DOI: 10.1093/jnci/djq119
Advance Access publication on April 22, 2010.

EDITORIALS

Solving the Overdiagnosis Dilemma

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In a review in this issue of the Journal (1), Welch and Black clearly document that surveillance routinely identifies lesions that many patients would not need to know about in their lifetimes. These lesions only become a problem because we feel compelled to diagnose and treat them. What motivates intervention is the opportunity to prevent disease progression, metastasis, and death and the philosophy that "early detection is always better." The patient's fear of cancer and clinician's concern about malpractice are also driving factors. But often overlooked are the profound consequences of treatment and diagnostic interventions. The article by Welch and Black should serve as a clarion call to acknowledge the spectrum of cancer behavior and the need to reclassify "indolent" lesions with a term other than "cancer" and to improve the specificity of our screening tests.

This study is not "bad news," but "good news" because it points a way forward. First, we must accept that population screening and diagnostic scans detect substantial numbers of indolent tumors and benign lesions in addition to potentially lethal disease. Second, we must resolve that we can and must address the problem.

The unintended consequence of finding a precancerous lesion is exemplified by the 41-year-old research scientist who called one of us in a panic. Her first mammogram showed a cluster of calcifications; magnetic resonance imaging showed another focus of ductal carcinoma in situ, which led to a mastectomy that showed both lobular and ductal carcinoma in situ and an axillary sentinel node biopsy that showed isolated tumor cells. Now she faces a decision about chemotherapy and prophylactic contralateral mastectomy. Have we "helped" this patient in her goal to avoid death from cancer? The answer is "unlikely."

Much of what we call cancer is not destined for an inexorable progression to metastasis and death. We can no longer say that we must intervene because we cannot tell the difference. Raising the fraction of people diagnosed with cancer has grave consequences. It adds the burden of diagnosis to hundreds of thousands and engenders needless fear. It obscures our ability to identify and focus on tumors that need more aggressive or tailored treatment where our current approaches are unsuccessful. Cancer is a serious disease, but we have to redefine what cancer truly is.

Many of the interventions that we perform to find and treat cancer will not have material value; some will cause harm. As cancer surgeons, we see the many biopsies that are performed just to make sure that a cluster of calcifications, an abnormal Papanicolaou smear, or a high prostate-specific antigen reading does not represent cancer. By demanding increased sensitivity for cancer detection, we lower our threshold for biopsy. In the United States, there is little to balance the need to resolve any uncertainty or push for greater specificity in cancer screening tests (here, we may have much to learn from our colleagues in Europe, where there is more emphasis on specificity). As a result, about 75% of biopsies are negative. While on the surface this may seem to be a fairly benign consequence, it is not. When women with prior biopsies are diagnosed with breast cancer, they are more likely to opt for bilateral mastectomy as treatment. Although the rate of cervical cancer has decreased, huge numbers of cervical biopsies are also performed for benign disease. The same is true for prostate cancer and incidental findings on computerized tomography scans where many biopsies are recommended for what turns out to be benign disease. An example is the 60-year-old man with a prostate-specific antigen level above 4.0 ng/mL, who had undergone five previous sets of prostate biopsies, involving more than 60 individual needle biopsies, without finding cancer. He was in tears, dwelling constantly about the possibility of yet another biopsy. All diagnostic procedures have costs, direct (financial, opportunity cost) and indirect (time off from work, away from families), and are associated with risk of complications and negative emotional consequences.

Prescription for Change

What we need now in the field of cancer is the coming together of physicians and scientists of all disciplines to reduce the burden of cancer death AND cancer diagnosis. We must advocate for and demand innovation in diagnosis and management, fueled by science, harnessing modeling, molecular, and immunology tools to address this problem.

By changing our clinical and scientific priorities to focus on distinguishing indolent from aggressive disease, we can improve the value of screening, reduce morbidity of treatment, and prevent lethal outcomes of cancer. The fact that the phenomenon of overdiagnosis is observed in all organ sites in substantial numbers should compel us to develop tools to reclassify disease as indolent at the time of diagnosis. We have previously suggested elimination of the use of the word "cancer" and substitution of a term like "IDLE tumor" (InDolent Lesions of Epithelial origin) for low-risk disease (2). Together, the biomedical research and clinical communities must also make it a priority to develop, refine, and use tools that distinguish indolent from aggressive tumors and the guideline bodies and payers should support the use of such markers (3,4). Effective screening must combine diagnostic and prognostic tests, and the Food and Drug Administration's approval of new biomarkers must include this consideration.

If we make the distinction between indolence and aggression a focus of our efforts, we are much more likely to achieve it as a goal. A better understanding of the host environments and/or tumor

genetics that lead to aggressive or indolent phenotypes could also hold promise for new approaches to prevention.

We need to be more judicious about how we screen. By recognizing where we have and have not made a difference, we can identify opportunities for improvement. Screening has been most effective for moderate to slow growing tumors, such as cervical and colon cancers. Recognition of this fact may help us to set better thresholds for intervention and more appropriate screening intervals. If less frequent screening is as effective as more frequent screening and results in fewer diagnostic procedures (5,6), this should be welcome news and embraced, not dismissed out of fear. The target of screening should be to identify persons with those lesions for which screening will make a difference and the populations most likely to benefit from early detection. Indolent disease, if missed this year, will not have grown much by the next screen. We agree with Welch and Black that for many small radiographic findings, evidence of growth over time may help sort out which lesions are worthy of biopsy (1). For rapidly growing tumors, development of more targeted therapies and predictive biomarkers may be more likely to reduce mortality.

Moving forward clinically, we must focus on three tasks. First, we must redefine cancer using our biological understanding of this disease. Second, we must be clearer about what it is we are seeking to detect; and third, we must work in multidisciplinary teams to test and improve our reporting and thresholds for intervention. Our radiology colleagues must participate, redefining what they call "suspicious" or "abnormal" on imaging. It will be challenging and take courage, but we need to make it an explicit goal to raise the threshold for what we biopsy and diagnose.

Is it too risky to not biopsy and to potentially miss a cancer? Perhaps it is just the opposite. It is too risky to continue on the path where we are compelled to know what every lesion is, and then invoking the occulopathologic reflex, the reflexive need to treat anything that resembles cancer (7). We need to curb the urge to intervene with more thought about what is truly valuable. We can ill afford to spend resources for diagnosis and treatment if we do not make a material contribution to a person's well-being.

Perhaps most importantly, we have an obligation to educate patients and clinicians to explain more and do less when appropriate. We need to make sure that patients understand that not all cancers have the potential to kill and use language that engenders less fear, for example, IDLE tumors. The challenge for the scientific and medical community is to work alongside our patients to make care more appropriate, more tailored, less resource intensive, and less morbid.

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