COMMENTARY

Conceptualizing Overdiagnosis in Cancer Screening

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Abstract

The aim of cancer screening is to detect asymptomatic cancers whose treatment will result in extension of life, relative to length of life absent screening. Unfortunately, cancer screening also results in overdiagnosis, the detection of cancers that, in the absence of screening, would not present symptomatically during one's lifetime. Thus, their detection and subsequent treatment is unnecessary and detrimental. This definition of overdiagnosis, while succinct, does not capture the ways it can occur, and our interactions with patients, advocates, researchers, clinicians, and journalists have led us to believe that the concept of overdiagnosis is difficult to explain and, for some, difficult to accept. We propose a dichotomy, the "tumor-patient" classification, to aid in understanding overdiagnosis. The tumor category includes asymptomatic malignant disease that would regress spontaneously if left alone, as well as asymptomatic malignant disease that stagnates or progresses too slowly to be life threatening in even the longest of lifetimes. The patient category includes asymptomatic malignant disease that would progress quickly enough to be life threatening during a lifetime of typical length, but lacks clinical relevance because death due to another cause intercedes prior to what would have been the date of symptomatic diagnosis had screening not occurred. Cancer screening of most organs is likely to result in overdiagnosis of both types. However, the ratio of tumor- to patient-driven overdiagnosis almost certainly varies, and may vary drastically, by organ, screening modality, patient characteristics, and other factors.

The aim of cancer screening is to detect asymptomatic cancers whose treatment will result in extension of life, relative to life span absent screening. It is intuitively appealing that outcomes could be improved for most cancer types if detection occurs early enough. Many healthy individuals who participate in screening programs are willing to accept downsides of screening, such as a false-positive screening examination and accompanying diagnostic evaluation, if they believe that an occult cancer might be detected and death averted. The concept of a false-positive screening exam is easy to understand, and data are available to help clinicians and patients understand the chance of such an event. In contrast, overdiagnosis, another negative consequence of cancer screening, is typically not well understood by clinicians, patients, and others.

Overdiagnosis refers to the detection of cancers that, in the absence of screening, would not present symptomatically. Overdiagnosis is a harm of screening because detection and subsequent treatment are unnecessary. Furthermore, cancer treatment has well-known sequelae that at best are unpleasant and debilitating and at worst can cause premature death. Although the definition of overdiagnosis is succinct, it does not convey how overdiagnosis occurs. Given that the existence of overdiagnosis in cancer screening is counter-intuitive and often poorly understood, we suggest that the manner in which overdiagnosis can occur be discussed when explaining the concept. We have developed a simple dichotomy, the "tumor-patient" classification, to aid explanation. Our goal in developing this classification is to allow for better understanding of this real harm of cancer screening.

We hope that health care professionals, researchers, and patients, respectively, will gain understanding so they can better counsel patients, more appropriately interpret cancer screening data, and make decisions that are informed and right for them. We also hope that advocates and journalists, individuals who play important roles in public education, will use our conceptualization to craft understandable messages about the harms of screening.

Cancer Screening

Morrison defined screening as "the examination of asymptomatic people in order to classify them as likely or unlikely to have the disease that is the object of the screening;" he noted that those classified as likely to have disease receive further medical investigation to arrive at a final diagnosis (1). In the instance of cancer, screening and associated diagnostic evaluation for those who test positive lead to the detection of four types of disease (adapted from Miller [2]).

1) Favorable outcome after screen detection, unfavorable outcome if detected because of symptomatic presentation
2) Favorable outcome after screen detection, but equally favorable outcome if detected because of symptomatic presentation
3) Unfavorable outcome after screen detection, and equally unfavorable outcome if detected because of symptomatic presentation
4) Favorable outcome after screen detection, but no symptomatic presentation in the absence of screening: overdiagnosed disease

Screening aims to identify Type I disease. There is no benefit to finding Type II or III disease through screening, as the outcome is the same if detection is because of symptomatic presentation, but the harm of spending more of one's lifetime as a cancer patient accompanies the earlier diagnosis.

Overdiagnosis: The Tumor-Patient Classification

We have identified three ways in which overdiagnosis occurs in cancer screening. Two are driven by tumor characteristics, while one is driven by patient experience. Though we use the term "cancer" and write in terms of malignant disease, these ideas are of relevance to in situ disease and precursor lesions as well.

Tumor A: Asymptomatic malignant disease that regresses spontaneously if left alone

Tumor B: Asymptomatic malignant disease that either stagnates or progresses too slowly to be life threatening in even the longest of lifetimes

Patient: Asymptomatic malignant disease that progresses quickly enough to be life threatening during a lifetime of typical length, but death because of another cause occurs prior to what would have been the destined date of symptomatic diagnosis had screening not occurred

The tumor A and B categories represent indolent disease, but the patient category does not. We believe that the ratio of tumor-to patient-driven overdiagnosis almost certainly varies by organ, screening modality, patient characteristics, and other factors. For example, patient-driven overdiagnosis is likely to be more frequent in lung cancerscreening because of the competing causes of smoking-associated death.

Examples of Overdiagnosis in Cancer Screening

We next discuss, for each type of overdiagnosis, screening for one cancer that is accepted to result in that type of overdiagnosis. We chose these cancers because they provide the strongest evidence for each type of overdiagnosis. By discussing only one example per overdiagnosis type, we do not mean to imply that screening for the specific cancer results in only one type of overdiagnosis, nor that the one cancer is the only cancer for which screening results in that type of overdiagnosis. Screening for every cancer is likely to result in each type of overdiagnosis, though perhaps to degrees that vary quite drastically. Given that the magnitude of overdiagnosis for a given organ is dependent on many factors, most notably modality, it is likely that the distribution of the types of overdiagnosis for a given organ is dependent on many factors as well and is not fixed.

Tumor A: Asymptomatic Malignant Disease That Regresses

Example: Screening for Neuroblastoma in Infants

Screening for neuroblastoma examines urinary levels of vanillylmandelic acid (VMA) and homovanillic acid (HVA), which are known to be excreted by most neuroblastomas (3). A nationwide neuroblastoma mass screening program for infants age six months began in Japan in 1984 but was halted in 2003 (4) after the publication of data from other countries that suggested no reduction in neuroblastoma mortality for infants who were screened (5,6). Early experience in the Japanese program indicated that many resected screen-detected neuroblastomas showed favorable biologic features, and in response some doctors adopted a watch-and-wait approach. One Japanese facility established an observational study of patients who met criteria for favorable prognosis and whose guardians were willing to accept careful observation without initial surgery (7). Fifty-three of the 101 patients referred to the facility were enrolled in the study. Of the 53, 17 experienced complete regression (that is, their tumors became undetectable) and 22 partial regression with long-term follow-up (median follow-up of 84 and 76 months, respectively); in these 39 patients, VMA and HVA levels either decreased or normalized. Spontaneous regression of neuroblastomas also was observed among German infants (manner of detection not stated) (8) and in a series of Japanese infants whose tumors were detected serendipitously by ultrasound (9).

Tumor B: Asymptomatic Malignant Disease That Progresses Too Slowly to Be Life Threatening in Even the Longest of Lifetimes

Example: Screening for Prostate Cancer

The ability of screening with PSA to reduce prostate cancer mortality is controversial, but the ability of screening to detect prostate cancers that progress too slowly to be life threatening in even the longest of lifetimes is not. Findings from autopsy studies and randomized controlled trials of prostate cancer treatment for early-stage disease provide compelling evidence that this phenomenon occurs. The autopsy studies demonstrate that some men not diagnosed with prostate cancer during their

lifetimes are found to have low-grade cancerous and preinvasive prostate lesions at autopsy (10–14). For example, Zlotta et al. examined prostates from deceased Japanese and Russian men, all of whom died of causes other than prostate cancer and resided in areas with no widespread PSA screening, and 44% percent of prostates from both Japanese and Russian men age 71 to 80 years harbored malignancies (10). Yin et al. identified adenocarcinoma in 35% and high-grade prostate intraepithelial neoplasia (without the presence of invasive disease) in an additional 27% of prostates from registered organ donors ages 60 to 69 years and without history of prostate cancer, who died in Pittsburgh between August 1994 and April 2007 (11). Konety et al. reviewed autopsy records from the University of Iowa for the years 1955 to 1960; 23% of men who died at ages 90 to 99 years during those years, all of whom who were not known to have prostate cancer prior to their deaths, had prostate cancer identified at autopsy (12).

In two RCTs of radical prostatectomy vs watchful waiting for localized prostate cancer, most men randomly assigned to watchful waiting died of causes other than prostate cancer. Of the 367 men randomly assigned to watchful waiting in the US PIVOT trial, many of whom had screen-detected disease, 183 had died after a median of 10 years of follow-up, but only 31, or 17%, had died of prostate cancer (15). Of the 348 men randomly assigned to watchful waiting in the Scandinavian SPCG-4 trial, the large majority of whom were clinically diagnosed, 247 had died after 23 years of follow-up, but only 99, or 40%, had died of prostate cancer (16). Stated another way, only 8% (PIVOT) and 28% (SPCG-4) of those randomized to the watchful waiting arm died of prostate cancer.

Patient: Asymptomatic Malignant Disease That Progresses Quickly Enough to Be Life Threatening During a Lifetime of Typical Length, but Death Because of Another Cause Occurs Prior to What Would Have Been the Destined Date of Symptomatic Diagnosis Had Screening Not Occurred

Example: Screening for Lung Cancer

The National Lung Screening Trial (NLST) demonstrated that lung cancer with low-dose computed tomography (LDCT) can reduce lung cancer mortality among heavy, long-term smokers (17). Lung cancer screening may be more prone to overdiagnosis because of patient experience than screening for other cancers, because persons screened for the disease often have serious smoking-related cardiac or pulmonary comorbidities. Of the 76 deceased NLST participants in the LDCT arm who were screen-detected with stage IV disease, five, or 7%, were deemed by a blinded review board to have died of causes other than lung cancer (18). Review board–assigned causes were available for four and were as follows: bile duct carcinoma, pneumonia, pancreatic cancer, and atherosclerotic heart disease of a coronary artery.

Concluding Remarks

Our interactions with patients, advocates, researchers, clinicians, and journalists have led us to believe that the concept of overdiagnosis is difficult to explain and, for some, difficult to accept. We can identify three factors that contribute to that difficulty. First, the thought that early detection could be of no

benefit in some instances runs counter to the view that most people hold of cancer: a disease that is always fatal unless identified at an early stage and treated aggressively. This view has been reinforced by the many pro-screening messages in the media. Second, the terms "overdiagnosis" and "indolent disease" are frequently but incorrectly used interchangeably. This imprecise terminology is employed even by those who aim to bring about an awareness and understanding of the phenomenon; as such, more confusion ensues because of inconsistent messages. Last, the magnitude of overdiagnosis is rarely discussed in concert with efforts to explain its existence or how it can occur. This may be because published estimates of overdiagnosis, even for a given cancer and modality, are quite variable (ranging often from 0% to over 50%) and much disagreement exists as to which estimate provides the "correct" answer. But strong messages about the existence of overdiagnosis may be misinterpreted by some to mean that most cancers do not require treatment, which runs contrary to perceptions about the fatality of cancer, as well as the practice of treating nearly all cancers given the current difficulties in distinguishing overdiagnosed cancers from others. Such disconnects can lead to the rejection of the notion that overdiagnosis occurs.

We believe that the tumor-patient classification will lead to a better understanding and appreciation of overdiagnosis. It is only with a full understanding of the benefits and harms of cancer screening, including overdiagnosis, that individuals contemplating screening can make decisions that are informed and right for them.

Funding

Notes

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