Wherein the authors attempt to minimize the confusion generated by their study “Breast cancer mortality after a diagnosis of ductal carcinoma in situ” by several commentators who disagree with them and a few who don’t: a qualitative study

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Various parties might wish to measure the impact of a given paper for the purpose of assigning merit to an author or institution. The value of a scientific publication can be measured in several ways. The gross number of citations a paper receives (provided they are not self-citations) is the traditional indicator of the level of interest in the paper. More recently adopted measures of impact include the extent of press coverage that a paper receives and the number of times that it is downloaded. Each of those metrics helps in gauging the importance of a particular work of science, but a paper can also be cited for reasons that are not laudatory. For example, the authors of a letter to the editor might disagree with the findings and want to propose an alternative interpretation of the data or to point to faults in the methods. Others might seek to piggyback their own (hitherto unpublished) observations into the journal, and they find in the letters-to-the-editor section a convenient platform to do so.

If other authors confirm an original report with a second original report, they see value in the original article. However, in some cases, authors might cite the original paper selectively to validate their own opinion or their own scientific approach or a favoured clinical position. Often, two authors will cite the same paper at cross purposes, with each author selecting from the paper matter that is affirming and subduing matter that is contradictory. Some might misinterpret the data entirely. The latter group poses a particular danger if they cite the original paper despite never having read it (that is, they have read only the secondary literature or the press coverage). Given the vagaries of public opinion and the judgment of our peers, we question how much we, as authors and as adjudicators, should weigh the number of citations or downloads that a paper receives as a measure of its impact.

Precis of Our Main Findings

In 2015, we published a paper1 on the natural history of breast cancer, in which we proposed that ductal carcinoma in situ (dcis) was not a precursor lesion (as was generally believed), but was a bona fide cancer in its own right with the ability to metastasize (summarized shortly). In the weeks after publication of that work in August 2015, we were delighted to find that the paper received much press coverage; however, after reading the articles, we were dismayed to discover how few of the journalists interpreted the data as we did. In fact, it was nearly universally reported that dcis is a precursor that lacks the potential for spread and is not a cancer—which is not what we meant at all. The paper was covered, but not for the message that we wished to convey. To satisfy our curiosity, we systematically reviewed the press coverage and citations that our paper received in the 28 months after its publication for the purpose of conducting a qualitative analysis of the citation process.

In the dcis study, we followed—for local invasive recurrences and for death from breast cancer—women with dcis who were treated with mastectomy, with lumpectomy alone, and with lumpectomy and radiotherapy. There was no untreated group. The conclusion that dcis is an invasive cancer and not a precursor follows logically from these observations (the “main findings”):

- The 20-year actuarial breast cancer–specific mortality rate after dcis was 3.3%.
- Compared with their counterparts who did not develop ipsilateral invasive recurrence, women with dcis who did develop such a recurrence were 18.1 times more likely to die of breast cancer.
- Prevention of ipsilateral invasive breast cancer (with radiotherapy or with mastectomy) did not prevent death from breast cancer.
- Approximately half the dcis patients who died of breast cancer did not have an invasive cancer recorded before their death from breast cancer.

Based on those observations, we argue that dcis is de facto cancer and not a precursor lesion. If dcis were a
precursor, then the invasive recurrence would be the real breast cancer, and preventing the invasive recurrence would prevent death, which it did not.

**Media Response**

Since 20 August 2015, our paper has been mentioned in 86 news stories from 47 different news outlets, including 5 separate articles in *The New York Times*3-7, 1 article in *Time Magazine*, and articles in several other online and print media outlets worldwide.2

The initial article in *The New York Times*,3 titled “Doubt is raised over value of surgery for breast lesion at earliest stage,” set the stage for many articles to follow, which suggested that our study provides evidence that treatment might not be necessary for dcis and that it “justifies the use of watchful waiting”9-13. We did not have and that it

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Even though the majority of articles were accurate, some were not. For example, Benson et al.19, in the article titled “Treatment of low-risk ductal carcinoma in situ: is nothing better than something” write: “They reported a very low breast cancer–specific mortality rate at 20 years of 3.3% overall, which is only marginally higher than that in the general female population (1.5%);” Wahl et al.21 say that “the mortality rates of women with dcis have been low over 20 y, at about 3%, and in the range of the death rate seen in the general context: that is, that dcis can metastasize, or that breast cancer is a systemic disease that disseminates and metastasizes early44-48. Representative examples of citations are provided below.

**DCIS Is a Precursor, Not Cancer**

Authors of several papers take our estimate of the 20-year mortality rate from breast cancer after a diagnosis of dcis (3.3%) to mean that dcis is not malignant. Survival in stage 1 breast cancer is also excellent (95% at 10 years), but no one argues that the condition is not breast cancer.

For example, Pilewskie et al.16 cite our paper in support of the statement that “ductal carcinoma in situ (dcis) is a noninvasive breast lesion with no theoretic metastatic potential and excellent survival”; Shieh et al.16 deem dcis “likely to be a true precursor lesion” rather than a cancer; Ganz et al.17 note that treatment for dcis is “thought of as breast cancer prevention, because ductal carcinoma in situ is rarely lethal”; and Masood et al.18 suggest that our paper “raises the question of why we are calling an entity ‘cancer’ when it does not act like a malignant lesion,” which is “sufficient evidence to consider a definitive change in the use of the term ‘carcinoma in situ ’ and replace it with a less threatening terminology.” It is interesting to note that in regard to that issue (and the three other issues discussed in the subsections that follow), none of the commentators actually said that we were wrong—that is, that dcis is not a fully-fledged cancer. Rather, they used agreeable language to state the contradictory view that dcis is a precursor, and as such, they seemed not to wish to engage in a serious scientific debate—perhaps for fear of giving offense ... or perhaps because they have borrowed the idea of “alternative facts.”

**DCIS Is Overdiagnosed and Does Not Need to Be Treated**

Four articles suggested that the mortality rate for dcis subjects is comparable to the mortality rate for the general population, and the authors used that comparison to promote the “watch and wait” approach. For example, Lippey et al.19, in an article titled “Can we avoid surgery for low-risk ductal carcinoma in situ,” stated that “a 20-year breast cancer–specific mortality rate of 3.3% [is] comparable to the general population all-cause mortality over the same time period.” It is not true that the two rates are “comparable.” Lippey et al.19 did not provide a reference for the all-cause mortality rate in the general population; however, using the U.S. National Vital Statistics System,65 we estimated the 20-year cumulative risk of dying from all causes to be about 4.8% for a 35-year-old woman and to be about 69.4% for a 70-year-old woman (the oldest age at diagnosis in our study). That range (5%-70%) is clearly well beyond the 3.3% mortality rate for the dcis subjects reported in our study.

Likewise, Benson et al.20, in the article titled “Treatment of low-risk ductal carcinoma in situ: is nothing better than something” write: “They reported a very low breast cancer–specific mortality rate at 20 years of 3.3% overall, which is only marginally higher than that in the general female population (1.5%);” Wahl et al.21 say that “the mortality rates of women with dcis have been low over 20 y, at about 3%, and in the range of the death rate seen in the general literature.”

**Citations in the Medical Literature**

To date, our paper has been cited in the medical literature 50 times.55-64. Most articles accurately stated that the mortality rate from dcis is low (3%) and that mortality was equivalent regardless of treatment type. Nevertheless, many commentators misinterpreted the finding of low mortality to infer either that dcis is a precursor, and not a cancer15-18; that dcis is overdiagnosed and does not need to be treated (that is, “watch and wait”)19-20; or that dcis is overtreated (that is, omit radiotherapy).30-34. Most troubling from our point of view was that several commentators interpreted the finding that the increased risk of death from breast cancer in dcis patients who developed an ipsilateral invasive recurrence justified efforts to prevent the invasive ipsilateral recurrence as a life-saving measure.35-43. Only 5 of the 50 articles referenced our paper in the intended context: that is, that dcis can metastasize, or that breast cancer is a systemic disease that disseminates and metastasizes early.44-48. Representative examples of citations are provided below.
population of women”; and Hoag et al.22 say that affected women “had just a 3.3% chance of dying of breast cancer in the next 20 years, not much different than the risk to women in the general population (2.7%), according to the American Cancer Society.” The 2.7% breast cancer mortality rate reported by Hoag et al.22 refers to the lifetime risk of dying of breast cancer for a woman in the general population (that is, from age 0 to age 95+), which is clearly not comparable with our 20-year risk estimate. In the U.S. Surveillance, Epidemiology, and End Results database, the 20-year risk of dying of breast cancer for a woman age 35 in the general population is only 0.34%,66 and for a woman age 70, it is 1.6%.67 In any case, we estimated the standardized mortality ratio in our paper (that is, the risk of dying of breast cancer in our cohort of patients diagnosed with dcis compared with the risk in the general U.S. population) to be 1.8—a small but significant increase.

But most importantly, it is not logical to compare the 20-year breast cancer–specific mortality rate in dcis patients with the 20-year all-cause mortality rate in the general population. Suppose the two rates were in fact identical at 3.3%; given that supposition, 3.3% of the general population will die in 20 years of all causes, and 3.3% of dcis patients will die of breast cancer alone. Presumably another 3.0% or so of the dcis patient population will die of other causes, bringing their all-cause mortality rate to 6.3%—hence the standardized mortality ratio of 1.8.

Ipsilateral Invasive Recurrence After DCIS Is Life-Threatening

Some authors who acknowledge that dcis is potentially lethal nevertheless continue to claim that it is dangerous only when it results in a cancer recurrence. For example, Masood et al.18 suggest that our finding that “there are subsets of dcis cases associated with a higher risk of dying from subsequent development of invasive breast cancer” is important because it allows for the stratification of dcis patients into relevant treatment categories, with those at a higher risk of subsequent development of invasive cancer being treated differently than those at a lower risk.

Merrill et al.35 point out that “while it is true that radiation therapy is not as effective in reducing breast cancer-specific mortality at 10 years,” it does reduce the risk of recurrence, and women with recurrence are significantly more likely to die of breast cancer than women without recurrence. Margolese et al.36 say that, although radiotherapy might not improve overall survival, “a local recurrence of invasive cancer ... carries an increased risk of death and is, at the very least, a serious event.” And Lebeau et al.37 write that “although the more aggressive treatment does not provide a survival benefit, we must consider that the risk of dying from breast cancer for a woman increases after the experience of an ipsilateral invasive recurrence by a factor of 18. Consequently, some women will benefit from a more aggressive treatment while others will not.” Buckley et al.38 say that “the occurrence of invasive cancer after dcis substantially increases the risk of cancer-related death” and “given the fact that the characteristics of dcis can predict those of subsequent invasive disease, more robust characterization of dcis can inform preventative strategies” and “other parameters, not only to treat but also to help decide the risk of recurrence or progression are required.”

It is true that certain subsets of dcis patients are at higher risk of recurrence than others and that recurrence is associated with increased mortality, but the main finding of our paper was that preventing recurrence does not prevent death. The authors quoted here have missed the point. The prevention of recurrence does not prevent death: Recurrence in this context is a marker for the presence of distant metastasis and should not be construed as a new primary cancer with malignant potential. It is analogous to the situation for local recurrence after invasive cancer. Predicting the risk of recurrence so as to guide decisions about localized therapies (radiotherapy or mastectomy) would therefore be expected to have no effect on mortality.

DCIS Has Metastatic Potential

Only 5 of the 50 papers interpreted our study as we intended. That is, they noted that patients with dcis can die of breast cancer in the absence of an intervening invasive cancer, interpreting that scenario to mean that dcis can metastasize or that breast cancer is a systemic disease and disseminates early. Suba et al.44 wrote: “In conclusion, women treated with adjuvant radiotherapy had higher risk for unrestrained tumour spread without a local invasive recurrence of breast cancer.” Le et al.45 said “for this reason, its classification as a precursor disease has been questioned.” Hartkopf et al.46, in an article titled “Detection of disseminated tumor cells from the bone marrow of patients with early breast cancer is associated with high 21-gene recurrence score,” wrote that “patients with non-invasive breast cancer may suffer from metastatic disease, even without experiencing an in-breast invasive breast cancer prior to death.”

Interestingly, in December 2016, two papers in Nature cited our paper as support for their findings. Harper et al.47, in a paper titled “Mechanism of early dissemination and metastasis in HER2+ mammary cancer,” said that “the related study and our work may also open doors to explain phenomena like metastases in cancer of unknown primary origin and in patients with dcis that never developed any local recurrence.” Hosseini et al.48, in a paper titled “Early dissemination seeds metastasis in breast cancer,” wrote that “relevance to human disease is highlighted by a careful analysis of mortality from dcis, hitherto defined as preinvasive lesion. Of the 3% of dcis fatalities, more than 50% die of metastasis without local relapse, indicating lethal dissemination before surgery of the preinvasive lesion.”

SUMMARY

This qualitative review of a single high-impact paper questions the extent to which media mention and citations in the literature adequately reflect the contents of a scientific paper. In the case of our dcis paper, almost all commentators opposed the view we wished to convey, and only a handful of writers agreed with us. It is important that scientific discussion be frank and objective if we are to properly translate the findings of our research projects into optimal care for women with early breast cancer. The medical community continues to refer to dcis as a precursor
lesion without the potential to metastasize, and the search continues unabated for molecular markers to predict invasive recurrence with the optimistic hope that prediction will lead to targeted treatments that will reduce mortality.

CONFLICT OF INTEREST DISCLOSURES
We have read and understood Current Oncology’s policy on disclosing conflicts of interest, and we declare that we have none.

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