

Editorial Comment

Search and destroy – the right cancer strategy for Europeans? ☆

H. Gilbert Welch

VA Outcomes Group IIIB, White River Junctions, VT 05009, USA

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1. Introduction

The United States is at war. And we would like to see the European Community join us in the effort. But it may not be the war you are thinking about – because this war has been going on for over 35 years (and was started by President Nixon, not President Bush). It is our war against cancer.

This war has several fronts. There has been an explosion of basic research into the genetic mechanisms of uncontrolled cellular division. There has been an aggressive search to identify and eliminate the environmental culprits of carcinogenesis. And there has been an intense push to develop a therapeutic arsenal of smart weapons: drugs that target tumour-specific antigens. While many good things may be happening, like all wars there are unintended casualties. Not surprisingly, the front with the most unintended casualties is the front involving the most civilians – our unrelenting effort to find early cancers among the well.

To be fair, cancer screening has a lot of appeal. Everybody likes the idea of preventive medicine. And even though cancer screening is not disease prevention in the classic sense, it certainly holds the promise of

reducing the morbidity and mortality of advanced cancer. The idea is simple and persuasive. Cancer grows and spreads to distant parts of the body. When cancer is this far along it is really hard to treat. But if doctors “catch” cancer earlier, before it spreads, it will be much easier to treat. It's an idea familiar to all: fix small problems before they become big ones.

Of course, the reality is not that simple. Not only have the benefits of screening been exaggerated, but there are real downsides to the process. So before the European Community enthusiastically joins the United States in taking up widespread screening, physicians and the public ought to be clear about what those downsides are.

2. The most aggressive cancers will tend to be missed

Many might argue this is not a downside to screening, simply a limitation. But it is very important that it be explicitly communicated so that people have realistic expectations. Patients should understand that cancer can appear during the interval between screening tests. These are the cancers that are not detectable at one screening test, yet are clinically obvious before the next. Not surprisingly, interval cancers are the fastest growing tumours. They are among the worst forms of cancer, more deadly than those detected by screening [1,2]. Understanding that screening misses these cancers is important because it invalidates a common belief: anyone who dies of cancer and was not screened would have been saved if only he or she had had the test.

3. People will receive ambiguous results and undergo cascades of testing

Screening tests are imperfect. Patients with abnormal screening test results often do not have cancer. But be-

☆ *Editors Note:* The topic of cancer screening is more fully discussed in a book written by Dr. Welch while a visiting scientist at the International Agency for Research on Cancer. “Should I be tested for cancer?: May be not and here's why” (University of California Press, 2004) is a short, relatively easy read that is accessible to both physicians and the general public (yet it also provides important detail and references in the footnotes). The French version “Dois-je me faire dépister pour le cancer? Peut-être pas et voici pourquoi” will be published by Presses de l'Université Laval this spring. Dr. Welch is a senior research associate in the Department of Veterans Affairs and a Professor of Medicine in the Dartmouth Medical School. The views expressed herein do not necessarily represent the views of the Department of Veterans Affairs or the US government.

E-mail address: h.gilbert.welch@dartmouth.edu.

fore they are pronounced “cancer-free”, they may have to go through multiple tests – some of which are unpleasant and some of which can have serious complications. Additional testing may even become a regular event. Throughout the entire process, many will worry about whether they have cancer. Most physicians have developed some language to prepare patients for false-positive test results. For instance, an explanation for faecal occult blood testing might be something like this: “This card will test the stool for small amounts of blood... If it is positive, it does not mean you have cancer, it just means we need to look further.” But physicians are not as good at preparing patients for the reality that extra testing may become quite invasive and go on for a long time – perhaps indefinitely. More and more Americans are undergoing colonoscopies every 2–5 years; undergoing additional pelvic examinations, colposcopies, and cryocauterisations; and having repeat prostate biopsies. Patients should understand that more frequent testing can be a consequence of screening.

4. More people will be told they have cancer

The harder we look for cancer, the more we find. This phenomenon is most familiar with prostate cancer. Here the number of cancers detected appears to be directly related to how aggressively urologists biopsy different portions of the organ. Historically, 6 needle biopsies have been done, now many are advocating 12 or more – noting that the more biopsies that are taken, the more cancer is found [3–6]. Some have even advocated “saturation biopsy” (a procedure involving somewhere between 32 and 38 needle biopsies) demonstrating that microscopic cancers can still be found in men who have been cancer-free on three or more prior biopsy procedures [7]. The introduction of transrectal biopsy following prostate-specific antigen (PSA) testing has led to more than one million additional men being told they have prostate cancer in the United States.

But the phenomenon is not restricted to prostate cancer. Mounting evidence suggests that a reservoir of cancer exists in humans that is much larger than what is known to be clinically relevant. Increased diagnostic scrutiny has been found to result in an increase in the apparent prevalence of lung cancer [8], breast cancer [9], melanoma [10,11], renal cell carcinoma [12], as well as neuroblastoma [13,14] – a rare childhood cancer. Wherever we look harder, we find more cancer.

5. People will be treated unnecessarily

Ironically, the more cancer we find, the less likely an individual case matters. Screening can detect pseudodis-

ease: an abnormality that meets the pathological definition of cancer, but either does not progress or grows so slowly that an individual dies from another cause before the cancer ever causes symptoms. As screening tests become increasingly sensitive, the detection of pseudodisease is an increasingly common problem. Patients who have pseudodisease detected cannot benefit from early treatment. Instead, they only experience the morbidity of a cancer diagnosis and the morbidity (and occasional mortality) of our cancer therapies.

Again, the prostate cancer example is important. There has been a small decline in the death rate from prostate cancer, but whether the extent to which this reflects PSA screening instead of better treatment is simply not known. Even if one accepts that screening probably has helped a few men live longer, it is critical to acknowledge that it has also clearly hurt others. Millions have been biopsied who otherwise would not have. Hundreds of thousands with non-progressive disease have been turned into cancer patients unnecessarily. Of those who have been treated many have suffered ill-effects: notably, impotence and incontinence. A few have even had their life shortened by treatment.

6. Pathologists will disagree about who has screen-detected cancer

To be fair, most physicians are rarely ever made aware of this downside. But that speaks less to the underlying frequency of disagreement than to the fact that few biopsy specimens are independently read by 2 pathologists. When investigators look for disagreement, they generally find it [15] – be it in prostate cancer [16,17], melanoma [18,19] cervical [20] or breast cancer [21–23]. The problem is not that pathologists disagree about large obvious cancers that are invading surrounding tissue. Instead they disagree about the subtle abnormalities – the very abnormalities most commonly identified with screening. Physicians and patients should recognise that this exposes the fundamental problem of cancer screening: there is not a single operational definition for cancer.

7. Physicians will be distracted from other issues that are more important to patients

In the past, physicians came to most clinic visits without a preset agenda. Now, we increasingly have one: “You are due for A, B and C, and we also recommend that patients do X.” Much of that agenda relates to screening. There is a lot of appeal to screening from the physician’s perspective. Screening is a concrete service (it can be written in the patient’s plan), and it identifies actionable lesions. By contrast, discussing concerns

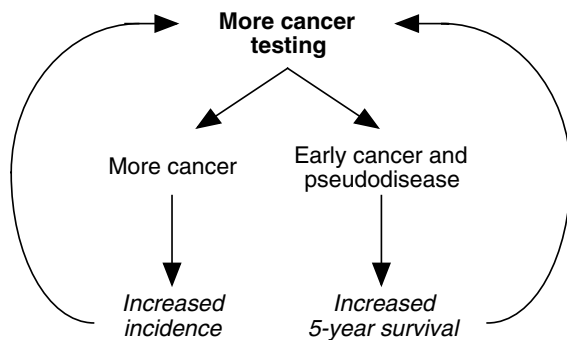


Fig. 1. Cycle of increasing aggressiveness in the search for cancer.

on the patient's agenda can feel ethereal and frequently concludes with sympathy, not an actionable plan. Given the limited time for clinic visits, one service may compete with the other. However, this downside of screening is not frequently discussed, and the evidence that it exists is anecdotal. But I believe its real. The more time we spend describing, ordering, communicating results, and following-up abnormal findings, the less time there is to spend dealing with the patient's concerns.

8. More screening will beget more screening

Finally, cancer screening tends to provide its own positive feedback. Because screening finds more cancer, incidence rates may climb dramatically as screening is used more frequently. But even more important, 5-year survival also climbs dramatically. Of course, 5-year survival will increase simply because we are telling people they have cancer earlier in their life (not changing their time of death) and because we are telling more people they have cancer (that is, finding more pseudodisease). So expect that every screening programme will be associated with increased 5-year survival – even if it does not help people live one day longer.

The effect of screening on incidence and 5-year survival can create a cycle of increasing aggressiveness in the search for cancer. The cycle looks something like this (see Fig. 1):

Here is how it goes. A new test is developed (or an old one is done more frequently). More cancer is found. Incidence goes up. Someone uses the word “epidemic”. More testing is recommended. At the same time, cases of cancer are found earlier. Some are pseudodisease. 5-year survival rises. Someone uses the phrase “save lives”. More testing is recommended.

9. Conclusion

The way we Americans wage our war against cancer through aggressive early detection is clearly at one

extreme. Literally millions of Americans (of all ages) are receiving mammograms, colonoscopies, PSA tests, (Pap) smears, as well as (MRIs) and (CT) scans to look for a broad range of cancers. However there are also extremes, albeit less dramatic, within the European Community. The typical Finnish woman will have 7 Pap smears recommended in her lifetime, for example, while the typical German woman will have over 50 [24]. English and Dutch women will have mammograms recommended as part of a national screening effort, while Italian and Spanish women will not [25].

We can all learn from studying these extremes. Cross-country comparisons provide a type of natural experiment with which to examine the wide range of effects that screening can have on a population. A few may have their lives saved, a few will die of cancer anyway. Many more will face testing cascades and uncertainty, some will be treated unnecessarily, and a few may die from treatment. And patients, physicians and national health programmes can be distracted from more important health pursuits.

It has been said that the first casualty of war is truth. Screening evangelists tend to exaggerate the benefits of screening and minimize its downsides. Worse yet, they may fail to mention downsides entirely. More secular scientists need to work hard to make sure that the public (and policymakers) have access to both sides of the story.

Conflict of interest statement

None declared.

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