REVIEW

CME CREDIT

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Whole-body CT screening for cancer and coronary disease: Does it pass the test?

ABSTRACT

Even though whole-body CT scanning is being marketed directly to patients and they are starting to demand it, does it meet the standards of a good screening test for cancer and coronary artery disease? This article is a step-by-step, disease-specific discussion of the characteristics of a good screening test, and whether whole-body CT scanning meets these standards.

KEY POINTS

CT is not an ideal screening tool, but neither is any other screening or diagnostic test. Given that the test is already available and in use, the medical community should set standards based on scientific criteria.

CT screening should be done only after patient education and informed consent, with appropriate follow-up. It should be integrated into the traditional patient-physician relationship, not replace it.

CT can detect early lung cancer better than any other method available. It often detects indeterminate nodules, but they can be followed in serial examinations to determine if they are likely to be malignant.

CT screening for colorectal cancer may be more acceptable to patients than is fiberoptic colonoscopy.

CT can detect and quantify coronary arterial calcification, a marker of atherosclerotic coronary artery disease. The clinical significance of coronary calcifications, however, is evolving.

SHOULD WHOLE-BODY MULTISLICE computed tomography (CT) be used as a screening test in healthy people? The issue is controversial, and experts disagree on scientific, social, economic, and even ethical grounds.

No one disputes that multislice CT can detect and measure some disease processes earlier than routine history and physical examinations can, and some patients—a few—would benefit from CT screening. But others would be harmed, owing to drawbacks inherent in any screening process, including:

- False-positive results, which lead to mistaken labeling and unnecessary workup
- False-negative results, leading to wrong reassurance and delayed treatment
- Discovery of latent or nonprogressive disease, leading to unnecessary workup and treatment.

Complicating this issue, CT screening is being marketed directly to consumers, and patients are starting to demand it.[1] But before we can recommend CT screening to our patients, we ought to have some idea of how many would benefit vs how many would be harmed—and how to decide that the balance is acceptable.

This article evaluates multislice CT as a screening test to detect early cancer of the lung and colon, and coronary artery calcification, a risk factor for coronary artery disease. We base our discussion on previously published criteria for evaluating screening programs such as mammography.

CT TECHNOLOGY IS IMPROVING

Electron-beam CT became available in the mid-1980s. It had the advantage of very rapid data acquisition; for example, it could image the coronary arteries by scanning the entire heart during a time period no longer than diastole. However, because image quality was poor, it was not widely used.

In the early 1990s, the first generation of multislice CT scanners was introduced. A second row of detectors was later added, allowing the scanner to capture two image slices for every rotation of the gantry. By 1998, scanners with four rows of detectors were developed; now, some scanners offer 16 slices per rotation, and even more sophisticated ones are expected.

The new scanners offer excellent spatial resolution of large anatomic regions (such as the chest and abdomen) and can obtain images in a single breath-hold (< 20 seconds).

If a large area of coverage is not needed, the spatial resolution can be increased or the time can be shortened. For instance, images of the heart can be obtained with breath-holds and cardiac gating (synchronizing the data acquisition to coincide with diastole). This technique minimizes cardiac motion and allows us to detect and quantify coronary artery calcification. Adding intravenous iodinated contrast media, we can also visualize the coronary artery tree or other blood vessels to identify vascular abnormalities such as stenosis or aneurysms.

A few would benefit from CT screening; others would be harmed

CRITERIA FOR A GOOD SCREENING TEST

The logic behind screening for disease in people without symptoms is that earlier detection may lead to earlier intervention, when the disease is more amenable to therapy.

Obuchowski et al[2] devised 10 criteria for evaluating screening programs, based on characteristics of the disease, the test, and the possible treatments: the disease must have serious consequences and be common in a detectable preclinical phase; the test must detect little pseudodisease, detect the preclinical phase with high accuracy, detect the disease before the "critical point," cause little morbidity, and be affordable and available; and the treatment must exist, be more effective when applied before symptoms appear, and not be too risky or toxic.

In the following sections we apply these criteria to multislice CT screening for lung cancer, colon cancer, and coronary calcification, a risk factor for coronary artery disease. The same criteria will be applied to mammography for breast cancer, an accepted screening approach.

CHARACTERISTICS OF THE DISEASE

The disease must have serious consequences

The diseases under discussion unquestionably fulfill this criterion. Coronary artery disease is the leading cause of death in adults, and cancers of the lung, colon, and breast cause the most cancer deaths.

The disease must be common in a detectable preclinical phase

Screening programs are more cost-effective if the disease is common in the screened population and has a long and predictable preclinical phase during which it can be detected. If the disease is rare, many people must be screened to detect it. If the preclinical phase is short, the test will be less likely to detect disease before it becomes clinically manifest.

The diseases under discussion seem to meet this criterion.

Lung cancer prevalence in logical candidates for screening (people older than 40 years who have smoked at least 1 pack of cigarettes per day for 10 years) is 2% to 4%.[3–5]

Colorectal cancer prevalence. In symptom-free people older than 50 years without risk factors for colorectal cancer, the prevalence of adenomatous polyps 1 cm or larger is 3%, increasing to 5% to 6% by 80 years.[6]

Breast cancer prevalence in the general population is 0.6% to 1%.[7–9]

Coronary artery disease is ubiquitous, and atheromatous lesions begin developing in childhood.

CHARACTERISTICS OF THE TEST

The test must detect little pseudodisease

A screening test is not cost-effective if many of the cases it detects are actually "pseudodisease," ie, cases that would not cause any prob-

lems in the patient's lifetime. There are two types of pseudodisease[10,11]:

- Type 1, in which the disease never progresses and may in fact regress naturally; and
- Type 2, in which the disease progresses so slowly that patients never develop symptoms.

Pseudodisease in lung cancer screening is probably uncommon, given that 80% to 100% of people with untreated lung cancer die within 5 to 10 years.[12,13]

Pseudodisease in colorectal cancer screening may be of concern, especially type 1 (nonprogressing) pseudodisease, as there is evidence that many adenomatous polyps smaller than 1 cm regress.[14] In fact, the rate of progression for polyps of this size has been estimated at only about 2.5 polyps per 1,000 patient-years.[15]

The frequency of type 2 (slowly progressing) pseudodisease was evaluated in a large autopsy series[16]: colorectal cancer unrelated to the cause of death was detected in 0.5% of those age 50 to 60, 1% of those age 60 to 70, and 1.5% of those age 70 to 80.

Pseudodisease in breast cancer screening. The prevalence of ductal breast cancer in situ in women who die of other causes is 6% to 14%.[17–19]

Pseudodisease in coronary screening is more complicated because CT measures calcification, a marker of disease rather than the disease itself.[20–24] Screening is based on the assumption that the amount of calcified plaque is proportional to the total amount of plaque present. But in people with atherosclerosis, more of the plaque is noncalcified than calcified. Furthermore, the calcified areas of atherosclerotic plaque are likely more stable than the noncalcified portion; most acute coronary events occur when a noncalcified lesion ruptures, triggering a cascade of thrombosis and occlusion.

The measure of calcification is the Agatston score. The higher the Agatston score, the greater the risk for coronary events; however, the studies that found this association did not adjust for other cardiac risk factors.[25,26] A pooled analysis from these studies[27] found that the Agatston score is sensitive and very specific for the presence of calcification, but is insensitive to the total atherosclerotic burden that is uncalcified.

What does this mean for patients? A low Agatston score (< 10) predicts a very low risk for developing coronary heart disease.[27,28] On the other hand, a high score does not necessarily mean the patient will have a coronary event, but it may be valuable to know about in a patient who seems to be at only intermediate risk on the basis of other risk factors—the high score would indicate that he or she is actually at high risk and should undertake intensive preventive measures.[27,28] However, even though the prognostic value of calcium scoring has been extensively reviewed in several expert consensus documents, published studies have not yet defined which symptom-free patients would benefit.[27,28]

The test must accurately detect preclinical disease

Ideal screening tests should be highly sensitive (correctly identify patients who have the disease in question) and highly specific (correctly identify patients who do not have the disease).

Most diseases have a prevalence of less than 5%. To give more true-positive results than false-positive results in such cases, the screening test must have a sensitivity greater than 95% if the specificity is 95% or less, and vice versa.

Prevalence of lung cancer in smokers > 40 years old is 2%–4%

Most tests, even diagnostic ones, do not meet this standard. Screening programs must absorb the cost of false-positive results and accept responsibility for the mistaken sense of security conferred by false-negative results. Improving specificity increases cost-effectiveness, but improving sensitivity may not.

Accuracy of CT for lung cancer screening (FIGURE 1). No good studies of multislice CT for detecting lung cancer have been performed, as there is no gold standard with which to compare it. Recent studies found CT to be superior to conventional chest radiography, however.[5,29,30]

CT often detects benign lung nodules, giving a high rate of false-positive results. If CT reveals an indeterminate nodule (ie, noncalcified and smaller than 1 cm), we recommend follow-up CT scans at 3, 6, 12, and 24 months. If the nodule remains the same size, one can assume it is benign. If we view lung

A suspicious lung nodule

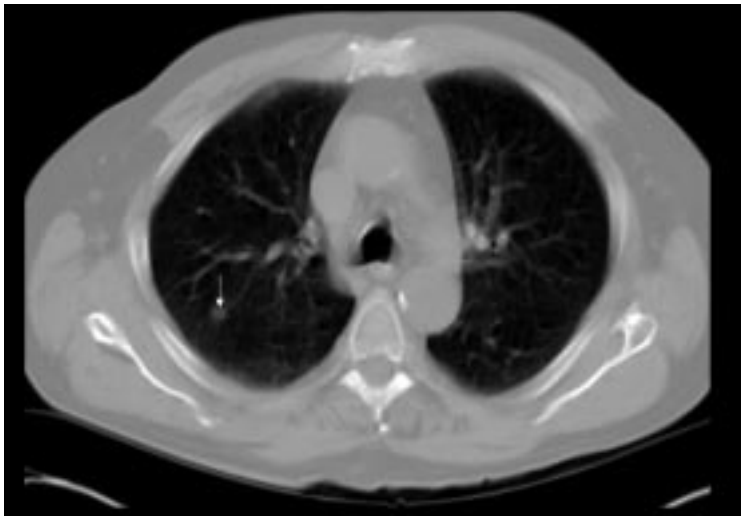


FIGURE 1. An axial CT image through the chest demonstrates an 8-mm noncalcified nodule in the left lung (arrow). Given the absence of calcification, this mass, which was not seen on a conventional chest radiograph, would be considered suspicious for a malignancy until proven otherwise.

We follow up indeterminate lung nodules at 3, 6, 12, and 24 months

cancer screening as a dynamic ongoing process rather than a single event, the false-positive rate is likely to be acceptable.[31–33]

Accuracy of colorectal cancer screening. CT colonography (FIGURE 2) has shown promising results compared with conventional colonoscopy. Recent studies found CT colonography to be more than 90% sensitive and specific for detecting polyps larger than 1 cm.[34–40] We need to specify the cut-off polyp size because the prevalence of invasive cancer is low in polyps smaller than 1 cm, whereas the prevalence in polyps between 1 cm and 2 cm is 10%.[41] Currently, the sensitivity of CT for detecting polyps smaller than 6 mm is less than 60%. (It is assumed that colonoscopy, the gold standard, is 100% sensitive and specific.)

For both lung and colon cancer screening, it is also important to consider the techniques for acquiring and processing samples. Sensitivity increases as slice thicknesses decrease from 5 mm to 1 mm. Volumetric analysis is also likely to improve reproducibility and accuracy of predictions of lesion behavior over time.

Accuracy of breast cancer screening. A number of studies assessed the accuracy of mammography screening for breast cancer; a meta-analysis published in 1998 reported its sensitivity to be 83% to 95% and the false-positive rate to be 0.9% to 6.5%.[42]

Accuracy of CT screening for coronary artery disease (FIGURE 3). The sensitivity and specificity of calcium scoring with multislice scanners is based on data from electron-beam CT. While both multislice and electron-beam CT are very sensitive and specific for calcification based on attenuation values, they are insensitive to the greater noncalcified burden. The current Agatston-based scoring method is further plagued by poor reproducibility. Efforts are under way to develop techniques that rely on volume or mass scores, which are less operator-dependent and more reproducible. As for detecting actual coronary disease, as noted, CT is very sensitive but not specific.[27]

Comment. The lack of data on sensitivity and specificity is to be expected at this early stage of a new screening technique. Some argue that until this information is available one cannot objectively advise patients whether a screening test is in their best interest. Especially in the case of lung cancer, however, the question we face is whether it is better to screen or to do nothing.

The test must detect disease before the 'critical point'

A good screening test should detect the disease before the "critical point," ie, while there is still a good chance of curing it. For most types of cancer, the critical point is when the primary tumor metastasizes.

Multiple models exist for determining the timing of screening if there are good data on the disease's natural history.[43–47]

Does CT detect stage I lung cancer? Although CT seems to be superior to other methods in detecting stage I cancer, we still don't know if it catches it before the critical point. In published studies,[5,29,30] 71% to 93% of people in whom pulmonary cancer was detected by CT screening had stage I disease. Of 1,000 symptom-free patients screened, 27 (2.7%) had cancers, of which 23 were stage I. The 5-year survival rate for stage I lung cancer is between 49% and 75%, depending on cell type.

Thus, although CT is promising, whether it detects lung cancer before the critical point

A polypoid mass in the colon

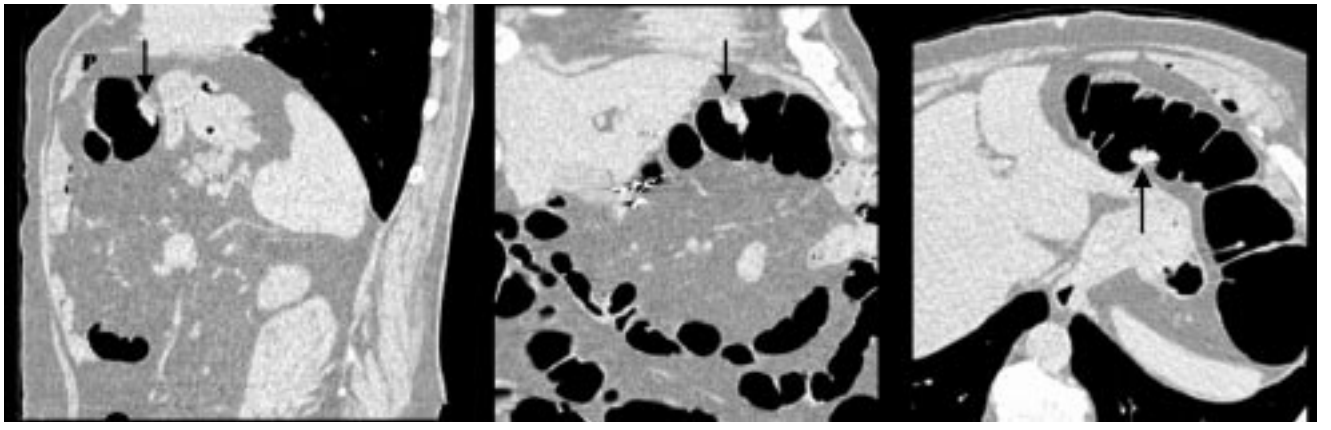
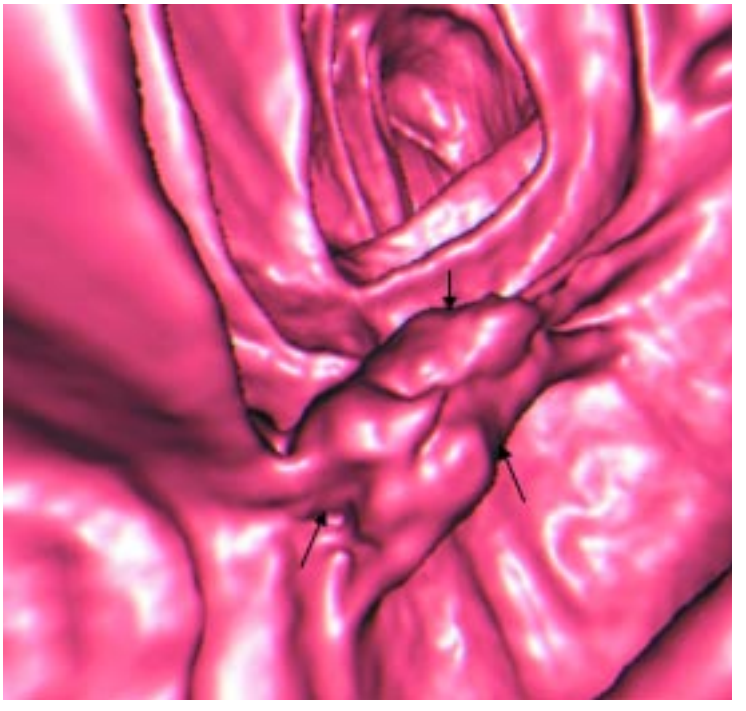


FIGURE 2. Above, sagittal, coronal, and axial multiplanar reformatted images from a CT colonography examination. Arrows point to a polypoid mass within the colon. **Right**, a virtual colonoscopy internal projected image of the lumen of the colon again demonstrates this polypoid mass.



remains unclear. Other unresolved issues include the optimal age to start screening (current practice is after age 45) and how often to repeat screening.

Prognosis is better for colorectal and breast cancer. The 5-year survival rate for patients with stage I colorectal cancer is 92%.[48] The critical point for colon cancer is considered to be when an adenomatous polyp grows to larger than 1 cm.[14] For breast cancer the survival rate for stage I disease is 97%.[48] Therefore, CT colonography and mammography meet the standard of detecting disease before the critical point.

In coronary artery disease, the critical point is defined as when symptoms of ischemia appear. Unfortunately, this definition is inadequate, since the first symptom is often sudden death due to a coronary event.

The test must cause little morbidity

CT causes no short-term morbidity; the only possible harm is the long-term risk of cancer due to radiation exposure. The x-ray dose is low, however, and very unlikely to cause cancer later in life.

The lay press often displays considerable confusion, speculation, and conjecture about radiation risk, and health care professionals often respond with uncertainty and imprecision. A problem is that various methods are used to calculate and express the dose from radiographic examinations. The risk posed by exposure to ionizing radiation has been extrapolated downward from studies of survivors of the atomic bombs dropped on Hiroshima and Nagasaki, in whom high doses of ionizing radiation led to an increased incidence of cancer-related deaths.

However, all available sources indicate that extrapolating downward is not justified. Cancer-inducing effects are not observed with

Coronary calcification

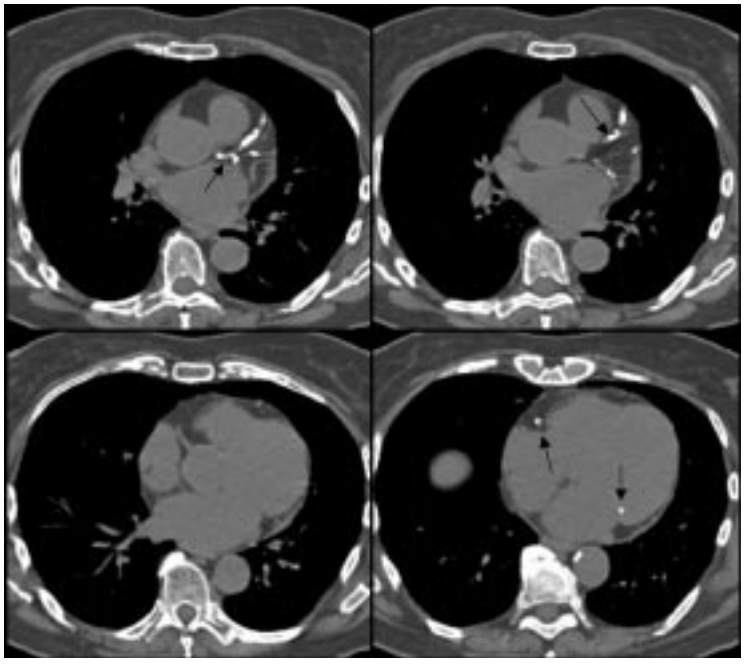


FIGURE 3. Multiple axial images of the heart from a cardiac CT examination demonstrate calcification within the coronary arteries (arrows).

X-ray doses from CT are low: one whole-body scan = 2 years of background radiation

doses below 200 mSv. In fact, in low doses, radiation may even have positive effects such as stimulating biologic defenses that protect against cancer.[49,50]

Radiation doses from whole-body CT are well below 100 mSv—not in the high-dose region (> 200 mSv), as some have suggested.[51] With doses so low, it is not possible to make any definite predictions about deleterious effects.

For patient information, Cameron[52] suggests describing the radiation dose from a radiographic study as a multiple of the average yearly natural background radiation exposure in the United States—about 3.0 mSv.

Conventional CT of the chest gives an effective dose of approximately 6.4 mSv, conventional CT of the abdomen gives 6.8, and if the two are performed together, the total is 13.2. The doses used in CT screening are at least 50% lower. Thus, the effective whole-body dose from CT screening is probably equivalent to 2 years of natural background radiation.

However, if the prevalence of the disease is low, even small adverse effects of screening can offset any benefit.

The test must be affordable and available

Health insurance companies currently do not pay for whole-body CT screening. A recent unpublished survey revealed the following average charges:

- $350 for each region screened
- $900 for a scan of the chest, heart, and abdomen, done as a single examination
- $700–$900 for virtual colonoscopy
- $200 for screening mammography (covered by almost all payers).

Screening for lung cancer often necessitates additional tests to clarify uncertain findings. For example, nonspecific, small nodules call for serial follow-up CT studies, at a cost of $200 to $400 per study. Breast cancer screening also often turns up suspicious findings that require more involved diagnostic studies. Some worry that this type of follow-up testing leads to spiraling health care costs, but this has not been documented.

CHARACTERISTICS OF THE TREATMENT

Treatment must exist, be safe, and be more effective early on

For screening to be justified, treatment must be more effective (or less harmful) during the detectable preclinical phase than after symptoms begin.[53] However, it is difficult to demonstrate that early treatment is beneficial, even if it is known to be effective once symptoms appear, owing to four main problems with comparing length of survival in patients with disease detected by screening vs by signs and symptoms.

- **Lead time bias.**[54–57] If a disease is detected earlier, patients appear to survive longer, even if early treatment has no benefit.
- **Length bias.**[57,58] Not all cases of a disease progress at the same rate. Slower-progressing cases may be easier to detect in a screening program and thus may be overrepresented in the screening cohort. This appears to improve survival time.
- **Overdiagnosis bias**[11] occurs if pseudodisease is not adjusted for in the screened cohort.
- **Stage migration bias**[59] can occur when a new test (eg, whole-body CT) uncovers cases of a disease in higher stages (eg, metastatic cancer) that would have been classified as a lower stage by older tests. Survival appears to

be better with the new test in both the lower-stage group (because it will include fewer patients with occult metastases) and the higher-stage group (because it will include more patients with metastases that are not yet clinically apparent).

In view of these biases, it may be better to compare disease-specific *mortality* rates rather than disease-specific *survival* rates when studying the effectiveness of screening.[10] The disease-specific mortality rate is the number of deaths from the disease divided by the number of people at risk. This method avoids the biases noted above, but it may not be sensitive to some types of treatment benefits, such as a true increase in the length of survival without a decrease in the mortality rate.

Benefit of early detection

Lung cancer. Two studies showed that patients with lung cancer survive longer if their tumors are smaller at the time of diagnosis.[60,61] These studies were potentially flawed, however, because of length bias.

Surgery, radiation, and chemotherapy are available for lung cancer, and their effectiveness is related to the histology and stage at which the disease is detected. While preliminary data suggest that more stage I cancers are found by CT than by conventional chest radiography, it remains to be determined if this will truly improve long-term survival or merely lengthen the lead time.

Colorectal cancer. A meta-analysis of randomized controlled trials of colorectal cancer screening with fecal occult blood tests used disease-specific mortality rates to assess the benefits of screening and found that early detection reduces mortality from colorectal cancer by 16%.[62]

Breast cancer. Early detection and treatment may reduce mortality by as much as 50%. The difficulties inherent in analyzing such results are underscored by the highly controversial nature of the literature even in breast cancer screening, for which we have far more experience than for the other diseases.

Coronary artery disease. Analyzing the impact of CT screening on mortality from coronary artery disease is even more complex because CT only detects a marker of underlying disease. Lifestyle, pharmacological, and surgical interventions can lower risk.[20–24]

SHOULD CONSUMERS DRIVE SCREENING?

While the wisdom of whole-body CT screening is being debated in professional circles, screening is currently being offered directly to patients. Mainstream medicine has become more consumer-driven, fueled by easily accessible information available to the public and a desire for more individual control over health. With a burgeoning aging and increasingly active population in the United States, this trend is likely to continue for decades.

Medical imaging has become a focus of self-prescribed health care because of its easy access, instant feedback, potential for reassurance, and appeal to patient self-reliance and control.

Proponents of greater personal control over health care argue that marketing heightens awareness, enabling people to examine and make their own choices. Consumers should be free to choose a test with an unproven benefit if the risks associated with it are small, potential benefits are significant, and the consumer is adequately informed.

The question: to screen for lung cancer or to do nothing?

Opponents argue that physicians should only recommend tools in which a consensus has been established that an entire class of patients benefits. The major clinical objections to whole-body CT relate to the absence of any rigorous published data regarding its sensitivity and specificity for low-risk disease and evidence that earlier detection of disease leads to better patient outcomes. Another argument against consumer-driven health decisions is that not all consumers have the financial resources to access the system or the knowledge to navigate it wisely.

These arguments have merit, but similar criticisms apply to most tests, including the physical examination. Furthermore, for certain diseases such as lung cancer there is no good alternative screening tool.

DOES CT SCREENING PASS THE TEST?

Whole-body CT is not an ideal screening test. But perfect diagnostic tests do not exist,

whether used for screening purposes or in patients with symptoms. Instead of expecting perfection, we should determine to what standard a test should be held and decide who should set that standard.

Lung cancer. CT detects early lung cancer with greater sensitivity than do existing tests. Recent trials have proven that screening for lung cancer in high-risk groups can be as beneficial and more cost-effective than analogous programs such as breast cancer screening with mammography. We do not yet know if CT screening improves mortality rates, but given the dismal 14% 5-year survival rate and lack of other options for early detection, screening is deemed by many to be a practical approach.

Mahadevia et al[63] evaluated whether lung cancer screening using CT might be an appropriate strategy for adult smokers and those who have recently quit smoking. They predicted a 13% lung cancer-specific mortality reduction and a 1.2% incidence of false-positive results leading to unnecessary invasive tests. The authors concluded that this approach is very expensive from both a health policy and societal perspective.

CT screening should be available for patients at risk

Unfortunately, cost-effectiveness analyses depend heavily on a large number of assumptions and are only as good as those assumptions. With improvements in technology and interpretation, including computer-aided diagnosis, this type of analysis will need frequent revision and reassessment.[64]

Colorectal cancer. Recently, the case has been made that all persons over the age of 50 should undergo comprehensive evaluation of the entire large bowel.[65] While fiberoptic colonoscopy remains the gold standard and is recommended in the American Cancer Society's screening guidelines along with flexible sigmoidoscopy, low compliance is a problem.[66,67] To be effective, screening procedures require patient acceptance, and studies suggest that patients consider CT colonography to be a less painful and less difficult procedure.[68] CT colonography also costs less and has the additional advantage that abdominal screening is performed simultaneously. Identifying extracolonic lesions, though such lesions are infrequent, may still be important.[69]

On the other hand, CT colonography requires a high degree of skill and time. It is also not clear how accurately it identifies flat lesions. Ideally, suspicious lesions identified by CT colonography should be evaluated by fiberoptic colonoscopy and perhaps biopsied on the same day with the same preparation.

Coronary artery disease. Studies that included risk-adjusted outcomes that controlled for established cardiac risk factors have failed to consistently show the incremental value of coronary calcium scores over traditional multivariate risk assessment models such as the Framingham risk model.[70,71] However, others have suggested that there is a complementary role for these methods in identifying patients at high risk.[72]

For instance, some argue that the Framingham risk model underestimates subclinical calcified coronary atherosclerosis and recommend calcium scoring to identify those who should be in a higher risk category.[73] Additional information for risk stratification can be gained by determining a percentile ranking of a patient's calcium score compared with asymptomatic people of the same gender and age.[74] The value of calcium scoring may be to provide a "biologic age" of the coronary artery to complement the Framingham risk model.

MORE STUDY NEEDED, BUT CT SCREENING IS HERE

It is clear that we need controlled studies of the use of CT screening for specific diseases, as well as consolidated data from multi-institutional experiences. Nevertheless, CT screening is here, it is being used, and we need to come to grips with it. We recommend:

- CT screening should be available for patients at risk, eg, certain patients with a strong family history of cancer, current or former smokers, and those at risk for coronary artery disease.
- CT screening should be available if patients choose it, after appropriate education and informed consent.
- Screening is not a one-time event; it is a longitudinal process that should be integrated with the traditional patient-physician relationship and should include appropriate follow-up.

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