possibility that mindful alteration of the randomization could have affected the results, the review team's report frees us to view the data as they stand.

What, then, is a practising clinician to make of Bailar and MacMahon's report? Does it change our evaluation of the overall recommendations for screening with mammography among women in their 40s?

The review does not, of course, mean that the NBSS was a study perfectly designed to answer the controversial question on its own. In fact, in clinical and epidemiologic research, individual studies are rarely able to accomplish this feat because of the complexity of studying individuals who are essentially healthy members of a large population. Rather, it means that the NBSS can be evaluated, along with the other population-based trials of screening mammography, with the same considerations for potential confounding and biases that exist in most studies.

These types of intervention studies should be examined as a group. The NBSS was, no doubt, an important study addressing the issue of screening mammography. However, it was not the only one to provide evidence on screening mammography among women in their 40s, and its results must be weighed along with those from the several other studies that have been performed. In fact, another consensus conference is to be held later this month, under the auspices of the US National Institutes of Health, to review the data from the several studies that have taken place world wide.

It is impossible, of course, to predict whether these new data to be reviewed at the conference will result in any change in recommendations. However, there are some central points that need to be borne in mind when considering the current recommendations.

First, although there is a general consensus that screening mammography is beneficial among women 50–69 years old, substantial numbers of these women are not being screened.[5] It is critical for clinicians and public health professionals to ensure that these women are reached and appropriately screened if the population-based rate of death from breast cancer is to be lowered.

Second, the recommendations are relevant only to the use of mammography as a screening tool. They were never intended to limit the use of mammography as a diagnostic test in women with clinical signs requiring follow-up. Thus, women under the age of 50 who present with worrisome clinical signs should not be denied mammography based on the screening recommendations in their age group.

Third, the thrust of population-based recommendations is to ensure that the evidence is strong enough in order to actively seek out women in the target population who are asymptomatic and believe themselves to be well and to advise them that this additional test would benefit them. The quality of evidence required to make such recommendations must be very high, because the potential for doing harm always exists and because most people who undergo screening tests will have normal results. This means that a large number of people will be exposed to the test with no clinical benefit to themselves. Others will have an abnormal result that will require follow-up, potentially of an invasive nature; if the follow-up tests eventually fail to reveal any condition for which early intervention is helpful, there is a potential for actual detriment from screening tests. Thus, in order to live up to our ideal of *primum non nocere*, one must be sure that the benefit outweighs the risks. We have yet to reach consensus that this is true for screening mammography among women in their 40s.

Nevertheless, women in their 40s who are at increased risk for breast cancer, either because of a family history or other risk factors, may ask their physicians about screening mammography. The evidence on the benefits of such testing in this subgroup is limited. What advice can be given to these women? On the one hand, if the possible reasons for a reduced benefit of screening mammography for women in this age group include decreased sensitivity of the test or different biologic characteristics of the tumours,[2] then these conditions are likely also to apply to women in their 40s with a family history of breast cancer. Thus, one could question whether there was any theoretical advantage to screening women under 50 who are at increased risk. On the other hand, if these women are at increased risk, even marginal theoretical benefits of such tests may be sufficient for them to request testing.

When discussing screening mammography, clinicians and those patients in their 40s at an elevated risk for breast cancer need to arrive at a clear understanding of the potential benefits and harms of this test to the individual woman. Whether the upcoming consensus conference

will provide further information that may make this discussion simpler remains to be seen. In the meantime, the results of the review by Bailar and MacMahon indicate that the NBSS can be considered, along with the other controlled trials, as an important contribution to the debate about screening mammography.

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