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Editorial Comment

The Nottingham Prognostic Index - from relative to absolute risk prediction

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Prognostic indices, such as the TNM system, the St. Gallen criteria and the Nottingham Prognostic Index, can integrate information from several validated prognostic factors and assign patients to different prognostic categories. However, these prognostic models do not provide estimates for a survival probability or absolute risk. The demand exists for tools that not only provide prognostic classification, but also give quantitative probabilities of survival.[1,2]

In the current issue of the *European Journal of Cancer*, Blamey et al. attempt to answer this demand by describing an approach for obtaining quantitative and disease-specific survival estimates for women with breast cancer.[3] The estimates are based on a series of patients diagnosed in 1990–99 ($n = 2261$) in a single institution in the UK who fulfil certain inclusion criteria (age 70 years or less and tumour size less than 5 cm). Survival probabilities are 'extracted' from this cohort by application of the Nottingham Prognostic Index (NPI), which accounts for tumour size, lymph node status and histologic grade.

The NPI is originally derived from a multivariate regression analysis and was first presented in the early 1980s by the same honoured research group.[4] In their current paper, Blamey et al., however, did not choose to fit a new regression model with the more recent data as a baseline. Instead, the authors calculate 10 year survival estimates for ten NPI subgroups in the 1990–99 cohort according to the original regression formula and determine a curve of best fit across the range of estimates. Accordingly they propose that a 10 year survival probability for an individual could be derived for any index value of the NPI by interpolation on this curve.

The proposal for a more 'individualised' and quantitative prediction of outcome is appealing and without doubt important in making treatment decisions. It can also be seen as part of a more general trend within medicine, with desires for personalised and absolute, in addition to relative, risk assessments.[5,6] Tools that provide quantitative prognostic estimates for breast cancer patients range from regression models and nomograms to projected outcomes based on subgroup analyses of large databases.[7–10] One of the models, based on NPI factors plus hormone receptor status, age and comorbidity, also provides survival estimates conditioned on action. This means that baseline probabilities can be adjusted for according to the expected effects of different adjuvant treatment strategies.[8]

Obviously, there are concerns and issues that need to be addressed with the current approach for quantitative survival

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estimation. In an accompanying paper Blamey et al. report a comparison of the survival estimates for the 1990–99 cohort with survival figures for a cohort from the same institution diagnosed in 1980–86.[11] An impressive survival improvement – an average 56% relative risk reduction in 1990–99 as compared to 1980–86 – is described and shown to be consistent across all subgroups of the NPI. This is good news, but at the same time there is a contradiction between proposing quantitative estimates in one article and describing a change in survival with time in the other. On the other hand, recent studies have also shown quantitative survival estimates to be generalisable and transportable across populations if comparable time periods are analysed.[12,13] However, estimates based on data from the early 1990s are probably not well calibrated for patients today. As an example, the increased use of targeted therapies, such as hormonal therapy and anti-HER2-selective antibodies, should result in improved survival in hormone receptor positive as well as HER2 positive patients. Therefore, regular updates of the estimates would be required as new data become available. These data should preferably come from diverse institutions and different countries and include information on treatments. The pooling of data could also provide more accurate estimates for rare subgroups, given that assessment of the prognostic factors can be standardised to an acceptable level.

Blamey et al. speculate that the improved survival over time must come from improved case management, since the distribution of patients into the NPI subgroups has remained essentially the same since the 1980s. However, there are also other possible explanations for the improved survival seen in all NPI groups, apart from better therapies. Improvement may also be explained by a more accurate lymph node staging in combination with more patients being detected within mammography screening. Patients classified as node negative in the 1980s, but actually being node positive, may have 'stage migrated' to a higher NPI category in the 1990s. In accordance with the Will Rogers phenomenon, moving these patients from a better NPI group to a worse will cause survival rates to rise in each group.[14] This should, on the other hand, be detected as a decreased proportion of patients in the lower NPI groups. However, such a decrease was not seen and may in turn be due to the lower NPI groups being populated with patients detected within mammography screening. Many of the screen-detected patients have a more favourable survival than those detected outside screening, even after adjustment for the NPI factors, and may therefore improve the survival within the NPI groups.[15]

The described quantitative prognostic formula provides impressive survival discrimination, definitely comparable to many of the best genomic classifiers. Ten-year breast cancer-specific survival ranges from 96% for the 'excellent prognosis group' (node negative patients, with a highly differentiated tumour up to 2 cm in diameter) to 38% for the 'very poor prognosis group' (more than three positive nodes, poorly differentiated tumour larger than 2.5 cm in diameter). This corresponds to a relative risk of at least 16 between the lowest and highest NPI groups at 10 years. With such a high discrimination, it would be justified to consider the NPI as a benchmark model for breast cancer prognosis. Genomic classifiers and other models intended to provide prognostic assessments should include NPI factors, as a minimum.[16] Except for predictive, therapy-specific models, molecular and other prognostic classifiers would have to add significant information to the NPI to be considered clinically important. It is also evident that in a subgroup of patients, such as the 'excellent prognosis group' of the NPI, it may not be easy to find additional prognostic or predictive discriminators. With regard to the treatment decision making, a maximum survival benefit of a few percentage points in the EPG group has to be carefully weighed against acute, but also chronic and late-onset toxicities.[17] Indeed, high quality studies evaluating the effectiveness of using prognostic information were found to be scarce in a recent technology assessment report.[18]

At the recent 10th anniversary St. Gallen conference on Primary Therapy of Early Breast Cancer, one of the keynote speakers declared that a new era of risk assessment had begun in 2005. This new era entails the moving away from crude measures of tumour burden towards the molecular assessment of tumour biology. Targeted therapy and tumour responsiveness were the main keywords at the meeting. Central to the new era is the hypothesis that genomic risk assessment will outperform clinical-pathological risk assessment. However, so far little evidence is available that would support genomic information as being substantially more accurate in the prediction of survival. Recently published validation studies of genomic predictors report only modest prognostic discrimination.[16,19] Even more unlikely is a situation where clinical-pathological factors could be substituted for entirely with gene-level data. Within the foreseeable future, accurate prognostic models will have to rely on a combination of indicators for the extent of disease, tumour morphology and molecular information.

Conflict of interest statement

None declared.

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