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LETTER – BREAST ONCOLOGY

Treatment Intensity Differences According to Participation in a Population Screening Program

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TO THE EDITORS:

We thank Dr. Lannin for his editorial interest[1] in our paper 'Treatment Intensity Differences After Early-Stage Breast Cancer (ESBC) Diagnosis Depending on Participation in a Screening Program'.[2] We believe that much of his analysis stems from a misunderstanding of the nature of our study and a number of questionable assumptions.

Our study assesses differences in breast cancer pathology and treatment according to screening status, combining outcomes for screen-detected and interval cancers among recent screening participants. We agree that length of time bias (screening detecting more favorable cancers) arises when screen-detected cancers are compared with all other cancers in the community. This bias is carefully minimized in this study by combining interval cancers and screen-detected cancers in the 'active screeners' group, and then excluding likely overdiagnosed screen-detected cancers from our analysis.

Dr. Lannin's re-analysis of our published figures purports to show that, without overdiagnosis, the extent of treatment would be the same in our two cohorts. This analysis is based on several questionable assumptions.

First, Dr. Lannin's calculations assume that adequate adjustment for overdiagnosis would reduce the proportion of invasive cancer rates among our study group's active screeners to match Australia's national participation rates of 55%.[3] In fact, active screeners are overrepresented in our treatment service because our hospital also manages a major BreastScreen service. While we should have acknowledged this in the manuscript, it does not affect the validity or generalizability of our analysis, which is to compare two groups within our service. It does however mean that Dr. Lannin's analysis (Table 1 in his article)[1] is overadjusted for overdiagnosis.

Second, while Dr. Lannin's estimated overdiagnosis rates of 32–37%[4] are higher than most previously published estimates,[5] our assumed overdiagnosis rate (22%) exceeds estimates from the independent UK review (19%)[6] and a recent Australian study (12%).[7] Our rate was estimated by conservatively assuming all screen-detected ductal carcinomas in situ (DCIS), and all screen-detected grade 1, < 10 mm, node-negative (except triple-negative breast cancer or human epidermal growth factor receptor 2-positive) invasive cancers in our study cohort were overdiagnosed. To achieve Dr. Lannin's rate (32%) would require inclusion of a total of 116 invasive screen-detected cancers, which is unreasonable given this would need to include, for example, all screen-detected grade 1 cancers irrespective of receptor or nodal status, and many grade 2 cancers.

On this basis, the tables included in Dr. Lannin's editorial are misleading, and his conclusion that treatment would not differ in the absence of overdiagnosis is incorrect.

One common assumption about the potential benefits and harms is that the biology of a breast cancer is set from the start and does not change. By this assumption, any low-grade cancer with a favorable phenotype is considered destined to become only a larger low-grade cancer with a favorable phenotype if not identified by a screening program and removed. Dr. Lannin explicitly states this several times, and refers to editorials making that assumption, without presenting any direct evidence for it. Emerging evidence shows that there is considerable heterogeneity within tumors.[8] It is easily conceivable that tumors evolve as higher grade, and more rapidly growing clones

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dominate—it is unsafe to assume that screen detectable but impalpable low-grade cancer will reliably remain so if left untreated.

Our study presented a reasonable adjustment for overdiagnosis that possibly erred toward overadjustment. For example, in our adjusted analysis we excluded all screen-detected DCIS, regardless of hormone receptor status. In truth, the detection and treatment of DCIS, while causing some overdiagnosis and overtreatment, must also reduce subsequent invasive cancer diagnoses to some degree.[9] We maintain that treatment is less intensive, on average, for active screeners, even after adjustment for overdiagnosis.

The debate around the value of population-based breast cancer screening is important, and peer-reviewed research that rigorously and objectively assesses overdiagnosis and subsequent overtreatment should be encouraged and supported. Dr. Bedrosian's editorial[10] regarding the need for screening tailored to individual risk is timely and trials of personalized screening, such as WISDOM, are underway or in development in the US and elsewhere.[11] We respectfully suggest that this is where intellectual energy should be spent.

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