Re: Role of Detection Method in Predicting Breast Cancer Survival: Analysis of Randomized Screening Trials

Method of detection is an independent prognostic factor for breast cancer survival, according to the analysis of the Health Insurance Plan (HIP) and Canadian trials presented by Shen et al. (1); i.e., there is an increased likelihood that mammography screening is detecting slowly growing, indolent tumors, compared with aggressive tumors diagnosed in clinical settings. However, the authors did not perform a survival analysis by intention to treat, with or without adjustment for tumor characteristics; this analysis would have provided an estimate corrected by selection that resulted from nonattendance. In screening population-based trials, but not in the Canadian trials that used volunteers, nonattendance is a well-known, potential indicator of selection bias for breast cancer mortality. Survival rates of patients with interval breast cancers vary among studies and are very dependent on the working definition of this kind of tumor.

Nonrespondent patients with breast cancer had worse survival than the comparison or control group in U.K. trial (2) and in the Two-County study (TCS) (3). Only about one-third of the survival benefit for patients with screen-detected breast cancer was explained by adjustment for tumor characteristics (in the U.K. trial by size and lymph node status and in the TCS also by tumor grade). Similar data have been published for an observational study of service screening in the Netherlands (4).

In the evaluation of service screening in Italy in which the registry-based records of 4444 patients with breast cancer were studied (5), we performed an intention-to-treat analysis between invited and noninvited patients. The hazard ratio (HR) of dying from breast cancer increased, after adjustment for tumor size, lymph node status, and grade, from 0.73 (95% confidence interval [CI] = 0.61 to 0.87) to 1.03 (95% CI = 0.85 to 1.24) (Table 1). In a parallel analysis by diagnostic modality, we obtained a higher hazard ratio for nonrespondents of 1.23 (95% CI = 0.98 to 1.55) than for noninvited women, after adjustment for tumor characteristics.

Baker et al. (6) suggested a causal estimate of the screening effect in which never-attenders have the same probability of cancer death in the screened and control groups; i.e., the probability of dying should be the same in the screened group (where it is observed) and in the control group (where it can be estimated). In contrast, attenders would have a higher probability of surviving than an average patient in the control group, also in the absence of the intervention. If the survival rate for nonattenders is worse than the average survival rate of the control groups, then the hazard ratio for screen-detected breast cancers compared with that of the causally corrected reference is moving toward unity.

Why should we study a subgroup with a different probability of dying that is not entirely explained by tumor characteristics but is related to compliance to the screening invitation? Important reasons for compliance to screening may include a differential opportunity for effective treatment and/or differential levels of comorbidity (4) or of socioeconomic status (7). Nonrespondents may have less access to treatment or may tend to seek treatment less promptly. In some instances, patients with screen-detected breast cancers might have been preferentially referred for higher quality treatment or more prompt diagnosis in the absence of screening. These factors are only partially related to the stage of the disease at presentation.

In conclusion, other, more recent randomized trials and observational screening trials reported results that differ from the

<table>
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<tr>
<th>Method of detection</th>
<th>HR (95% CI)</th>
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<tbody>
<tr>
<td></td>
<td>Model 1</td>
</tr>
<tr>
<td>All invited</td>
<td>0.73 (0.61 to 0.87)</td>
</tr>
<tr>
<td>Screen detected (prevalent)</td>
<td>0.30 (0.21 to 0.41)</td>
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<tr>
<td>Screen detected (repeated)</td>
<td>0.34 (0.22 to 0.53)</td>
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<tr>
<td>Clinical detected in screened group</td>
<td>1.32 (0.99 to 1.76)</td>
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<tr>
<td>Never-responders</td>
<td>1.60 (0.27 to 2.01)</td>
</tr>
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</table>

*Reference category was patients who were not yet invited with T2+ tumors, lymph node–positive status, and grade 3 tumors. All models were adjusted for city and age. Models 3 and 4 were adjusted for the number of patients studied, lymph node status (pN), and tumor grade. HR, hazard ratio; CI = confidence interval.
HIP and Canadian trials. The survival benefit associated with screen-detected breast cancers, if any, might be better estimated by 1) analyzing recent screening studies, 2) adopting an intention-to-treat analysis and comparing the unadjusted and adjusted (for prognostic covariates) estimates of probability of survival, and 3) using a model in which the selection related to nonattendance (or clinical detection) is taken into account when the estimate of the benefit is calculated.

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REFERENCES


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RESPONSE

We thank Paci et al. (1) for their correspondence. They suggest that we should have performed a survival analysis by intention to treat with or without adjustment for tumor characteristics. Intention-to-treat analyses are critical in assessing treatment (or screening) benefit in randomized trials. This assessment was not our focus. Rather, in Shen et al. (2), we were interested in comparing the cancer-specific survival distributions by actual method of detection. There were no “nonattenders” in the Canadian National Breast Cancer Screening Studies (CNBSS) trials because all women in the screening groups had at least one mammogram; subsequent cancers were either interval cancers or detected at a later screening examination. There were 81 cancers diagnosed among the 9931 nonattenders in the screening group in the Health Insurance Plan (HIP) trial (3). Such tumors were not diagnosed by screening examinations, and they were neither interval nor incident cancers. They were properly included in the screening group for any assessment of the benefits of screening. However, an analysis that was based on an intention to treat that compared the survival distributions between breast cancers in the screening group including nonattenders and those in the control group was not relevant for addressing our question, whether or not there was an adjustment for tumor characteristics. It is unclear what kind of intention-to-treat analysis Paci et al. would consider for these cases.

For the HIP trial, we summarized the tumor characteristics of nonattenders and control subjects separately in our Table 1 (2). Also, as indicated in Shen et al., we compared the cancer-specific survival distribution of the 81 nonattenders with that of the 301 control subjects and found no statistically significant difference. The calculations of Paci et al. in Table 1 in their study are actually quite consistent with this observation. Their 95% confidence intervals for the hazard ratio of disease-specific survival between never-responders (i.e., the same group that we called nonattenders in Shen et al.) and the noninvited women (i.e., control group) include 1.00 with (model 4) or without (model 2) adjustment for tumor characteristics. Even though the estimated hazard ratio is somewhat higher for never-responders, cancer-specific survival of “never-responders” in the invited group was not statistically significantly different from that of patients in the noninvited group. Regarding Table 1 of Paci et al., the “all invited” results are irrelevant for the question we addressed in our study (2). We were interested in how a woman’s cancer was actually detected and not how it might have been detected.

Paci et al. suggest that we should have analyzed more recent screening trials. We would like to have analyzed all eight of the randomized screening trials, but we had access to data from only these three trials. Actually, the two CNBSS trials were among the more recent of the randomized trials.

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