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Imaging-Based Screening: Understanding the Controversies

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Abstract

Objective—The goals of this article are to provide an overview of controversial aspects of imaging-based screening and to elucidate potential risks that may offset anticipated benefits.

Conclusion—Current controversial topics associated with imaging-based screening include false-positive results, incidental findings, overdiagnosis, radiation risks, and costs. Alongside the benefits of screening, radiologists should be prepared to discuss these additional diagnostic consequences with providers and patients to better guide shared decision making regarding imaging-based screening.

Keywords

false-positive; incidental findings; overdiagnosis; screening

As we transition into an era where the Patient Protection and Affordable Care Act will prioritize disease prevention in the United States, the importance of implementing screening programs that yield durable health and economic benefits is paramount [1]. Imaging-based screening will likely play a larger role in preventive medicine through cancer screening and surveillance. The U.S. Preventive Services Task Force recommends routine biennial screening mammography for breast cancer in women aged 50–74 years, annual CT lung cancer screening in adults aged 55–80 years who have smoked within the past 15 years and have a 30 pack-year smoking history, and one-time ultrasound screening for abdominal aortic aneurysm (AAA) in men aged 65–75 years who have ever smoked [2]. The role of imaging in disease screening will likely expand in the near future, with mounting evidence of effectiveness for technologies such as CT colonography [3–6].

The overall rationale behind screening is that early diagnosis of a particular disease has the potential to reduce morbidity and mortality, as found by multiple studies. Results from the National Lung Screening Trial found a 20% reduction in lung cancer mortality with CT

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versus radiography [7]. Multiple randomized controlled trials have reported a 15–30% reduction in breast cancer mortality among women undergoing routine screening mammography [8–10]. These women also experience decreased morbidity through detection of breast cancers at earlier stages, enabling less-extensive surgical treatment and leading to fewer women requiring systemic chemotherapy [11]. One-time ultrasound AAA screening in men aged 65–75 years who have ever smoked is associated with decreased AAA rupture and AAA-related mortality rates for up to 10–15 years [12].

However, at both the individual patient level and the population level, balancing potential benefits in mortality and morbidity reduction with the potential harms of screening, including health risks and economic costs, is a challenge. The remainder of this article provides an overview of current key controversies regarding the potential harms of imaging-based screening, including false-positive results, incidental findings, overdiagnosis, radiation risks, and costs. Radiologists need to be knowledgeable about these topics to educate patients and referring colleagues about the appropriate use of imaging-based screening.

False-Positive Findings

Because a screening population has no signs or symptoms of disease, it is important to consider the diagnostic consequences of a positive test result. A highly sensitive test, which will catch nearly all the patients with the disease in question (a high true-positive proportion), is an essential characteristic of a screening study. Patients with false-positive results, however, will incur the subsequent diagnostic consequences but gain none of the benefits. Thus, the ideal screening test should be highly sensitive and have a high positive predictive value to avoid unnecessary diagnostic workup. The important distinction between sensitivity and positive predictive value is that a test's positive predictive value depends on the underlying prevalence of disease in the population screened, whereas a test's sensitivity does not and is a test-specific characteristic. Therefore, a screening test could be highly sensitive but still have a poor positive predictive value, and therefore have lower real-world clinical value.

For example, the ACRIN 6666 trial evaluated the use of screening whole-breast ultrasound in addition to mammography in women with dense breasts and at least one other breast cancer risk factor [13]. There was increased cancer detection (higher sensitivity) when compared with mammography alone (four additional cancers per 1000 women screened). However, there was also a substantial increase in the biopsy rate, from 2% without ultrasound to 5% with ultrasound. Moreover, only 7% of biopsies after a positive supplemental ultrasound result yielded a cancer diagnosis. The low positive predictive value and high false-positive biopsy rate for the use of adjunct breast ultrasound are among the major barriers to its widespread adoption. Currently, the American College of Radiology (ACR) Appropriateness Criteria do not consider screening ultrasound to be usually appropriate for any women but suggest that it may be appropriate for use among intermediate- and high-risk women [14].

In the case of screening mammography, it is estimated that over a 10-year period, approximately one third to one half of all women who participate in breast cancer screening will receive at least one abnormal result requiring additional workup [15, 16]. False-positive results from breast cancer screening may lead to unnecessary patient anxiety, additional imaging, and the potential for more-invasive procedures [17, 18]. One recent estimate of additional costs associated with diagnostic workup was $371 for a false-positive mammogram versus $13 for a true-negative mammogram [19]. Nevertheless, given the mortality reduction benefits at the population level, the ACR and the Society of Breast Imaging continue to recommend annual mammography screening for women aged 40 years and older [20].

Incidental Findings

Incidental findings—that is, those discovered during image interpretation that are unrelated to the indication of the study—are a routine part of diagnostic radiology [21]. In examinations with larger FOVs, such as CT when used for lung cancer, colon cancer, or coronary artery disease screening, there is the potential for the discovery of multiple incidental findings that are unrelated to the disease of interest. This poses a challenge to radiologists and referring clinicians, because patients undergoing screening are by definition asymptomatic. For example, nearly half of all patients undergoing cardiac CT for screening of coronary artery disease will have an extracardiac finding [22]. An unknown extracardiac malignancy can be found in approximately 1 in every 150 patients studied (about 1%), with the majority (70%) being lung cancers [23]. Approximately 8% of patients who undergo CT for coronary artery disease screening and 14% of patients who undergo CT for lung cancer screening may have clinically significant incidental findings requiring diagnostic workup [24]. Potential harms include complications of unnecessary invasive procedures, increased costs, and undue patient anxiety for a finding that is ultimately determined to be benign [25]. These incidentalomas place patients, providers, and radiologists in a difficult situation, because it may not be possible to predict which findings will be clinically significant and which will not at the time of image interpretation.

In recent years, more evidence-based recommendations for the reporting and management of incidental findings have been developed and refined. As an example, non-calcified lung nodules may be detected in up to 66% of high-risk individuals older than 50 years with a 20 pack-year smoking history on screening lung CT [26]. The Fleischner Society has developed widely used consensus guidelines for the management of incidental pulmonary nodules. Because of the need for further discrimination between solid and subsolid (e.g., ground-glass) lung nodules and the reclassification of lung adenocarcinomas, the Fleischner Society recently adapted their long-standing guidelines to address subsolid pulmonary nodules [27]. However, standardized use of such guidelines and recommendations is not yet wide-spread [28–30]. The ACR Incidental Findings Committee has also published a series of white papers to help standardize the management of a multitude of common incidental findings on abdominal and pelvic CT and MRI [31–34]. To improve consistency of care and avoid confusion among referring providers and patients, radiologists should be versed in and better adhere to these consensus guidelines when available.

Overdiagnosis

As both diagnostic imaging utilization and imaging-based screening utilization increase, we are discovering more abnormalities at earlier stages, leading to the potential for overdiagnosis and overtreatment. Overdiagnosis and overtreatment may occur when imaging detects asymptomatic disease that would not have become clinically apparent over an individual's lifetime or when imaging-based detection results in treatment of disease that would not have shortened an individual's life expectancy. Both of these scenarios occur more frequently when older populations with higher competing mortality risks undergo imaging [35, 36]. Specifically, for cancer, this may be represented by a low-grade malignancy that will not metastasize or cause the patient morbidity or mortality if left alone. Because of the invasive treatment of certain cancers, it is purported that overdiagnosis and overtreatment may be among the most significant potential harms associated with imaging-based screening [36].

One emerging example of potential imaging-based overdiagnosis and overtreatment is the thyroid nodule, which is commonly found incidentally in patients who undergo CT of the chest for chronic respiratory symptoms or suspected pulmonary embolism [37]. In the United States, the incidence of thyroid cancer has nearly tripled in the past 30 years, with the majority of these new diagnosed cancers attributed to the papillary type of thyroid cancer [37, 38]. In general, about 85% of thyroid cancers are papillary type with an estimated mortality of approximately 1–2% in 20 years [37]. Also, approximately one third of autopsy studies from people who died of other causes revealed this type of thyroid cancer [39]. Despite the increase in diagnosis and treatment of thyroid cancer, the mortality rate from thyroid cancer has been stable from 1975 to 2009 [38]. Therefore, some papillary thyroid cancers that are currently being detected may be contributing to overdiagnosis and overtreatment, and their incidence may further increase with the adoption of screening CT for lung cancer.

Because more screening will generally lead to more cancer detection, the same questions regarding overdiagnosis and overtreatment can be asked in virtually any imaging-based screening setting. Current estimates for breast cancer screening overdiagnosis and overtreatment are in the range of 10–20% [40]. However, actual calculations of overdiagnosis and overtreatment are not possible; this is because once a serious disease such as cancer is identified and diagnosed, it is commonly treated because it is not possible to determine which lesions will progress and which ones can be safely managed with more conservative approaches. In rare settings in which patients with identified cancers are followed rather than treated immediately, a selection bias is commonly present that precludes generalizable comparison of the outcomes of treated versus untreated patients. As a result of these challenges, mathematic models that extrapolate population data on diseases, inferring true screening benefits by computing health benefits (if any) in calendar years before and after dissemination of screening, provide important insights into how alternative screening strategies and treatments can affect patient outcomes at the population level [41, 42]. Such models are increasingly used to inform screening guidelines, including U.S. Preventive Services Task Force recommendations [43, 44].

Radiation Risks

Imaging-based screening examinations involving ionizing radiation (e.g., mammography, chest CT for lung cancer, and CT colonography) carry the theoretic harm of radiation-induced carcinogenesis. When weighing associated risks, both their magnitude and timing must be considered. These attributes should be balanced carefully against the benefits of screening, accounting for both current and future anticipated screening tests. Three key factors regarding the magnitude, accumulation, and timing of radiation-induced cancer risks are particularly important to consider. First, their magnitude, per test, is likely to be very low. Second, associated risks are thought to be cumulative [45]. Therefore, when considering a screening program, as opposed to an isolated screening test, cumulative radiation-induced cancer risks must be weighed against the program's lifetime benefits. Third, radiation-induced cancer risks are greatest in younger patients, but in comparison with more immediate health risks (for which screening is being done), these cancer risks manifest much later in life [46, 47]. Conversely, older patients with lower life expectancy will experience relatively minimal risks from radiation imparted during imaging screening [48]. Because of the mathematic complexity of weighing these risks against screening benefits on the population level and in a lifetime horizon, disease modeling can be used to accomplish related risk-benefit analyses to inform policy [49–51].

Effective dose is a calculated quantity used to roughly estimate the relative effects of different sources of ionizing radiation to an individual. The average annual effective dose from background radiation, for instance, is about 3 mSv [52]. In comparison, the average estimated radiation dose associated with low-dose chest CT of average size participants in the National Lung Screening Trial was about 2 mSv [53]. Nevertheless, in the case of low-dose chest CT for lung cancer screening, the potential risks associated with annual chest CT scans for more than a 20-year period have raised concerns about risks of radiation-induced cancer [54]. Using modeling techniques, radiation-induced cancer risks associated with different lung cancer screening programs have been carefully weighed, yielding estimates that can help guide patient-level decision making [51].

Although the theoretic risk of radiation-induced cancer from medical imaging remains a controversial topic and a persistent source of queries from physicians and patients, radiologists can help provide reassurance that current screening technologies continue to undergo technologic advances specifically addressing the issue of radiation dose [55]. With campaigns such as Image Wisely, the specialty of radiology continues to take the lead in making radiation doses from medical imaging as low as reasonably achievable and diagnostically acceptable. For recommended routine imaging-based screening examinations, the current estimates for lifetime attributable risks of developing fatal cancer are extremely small and are far outweighed by the potential mortality benefit of early disease detection [56].

Costs of Screening

The financial “cost” of screening depends on the cost of the imaging procedure itself in addition to the costs associated with down-stream diagnostic evaluations, interventions, and

treatments associated with screening [57]. True cost also includes the indirect costs of patient time and out-of-pocket expenses, as well as costs to economic productivity in general. The productivity costs of cancer mortality in the United States in the year 2000, for instance, were estimated to be $115.8 billion. When including care-giving and household activities, the costs associated with cancer mortality increased to $232.4 billion. These annual figures are projected to be $147.6 billion and $308 billion, respectively, by the year 2020. With just a 1% collective annual reduction in mortality from lung, colorectal, breast, pancreatic, brain cancer, and leukemia combined, it is projected that cancer mortality costs will decrease by only $814 million per year [1].

Thus, with demands for increased health care quality at decreased costs, new technologies and treatments related to cancer care are increasingly being scrutinized for their potential to increase health care costs relative to the cost savings from decreasing cancer morbidity and mortality. It is, therefore, not a surprise that imaging-based cancer screening has been identified as a potential source of unnecessary expenses to the health care system. For instance, the cost of mammography screening in the United States was estimated to be $7.8 billion in 2010. Using health economic modeling, one recent analysis reported a potential savings of over $4 billion if the U.S. screening population adhered to the U.S. Preventive Services Task Force recommendations for biennial screening mammography at ages 50–74 years [58]. Moreover, a study using simulation modeling for more intensive breast cancer screening with MRI among *BRCA* mutation carriers estimated that up-front screening and diagnosis costs outweighed the downstream savings in both breast cancer treatment and mortality [59].

Radiologists should understand that most comprehensive economic analyses related to screening rely on simulation models. Given the paucity of large-scale screening trials and the expense and length of follow-up time required to establish outcomes, as well as the decentralized nature of cancer screening and care in the United States, direct population-level cost data are unavailable. Complicating the balance between the costs and benefits of newer imaging-based screening technologies is their rapid diffusion into community practices, with technology adoption occurring at a more rapid pace than the collection of effectiveness data [60]. Without definitive data from randomized trials, simulation modeling uses performance data from observational trials and intermediate outcomes from disease registries to integrate information from multiple disparate sources to project longer-term outcomes and provide quantitative estimates of other screening consequences [61].

Future Directions and Conclusion

Moving forward, radiologists will not only see increasing volumes of imaging-based screening but will also have the opportunity to advance the field by identifying new techniques for decreasing false-positive findings (e.g., tomosynthesis for breast cancer screening), differentiating aggressive malignancies from more indolent ones to minimize overdiagnosis and overtreatment (e.g., identification of new imaging biomarkers of cancer types at the molecular level), establishing best practices for managing incidental findings (e.g., improved adherence to ACR Appropriateness Criteria), and decreasing the radiation dose associated with screening modalities that require ionizing radiation (e.g., low-dose CT

techniques). Moreover, with increasing demand among patients for greater cost transparency in health care [62–64], radiologists should take an active role in helping to determine the true direct and indirect costs associated with screening-related imaging from different stakeholder perspectives.

Although the current controversies surrounding imaging-based screening are introduced here, the overall mortality benefit of most screening examinations is widely acknowledged. Patient-centered discussions regarding the balance between the benefits and risks of imaging-based screening will become more common as more personalized screening is advocated in the United States. Therefore, all radiologists involved in interpreting such studies should be well versed in explaining both the benefits and potential harms of imaging-based screening studies and should engage patients, providers, and other stakeholders to further minimize potential risks.

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