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Imaging-Based Screening: Maximizing Benefits and Minimizing Harms

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Abstract

Advanced imaging technologies play a central role in screening asymptomatic patients. However, the balance between imaging-based screening's potential benefits versus risks is sometimes unclear. Radiologists will have to address ongoing concerns, including high false-positive rates, incidental findings outside the organ of interest, overdiagnosis, and potential risks from radiation exposure. In this article, we provide a brief overview of these recurring controversies, and suggest the following as areas that radiologists should focus on in order to tip the balance towards more benefits and less harms for patients undergoing imaging-based screening: interpretive variability, abnormal finding thresholds, and personalized, risk-based screening.

Keywords

imaging-based screening; screening harms; false-positives; overdiagnosis; incidental findings

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1. Introduction

Diseases for which screening is appropriate include those that have significant impact on quality-of-life or mortality, are common enough to invest resources in screening programs, have a known natural history compatible with benefit from early detection and treatment, and for which an effective treatment is available. The ideal screening test, imaging-based or not, is safe, relatively easy to administer, acceptable to the public, inexpensive, and demonstrates acceptable test characteristics such as sensitivity and specificity. Finally, screening programs are appropriate only when those testing positive have reasonable access to follow-up, including access to appropriate treatment [1].

The role of medical imaging in disease screening continues to grow, presenting new opportunities for improving health outcomes for large patient populations. However, imaging-based screening is not without controversy, as current technologies can only detect disease that is grossly apparent on imaging rather than providing functional information about the aggressiveness of a disease process. This inherent limitation, in turn, opens the door to criticisms and debates about the actual balance between the benefits and harms of any imaging-based screening procedure. Indeed, the traditional public overconfidence in the benefits of screening has frequently come into question in recent years, creating a highly contentious political environment regarding routine imaging-based screening guidelines [2–6]. For radiologists, who are at the frontline of administering and interpreting advanced imaging, demonstrating overall value for these procedures is an increasingly important, yet complex task.

In addition to continuous technological improvements and refinement of advanced imaging technologies, including lowering associated radiation doses, what other aspects of screening should radiologists be addressing in order to maximize potential benefits and minimize unnecessary harms? This article provides a brief overview of a few controversial aspects of imaging-based screening, followed by a discussion of specific areas that would benefit from greater attention from the radiology community to improve the value of imaging-based screening.

2. Ongoing Concerns Regarding Imaging-Based Screening

2.1 False-Positive Exams

The most obvious potential harms from imaging-based screening are false-positive exams and the downstream sequelae, including morbidity associated with unnecessary diagnostic exams, invasive interventions, and ionizing radiation exposure. False positive results are not unexpected in screening tests, but the degree to which false positives occur depends upon patient, test, and interpreter characteristics [7, 8]. In addition, the cumulative false-positive rate needs to be considered as many individuals undergo these exams repeatedly over a lifetime. For example, more than half of the women undergoing screening mammography annually for a decade will experience at least one false positive exam [9–11].

The shift in the United States Preventive Services Task Force (USPSTF) recommendations towards less frequent mammography screening starting at an older age was largely driven by

the harms associated with the rate of false-positive screening among younger women [10]. While the addition of tomosynthesis to digital mammography screening could notably decrease the false positive rate [12], a discernible proportion of women will still need diagnostic imaging work-up and possible intervention for benign findings, incurring both additional medical costs, as well as adverse psychological effects [7, 13–15]. These latter psychological effects, however, may be quite transient and of lower magnitude than originally believed [16, 17]. Nevertheless, the false-positive rates, at least in the large trials, are higher for newer imaging-based screening exams [18, 19].

2.2 Incidental Findings

With larger areas of the body visualized by cross sectional imaging such as low-dose CT for lung cancer screening and CT colonography, incidental findings are likely to be a constant issue for screening programs where anatomy outside of the organ of interest is included in the field of view. Multiple reports suggest relatively high rates of incidental findings outside the organ of interest on CT screening for lung cancer, colon cancer, and coronary artery disease [20–24]. The cost of pursuing additional work-up of incidental findings is variably reported but not negligible [22], and it is contended that many studies underestimate diagnostic work-up costs of incidental findings [25]. Furthermore, the relative need for follow-up and the clinical significance of such incidental findings remain unknown. For example, in the case of cross-sectional imaging that includes the lower neck and upper chest, one incidental finding that has become highly publicized is the thyroid nodule, with suggestion of growing overdiagnosis of occult papillary thyroid cancers of little clinical significance [26–30].

2.3 Overdiagnosis

Overdiagnosis is defined as disease that, if it had not been screen-detected, would not have become clinically symptomatic during the patient's lifetime [31–33]. Overdiagnosis is not directly measurable, but rather estimates of overdiagnosis are derived from long-term population-level data comparing incidence among screened versus unscreened patients [31, 34–36]. Many note that published estimates of overdiagnosis are nonuniform in methodology, which may account for their extreme variability [13, 32, 35, 36]. The concept of overdiagnosis, and subsequent overtreatment of indolent disease, has been explored and debated extensively in the breast cancer screening literature [31, 34, 37–39], and similar analyses and criticisms are noted with respect to lung cancer screening [18, 21, 33, 40]. For breast cancer, estimates range from negligible amounts to more than half of screen-detected breast cancers [32, 34–37, 39, 41]. For lung cancer screening, estimates range between 10% and 25% based on the National Lung Screening Trial (NLST) data [18, 21, 40], although some contend that this percentage is likely much higher [33, 42]. Regardless of magnitude, overdiagnosis and subsequent overtreatment of disease that would never have become clinically relevant results in multiple potential harms, including physical morbidity, additional costs, and psychological harms of receiving a diagnosis [13, 43, 44].

2.4 Radiation Exposure

While the goal of imaging-based screening is to detect cancer at earlier stages, these examinations may inadvertently increase the risk of radiation-induced cancer among a small

proportion of patients. Screening mammography, CT lung cancer screening, and CT colonography all impart ionizing radiation, a potential carcinogen even at relatively low doses [45]. The lifetime attributable risk of fatal breast cancer from annual mammography screening between 40 and 80 years of age is estimated at about 0.02% [46]. One analysis estimates that a single low-dose chest CT results in 0.01–0.06% lifetime cancer risk and that annual CT scans from age 50 to 75 years could result in an incremental increased lifetime risk of 0.2–0.85% [47]. Accounting for follow-up CT evaluations for extracolonic incidental findings, CT colonography is associated with an estimated 0.15% increased risk of radiation-induced cancer for an individual undergoing screening every 5 years from age 50 until age 80 [48]. For each of these imaging-based screening examinations, there appears to be a small, but real risk of radiation-induced malignancy at the population level [49]. This risk will increasingly be included in the risk-benefit simulation modeling that informs the USPSTF recommendations, as is the case for the revised screening mammography recommendations to be published this year [50].

3. Decreasing Variability in Interpretation

It is well recognized that radiologists vary in their interpretation of screening examinations [51,52]. Radiologists, however, are not alone in interpretive variability, as similar challenges are noted among pathologists [53]. In order to demonstrate value, new imaging-based screening initiatives will need to ensure greater consistency in test interpretation.

Previous research on screening mammography offers some valuable lessons learned regarding decreasing interpretive variability. First, greater volumes of screening exams and more exposure to diagnostic work-ups for abnormal findings have been associated with improved overall radiologist performance, including a significant decrease in false positive rates [54,55]. Additionally, subspecialty training has been associated with reduced work-up of benign lesions while maintaining high disease detection rates [56]. Moreover, comparative research between U.S. and European practices suggests that double reading by two radiologists compared to single radiologist interpretation can significantly decrease the false positive rate for screening mammography [57].

Thus, for newer screening exams such as low-dose CT lung cancer screening and CT colonography, radiologists should consider evaluating similar practices. For instance, should only fellowship-trained thoracic imagers be interpreting low-dose CT lung cancer screening studies? Should there be minimal annual screening exam volumes set for those interpreting CT colonography studies? The NLST found substantial variability across radiologists interpreting studies, with the odds of a false-positive interpretation 2.5 times higher for one radiologist versus another [58]. Similar variability is being seen with CT colonography interpretive performance [59]. Unfortunately, there has been very little data collected thus far examining the relationship between radiologists' training and experience levels and improved interpretive accuracy for these newer imaging-based screening studies.

The issue of double reading in the U.S. for screening studies has largely been evaded with arguments that screening in the U.S. is decentralized, without dedicated national screening programs. Many have suggested that double reading would be unrealistic in the U.S. due to

manpower shortages, and instead suggest the addition of computer aided detection (CAD) software to fill the role of a second reader. However, contrary to its intended effect, CAD has been shown to actually reduce the overall accuracy of screening mammography [60]. Early studies involving CAD as a second reader on CT colonography suggest improvement in sensitivity for detecting lesions 6–9 mm in size, but at a lower specificity [61]. Heeding the lessons learned from CAD for mammography, rapid adoption of CAD software for newer imaging-based screening studies should be approached with caution. Moreover, the potential for double reading to help decrease variability in interpretation should likely be revisited given the growing efficiencies of modern telemedicine practices [62].

4. Adjusting the Threshold for Abnormal Findings

To adjust thresholds for diagnosing and treating lesions detected on imaging-based screening, altering the cancer vocabulary has been suggested as both patients and physicians may react strongly to the word “cancer” [2, 63]. Some have suggested that the term “cancer” be reserved for diseases known to be lethal and that a new term, “indolent lesion of epithelial origin” or IDLE, be used to describe slowly progressing disease without mortality certainty [2, 63]. Moreover, monitoring certain low-risk screen-detected lesions via “observational registries” has been suggested in lieu of aggressive treatment [2, 64]. However, it is recognized that altering medical terminology and changing current standards of practice would face great opposition and multiple challenges, including potential medical-legal ramifications for physicians [2, 65].

While the example above may appear extreme to some, radiologists can and should take a more active role in determining whether more appropriate thresholds for reporting potentially clinically significant disease can be reached based on imaging characteristics. By increasing the threshold to define a positive screening test, the number of false positives can be reduced. In the case of low-dose CT lung cancer screening, researchers demonstrated theoretical decreases in false positives by changing the threshold size at which radiologists should report a positive result, with a relatively small associated increase in the number of “delayed or missed” cancers [66]. With approximately 96% of abnormal lung cancer screening exams eventually found to represent false positives in the NLST [19], there is great potential for radiologists to develop improved interpretive thresholds based on imaging features. The American College of Radiology (ACR), moreover, has developed the Lung CT Screening Reporting and Data System (Lung-RADS) in an effort to standardize reporting and management recommendations. In addition to providing standard lexicon, ACR’s Lung-RADS, and similar efforts for breast imaging (BI-RADS), head injury (HI-RADS), liver imaging (LI-RADS) and prostate imaging (PI-RADS), aims to provide threshold guidelines for positive examinations, as well as suggestions for interval imaging follow-up [67].

Recent studies have also suggested that most incidental findings on imaging studies are not clinically significant but contribute to unnecessary diagnostic testing and interventions that add to overall healthcare costs [68–70]. Therefore, threshold values will need to be determined for reporting incidental findings, in addition to the findings of interest, for all cross-sectional imaging-based screening. Moreover, if incidental findings are reported, consensus follow-up recommendations will also need to be provided. Studies addressing the

evaluation of lung nodules detected by radiologists suggest relatively low agreement among radiologists regarding imaging follow-up recommendations [71, 72]. One study on screening for lung cancer found incidental thyroid nodules reported in nearly 3% of screening examinations with unclear diagnostic work-up recommendations [73]. Indeed, in the case of CT colonography where images are obtained of the entire abdomen and pelvis, the Center for Medicare & Medicaid Services' decision not to reimburse for the technology cited concerns for the costs of evaluating extracolonic findings of equivocal significance [25].

In the absence of long-term, downstream resource utilization data stemming from incidental findings on screening exams, radiologists should work towards developing best practice guidelines for determining when and if incidental findings should be reported, and providing guidance to referring clinicians on the most appropriate follow-up recommendations. The American College of Radiology has published a series of white papers on managing such incidental findings [74]. However, continued, multidisciplinary work is necessary to update appropriate imaging recommendations based on the growing literature on incidental findings.

5. Personalizing Disease Screening

Much of the controversy surrounding overdiagnosis stems from heterogeneity of disease behavior [2, 7, 64, 75–77]. Ideally, screen-detected diseases would follow a predictable progression to benefit from early detection and treatment, but this idealized behavior is not an absolute [76]. Many small cancers detected on screening may never become clinically apparent during a person's lifetime. In response, many cite the promise of imaging biomarkers for helping discern indolent from aggressive cancers. However, such tools are still in their early development phases and no imaging-based screening tools are currently equipped to provide this type of information.

In the meantime, the use of imaging-based screening exams can be better tailored towards those at higher risk for developing disease, and be provided at the most optimal screening intervals. Radiologists can help guide and encourage the use of risk stratification tools to aid in informed decision-making [64, 77]. Risk stratification may mean narrowing the screened population to higher risk individuals or larger intervals between exams, rather than encouraging screening among entire populations at more frequent intervals [13]. Lung cancer screening, for example, is recommended only for high-risk current and former smokers (having quit within the last 15 years) with a 30-year pack history aged 55–80 years [21, 78]. Similarly, in 2009, the USPSTF updated its recommendation on breast cancer screening by also effectively focusing on higher risk (older) patients by recommending routine biennial screening among women aged 50–74 years old, with screening before age 50 dependent on the individual woman [79].

In an era of shared-decision making in medicine, radiologists should support endeavors for more appropriate disease screening. Many propose that more public education regarding the benefits and risks of screening is key to ensuring the public's trust in medical screening efforts and to promote greater individual patient involvement in their health care [5, 13, 44]. Indeed, patients now have ready and open access to their radiology reports through patient

web portals. Rather than approaching greater transparency in health care with a sense of threat, radiologists should welcome increased interactions with referring physicians - and potentially patients themselves - regarding the most appropriate use of imaging-based screening studies. In breast cancer screening, for instance, a recent study of breast MRI use in the U.S. reports that the majority of women at high lifetime risk who would qualify for annual supplemental screening breast MRI are underutilizing this tool [80]. Thus, as the experts of advanced imaging technologies, radiologists have the opportunity to be leaders in improved adherence to screening guidelines and to help patients at high risk navigate towards improved utilization of appropriate, advanced imaging-based screening examinations.

6. Conclusion

Imaging continues to play an increasingly central role in early disease detection, with the promise of decreased morbidity and mortality from early intervention. Radiologists are at the forefront of population-based screening efforts that can positively influence patient health. In addition to continued refinement of imaging technologies, radiologists must also address key ongoing concerns regarding imaging-based screening, including how to minimize false-positives, manage incidental findings, deter overdiagnosis, and minimize radiation exposure. As stewards of advanced imaging, radiologists have the opportunity to decrease interpretive variability, minimize false positives, appropriately report and manage clinically significant findings, and contribute to risk stratification and informed decision-making among heterogeneous patient populations.

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