

## The Sea of Uncertainty Surrounding Ductal Carcinoma In Situ—The Price of Screening Mammography

H. Gilbert Welch, Steven Woloshin, Lisa M. Schwartz

Wouldn't it be easier if we lived in a binary world? Everything would be either black or white, yes or no, 1 or 0. And biopsy results would be either normal or cancer.

Unfortunately, in the world of cancer, our efforts to detect the disease early have made this a fantasy. We are increasingly faced with the reality of a big gray zone—a broad spectrum of pathologic findings between normal tissue and invasive cancer. And our nosology reflects the associated ambiguity—dysplasia, intraepithelial neoplasia, hyperplasia with atypia, and even abnormalities of “unknown significance.” The unifying theme for these findings is that they may progress to invasive cancer. Or they may not.

Despite the presence of the word “carcinoma,” ductal carcinoma in situ (DCIS) is the poster child for this problem (a senior pathologist involved in developing classification systems confided to one of us that he regretted the use of the term carcinoma in DCIS). No one believes that DCIS always progresses to invasive cancer, and no one believes it never does. Although no one is sure what the probability of progression is, studies of DCIS that were missed at biopsy (1,2) and the autopsy reservoir (3) suggest that the lifetime risk of progression must be considerably less than 50%.

There is an added complexity: DCIS is associated with not just one risk but two. In addition to the specific risk that the lesion might progress to invasive cancer, DCIS confers a general risk. It is a marker for an increased chance of developing invasive cancer elsewhere in the ipsi- or contralateral breast. Again, although no one is sure what this probability is, a recent prospective study of a cohort of patients with DCIS who were treated largely by excision alone suggested that the 5-year risk of subsequent invasive breast cancer elsewhere is less than 10% (4).

In short, there is a sea of uncertainty surrounding DCIS. Some lesions will progress to cancer, others will not. Some women with DCIS will develop cancer elsewhere in their breasts, whereas others will not. And we're not sure what the chances are.

It isn't surprising that among women with DCIS the uncertainty of being in this gray zone leads to anxiety. In this issue of the *Journal*, Partridge et al. (5) report that many women with DCIS are anxious—even months after the diagnosis. The authors also report that anxiety is associated with exaggerated risk perceptions—many women with DCIS estimate their risk of developing invasive cancer 5 years following treatment to be greater than 50%. Although it's tempting to hope that better educating women (and their doctors) about the actual risks of DCIS would reduce anxiety, it's entirely possible that our measures of risk perception and anxiety are simply markers for the same underlying construct—how women feel about being in the gray zone. They are told that they don't have cancer, but they are not normal; instead, they are at higher risk for developing cancer.

Because DCIS is an asymptomatic and nearly always nonpalpable lesion, the majority of women exposed to this sea of uncertainty got there the same way—via screening mammography. Thus, the associated anxiety must be considered to be a harm of mammographic screening.

But anxiety is certainly not the only harm. The fundamental paradox of early cancer detection is that, while some may be helped, others get a diagnosis they'd be better off without. The central harm of screening is overdiagnosis—the detection of abnormalities that meet the pathologic definition of cancer but will never progress to cause symptoms. Although this concept may seem implausible to clinicians, basic scientists have begun to uncover biologic mechanisms that halt the progression of cancer (6–8). Overdiagnosis has now been associated with early detection in a variety of cancers, including neuroblastoma (9,10), melanoma (11), and thyroid (12), lung (13), prostate (14), and breast (15,16) cancer. In fact, some degree of overdiagnosis in cancer screening is probably the rule, not the exception.

Long-term follow-up of the Malmö randomized trial (17) suggests that a quarter of mammographically detected breast cancers represent overdiagnosis (18). Although it is impossible to determine which individuals are overdiagnosed (unless they are not treated and ultimately die without ever developing symptoms from their cancer), it is possible to identify subsets of patients who are at high risk of overdiagnosis. In breast cancer, this subset is patients with DCIS. Because the “best guess” is that most DCIS won't progress to invasive cancer, the risk of overdiagnosis would be expected to be greater than 50%.

The problem with overdiagnosis is that it leads to overtreatment. Because it is impossible to determine which individuals are overdiagnosed, almost everyone gets treated as if they had invasive cancer. The notable exception is prostate cancer, for which active surveillance (ie, “watchful waiting”) is now an accepted treatment option, even among strong proponents of screening (19,20).

Patients who are overdiagnosed cannot benefit from treatment because their “disease” poses no threat; in fact, for them treatment can only cause harm, such as disfiguring surgery, radiation damage,

---

**Affiliations of authors:** Veterans Affairs Outcomes Group, Department of Veterans Affairs Medical Center, White River Junction, VT (HGW, SW, LMS); Norris Cotton Cancer Center, Dartmouth-Hitchcock Medical Center, Lebanon, NH (HGW, SW, LMS); Dartmouth Institute for Health Policy and Clinical Practice, Dartmouth Medical School, Hanover, NH (HGW, SW, LMS).

**Correspondence to:** H. Gilbert Welch, MD, MPH, Veterans Affairs Outcomes Group (111B), Department of Veterans Affairs Medical Center, White River Junction, VT 05009 (e-mail: h.gilbert.welch@dartmouth.edu).

**DOI:** 10.1093/jnci/djn013

Published by Oxford University Press 2008.

and side effects of systemic therapy. In the cohort studied by Partridge et al. (5), it appears that the vast majority underwent surgery, half received radiation, and a third underwent total mastectomy—a treatment pattern that is remarkably similar to that of early-stage invasive breast cancer.

And despite all this treatment, many of these women perceived that their breast cancer risk remained extremely high. Perhaps this observation simply reflects exaggerated risk perceptions. Or maybe these women believe their treatment had little effect on their overall risk of developing breast cancer. We just don't know the natural history of DCIS, but we can and we should.

More than 50 000 American women are diagnosed in this gray zone each year. Virtually all get some surgery. It's time to figure out whether they really need surgery or whether all they really need is repeat mammography (or magnetic resonance imaging). In other words, should they be treated for breast cancer or should they be managed as individuals with an elevated risk for the disease? Because the prognosis for women who are treated for early-stage breast cancer is so good, it's reasonable to test a strategy of active surveillance for DCIS. Active surveillance could help women whose DCIS does not progress avoid treatment and allow those whose DCIS does progress to invasive cancer be diagnosed and treated when the prognosis is still extremely favorable.

Investigators at the University of California at San Francisco are taking an important first step in this direction (21). In a pilot study, all women with estrogen receptor-positive DCIS will receive hormonal therapy for 3 months before surgery. The primary outcome is the change in tumor volume during this period. The investigators' ultimate goal is to identify nonsurgical means of treatment to prevent DCIS progression to invasive cancer.

Although active surveillance is a step that can mitigate the harms of treatment, we doubt that it will mitigate the effects of uncertainty and anxiety highlighted by Partridge et al. (5). To do this, we must go back a step and question the value of making the diagnosis in the first place.

Of all the randomized trials of screening mammography, only one included a physical examination in the control group, which offered some insight into the value of detecting DCIS. In the Canadian National Breast Screening Study-2 (22), women in their fifties were randomly assigned to either a carefully standardized, lengthy (5–15 minutes per patient) physical examination that was performed mainly by specially trained nurses or to the same physical examination plus mammography. In other words, the trial essentially tested the value of finding the microscopic nonpalpable lesions of DCIS. The trial found no statistically significant difference in breast cancer mortality (and, in fact, mortality was nominally higher in the mammography group).

Although it's not clear that screening mammography has any benefit over a carefully standardized clinical examination, we believe mammography has a role in women's health. The practical reality is that it is much easier to standardize the practice of the relatively few mammographers than the very large number of primary care practitioners who might perform a physical examination (not to mention the problem of their finding the time to do so). But the findings of the Canadian trial do raise the question of what the mammographer's threshold to recommend biopsy should be.

Maybe it's time to compare current practice with a more conservative diagnostic threshold and reserve biopsy only for lesions that can be plausibly palpated (say >1cm).

Or maybe this trial could only happen in a fantasy world. But we hope not.

## References

1. Eusebi V, Foschini MP, Cook MG, Berrino F, Azzopardi JG. Long-term follow-up of in situ carcinoma of the breast with special emphasis on clinging carcinoma. *Semin Diagn Pathol.* 1989;6(2):165–173.
2. Page D, Dupont W, Rogers L, Jensen R, Schuyler P. Continued local recurrence of carcinoma 15–25 years after a diagnosis of low grade ductal carcinoma in situ of the breast treated only by biopsy. *Cancer.* 1995; 76(7):1197–2000.
3. Welch HG, Black WC. Using autopsy series to estimate the disease “reservoir” for ductal carcinoma in situ of the breast: how much more breast cancer can we find? *Ann Intern Med.* 1997;127(11):1023–1028.
4. Hughes L, Wang M, Page D, et al. 5-year results of intergroup study E5194: local excision alone (without radiation treatment) for selected patients with ductal carcinoma in situ [abstract]. *Breast Cancer Res Treat.* 2006;100(Suppl 1):A-29, S15.
5. Partridge A, Adloff K, Blood E, et al. Risk perceptions and psychosocial outcomes of women with ductal carcinoma in situ: longitudinal results from a cohort study. *J Natl Cancer Inst.* 2008;100(4):243–251.
6. Mooi WJ, Peeper DS. Oncogene-induced cell senescence—halting on the road to cancer. *N Engl J Med.* 2006;355(10):1037–1046.
7. Folkman J, Kalluri R. Cancer without disease. *Nature.* 2004; 427(6977):787.
8. Serrano M. Cancer regression by senescence. *N Engl J Med.* 2007; 356(19):1996–1997.
9. Schilling FH, Spix C, Berthold F, et al. Neuroblastoma screening at one year of age. *N Engl J Med.* 2002;346(14):1047–1053.
10. Yamamoto K, Hanada R, Kikuchi A, et al. Spontaneous regression of localized neuroblastoma detected by mass screening. *J Clin Oncol.* 1998; 16(4):1265–1269.
11. Welch HG, Woloshin S, Schwartz LM. Skin biopsy rates and incidence of melanoma: population based ecological study. *BMJ.* 2005;331(7515): 481–484.
12. Davies L, Welch HG. The increasing incidence of thyroid cancer in the United States, 1973–2002. *JAMA.* 2006;295(18):2164–2167.
13. Black WC. Overdiagnosis: an underrecognized cause of confusion and harm in cancer screening. *J Natl Cancer Inst.* 2000;92(16):1280–1282.
14. Etzioni R, Penson DF, Legler JM, et al. Overdiagnosis due to prostate-specific antigen screening: lessons from U.S. prostate cancer incidence trends. *J Natl Cancer Inst.* 2002;94(13):981–990.
15. Zahl PH, Strand BH, Mæhlen J. Breast cancer incidence in Norway and Sweden during introduction of nation-wide screening: prospective cohort study. *BMJ.* 2004;328(7445):921–924.
16. Gotzsche P, Nielsen M. Screening for breast cancer with mammography [review]. *Cochrane Database Syst Rev.* 2006;4:CD001877.
17. Zackrisson S, Andersson I, Janzon L, Manjer J, Garne JP. Rate of overdiagnosis of breast cancer 15 years after end of Malmö mammographic screening trial: follow-up study. *BMJ.* 2006;332(7543):689–692.
18. Welch HG, Schwartz LM, Woloshin S. Ramifications of screening for breast cancer: 1 in 4 cancers detected by mammography are pseudocancers. *BMJ.* 2006;332(7543):727.
19. Carter HB, Kettermann A, Warlick C, et al. Expectant management of prostate cancer with curative intent: an update of the Johns Hopkins experience. *J Urol.* 2007;178(6):2359–2364.
20. Walsh PC, Dewese TL, Eisenberger MA. Localized prostate cancer. *N Engl J Med.* 2007;357(26):2696–2705.
21. [http://www.cancer.gov/clinicaltrials/UCSF-017513#ExpectedEnrollment\\_CDR0000465205](http://www.cancer.gov/clinicaltrials/UCSF-017513#ExpectedEnrollment_CDR0000465205) [Last accessed January 22, 2008].
22. Miller AB, To T, Baines CJ, Wall C. Canadian National Breast Screening Study-2: 13-year results of a randomized trial in women aged 50–59 years. *J Natl Cancer Inst.* 2000;92(18):1490–1499.