Active Surveillance for Ductal Carcinoma in Situ: Shining Light Into the Modeling Abyss

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The ductal carcinoma in situ (DCIS) conundrum is one of the most urgent and confounding problems in the management of breast cancer. While there is a sense that many early breast cancers—particularly DCIS tumors—are overdiagnosed and can safely avoid treatment, the comparative outcomes of active surveillance are unknown. Absence of primary data on the comparative outcomes of DCIS cases treated or undergoing active surveillance makes evidence-based decision-making about how best to manage these cases difficult if not impossible. Unfortunately, we don’t know the natural history of these cases and how much outcomes might change under delayed treatment.

Modeling is increasingly being used when gaps in the evidence exist. Ryser et al.’s “computational risk analysis” (1) is essentially a decision analysis based on a model of disease natural history, including progression from DCIS to invasive cancer, and through clinical stages of disease. While several models of DCIS incidence and progression (2,3) have been published in the last decade, Ryser et al. go further and project disease-specific mortality outcomes expected under active surveillance vs immediate treatment. The clinical usefulness of their study, however, hinges on their model.

Models can be complex and, in many cases, may raise more questions than they answer. Very often, as is the case here, the models rely on unobservable events in disease progression. While this may lead some to throw their hands up and claim that this alone makes models clinically useless (4), valid methods for learning about latent events in disease progression have been rigorously investigated and shown to be highly useful in clinical settings. For example, the breast cancer models of Zelen and colleagues (5–8) showed how to tease out information about the preclinical duration of invasive breast cancer from screening cohorts, and HIV models (9,10) yielded valuable information that enabled back-calculation of HIV incidence and projections of the future size of the AIDS epidemic.

In modeling different management approaches for DCIS, a most critical quantity is the rate of progression from in situ to invasive disease. If we know this, and we have a reliable estimate of the sensitivity of surveillance testing to detect invasive progression, we can calculate how active surveillance will impact the stage distribution at the time of treatment, and, from there, project the consequences for survival.

As described in an extensive appendix provided alongside the manuscript, Ryser et al. (1) chose to use empirical progression frequencies in five studies of women not treated for DCIS to ground their natural history model. The clinical usefulness of their study, therefore, rests largely on whether the progression risk estimated on the basis of these studies is accurate and generalizable. Certainly, if a representative cohort of untreated DCIS cases were to be closely monitored over the long term, the empirical frequency of progression to invasive disease could be highly informative about disease natural history. Unfortunately, cohorts of untreated DCIS cases are rare and selective. Ryser et al. (1) seem to recognize this and use a wide uncertainty interval around their point estimates of invasive progression. The clinical value of the study is almost certainly impacted by the lack of more authoritative data on the natural history of DCIS progression.

In the absence of such data, a few studies have used incidence patterns and stage distributions from screening cohorts to learn about the natural history of DCIS. However, the heterogeneous nature of breast cancer is a challenge. Invasive tumors may or may not have an in situ phase, and in situ cases may or may not become invasive. A relatively higher frequency of DCIS under screening may result from a large fraction of de novo breast cancers passing through a short in situ phase or a relatively smaller fraction transitioning through a longer in situ phase. Uncertainty about screening test performance characteristics can make it even harder to learn about the underlying natural history from screening studies. Indeed, Ryser et al. (1) note that their results depend critically on the sensitivity by...
which the original diagnostic test distinguished invasive disease from DCIS. When the key quantities of interest cannot be uniquely estimated by the available data, we say that the model is not identifiable. This means that different possible pathways of disease progression are consistent with the same observed data.

Studies that use screening cohort data to inform about DCIS frequently make assumptions to simplify the analytic model and avoid the identifiability problem. These might include fixing screening test sensitivities at prespecified values (3) or assuming that all cases must pass through an in situ phase (2). It is often difficult to judge whether the simplifications are acceptable from a clinical perspective and whether the resulting model is indeed identifiable. It is up to modelers to demonstrate that they have succeeded in devising a clinically reasonable, identifiable model, and it is up to readers of modeling studies to convince themselves that this is indeed the case. Screening cohorts with lengthy follow-up, large numbers of interval cases, and complete information on disease stage at diagnosis may mitigate the nonidentifiability problem in some settings, but they cannot, in general, eliminate it. It is unlikely that we will be able to learn everything we would like about the pathways of DCIS progression from screening cohort data.

In conclusion, while the study by Ryser et al. (1) may not justify an immediate change in clinical practice, it advances our understanding of what we need to know to project the outcomes of different management options for DCIS. The clinical value of future modeling studies will depend on the availability of relevant and representative empirical data and the continued development of high-quality models that assure reliable estimates of disease progression risks. Ideal datasets will include representative cohorts of untreated or minimally treated DCIS cases monitored for progression to invasive disease. The UK’s LORIS trial (11), which will randomly assign low-risk DCIS case patients to surgery or annual mammography for 10 years, should provide useful information about natural history for these cases. Ultimately, a change in clinical practice will require the convergence of a critical mass of scientific evidence, and this will need to include a solid understanding of the natural history of DCIS and the diagnostic properties of the tests to detect and monitor it.

**Funding**

This work was supported by R01 CA192402 from the National Cancer Institute.

**Note**

The authors have no conflicts of interest to declare.

**References**