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Perspective

Screening for disease with computed tomography (CT) is fast becoming an enterprise. Whole-body CT screening is heavily marketed in the US, and while marketing directed toward the European population is less aggressive, the interest is no less. Direct consumer advertisement reaches out to the “worried wealthy” individual, who is usually healthy! CT screening is advertised on billboards, in newspapers, on television, and through the Internet. Selective information, astute framing of the data, and subliminal messages lure the individual to undergo a scan. Health care consumers are increasingly well informed due to modern information technology and, as a result, are demanding high-technology health care. CT screening addresses the main killers of the Western world: coronary heart disease (CHD), lung cancer, and colorectal cancer. In addition, abdominal aortic aneurysms (AAAs) are easily detected with CT. Abdominal tumors, other than colorectal cancer, may also be detected with CT. Powerful anecdotes that favor screening abound. Employer, peer, and family pressure may also influence an individual to undergo CT screening in the absence of symptoms that would normally warrant investigation. But where is the evidence that screening with CT does more good than harm? This evidence is lacking. Currently, no large-scale randomized controlled trials (RCTs) of screening with CT are published in the literature. The cost-effectiveness analyses published thus far that evaluate screening with CT […]

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Screening for disease with computed tomography (CT) is fast becoming an enterprise. Whole-body CT screening is heavily marketed in the US, and while marketing directed toward the European population is less aggressive, the interest is no less. Direct consumer advertisement reaches out to the "worried wealthy" individual, who is usually healthy! CT screening is advertised on billboards, in newspapers, on television, and through the Internet. Selective information, astute framing of the data, and subliminal messages lure the individual to undergo a scan. Health care consumers are increasingly well informed due to modern information technology and, as a result, are demanding high-technology health care. CT screening addresses the main killers of the Western world: coronary heart disease (CHD), lung cancer, and colorectal cancer. In addition, abdominal aortic aneurysms (AAAs) are easily detected with CT. Abdominal tumors, other than colorectal cancer, may also be detected with CT. Powerful anecdotes that favor screening abound. Employer, peer, and family pressure may also influence an individual to undergo CT screening in the absence of symptoms that would normally warrant investigation.

But where is the evidence that screening with CT does more good than harm? This evidence is lacking. Currently, no large-scale randomized controlled trials (RCTs) of screening with CT are published in the literature. The cost-effectiveness analyses published thus far that evaluate screening with CT are generally based on sparse data and questionable assumptions. Published cohort studies provide some evidence of diagnostic and prognostic value, but that is not enough to support the large-scale use of CT screening of ostensibly healthy individuals. The trade-offs need to be clarified. As yet, it is not clear that true-positive findings lead to gains in life expectancy and quality of life. Furthermore, for some diseases, the large proportion of false-positive results and the risks, anxiety, and costs associated with the further diagnostic workup required argue strongly against screening. Recently, powerful anecdotes have illustrated the potential pitfalls of CT screening, particularly the high number of false-positive test results and their consequences (1). Furthermore, whereas the consumer sees only the out-of-pocket expense for the screening examination (often paid by the firm where he or she is employed), the follow-up diagnostic tests and treatment costs are paid for by medical insurance companies and Medicare or Medicaid, the effect of which will ultimately be reflected in a national increase in health insurance premiums and taxes. Finally, although the risk associated with exposure to radiation during a one-time scan is low, if CT scanning were to be repeated regularly, the cumulative radiation dose could become a significant risk. Given these uncertainties and risks, various professional societies have placed statements on their websites cautioning against CT screening.

The purpose of this review is to illustrate the trade-offs involved in screening with CT. We consider four diseases that can be diagnosed with CT: coronary artery disease, lung cancer, colorectal cancer, and AAAs. For each of these diseases a different CT examination is performed: multidetector row CT (MDCT) or electron-beam CT (EBCT) scan, designed to measure coronary calcification; helical lung CT; CT colonography; and abdominal CT scan, respectively. We will first discuss some general guidelines that indicate when screening is warranted, the impact of false-positive outcomes as they relate to scan sensitivity and specificity, the impact of significant secondary findings, the predicted benefit of screening in terms of life years gained, and the financial commitment. We will subsequently discuss each of the four diseases specifically in the context of these issues.

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Nonstandard abbreviations used: computed tomography (CT); coronary heart disease (CHD); abdominal aortic aneurysm (AAA); randomized controlled trial (RCT); multidetector row CT (MDCT); electron-beam CT (EBCT); myocardial infarction (MI); fecal occult blood test (FOBT).

True- and false-positive and true- and false-negative test outcomes

The most common and most desired outcome of screening is a true-negative outcome (i.e., true normal findings): the individual is healthy and reassured and quality of life may be positively affected (although the effect is generally short-lived). An individual with a true-negative outcome may in the future, however, interpret the normal finding as an argument against the presence of disease, implying that he or she may ignore signs and symptoms of early disease, which may subsequently develop. In addition, after a true-negative outcome, individuals may mistakenly believe that other well-established medical examinations such as pap smears are unnecessary. Furthermore, a true-negative outcome may be interpreted as sanctioning an unhealthy lifestyle, which would not be beneficial to the individual and may cause disease in the future.

A false-negative outcome (i.e., false normal findings) would give the individual false reassurance, and he or she may ignore signs and symptoms of early disease, which would cause a delay in diagnosis and treatment. Furthermore, normal findings may be interpreted as sanctioning an unhealthy lifestyle and may make other medical examinations seem unnecessary even though the individual is at increased risk.

False-positive outcomes (i.e., false abnormal findings, including lesions that are innocuous, such as cysts, hemangiomas, and masses that result from past infections) lead to further diagnostic workup and possibly even treatment. This may involve follow-up examinations to evaluate the lesion for progression, a CT or MRI examination with intravenous injection of contrast medium to study the characteristics of the lesion, percutaneous or open biopsies, intraarterial angiography, percutaneous therapeutic procedures, diagnostic wedge resections, or surgery. These procedures are associated with mortality and morbidity, anxiety, lost productivity, and medical and nonmedical costs. The proportion and consequences of false-positive outcomes generally drive the balance among risks, benefits, and costs in screening decisions.

True-positive outcomes (i.e., true abnormal findings) should lead to a real gain in order to make screening effective. It is assumed that, regarding detection of the disease, "earlier is better." With respect to atherosclerotic disease, the "body visualization" of subclinical cardiovascular disease can motivate lifestyle changes, risk factor management, and preventive medical therapy. Such actions may prevent more serious manifestations of cardiovascular disease such as myocardial infarction (MI) or stroke. With respect to cancer, "earlier is better" assumes that diagnosis of precancerous lesions or cancer in an early, localized stage will lead to survival benefit. For example, colorectal polyps are precancerous lesions that, if left untreated, may progress to colorectal cancer. Reported gains in survival by diagnosis of cancers in an early stage may, however, be biased in several ways, as may the reports on survival gains with the treatment of subclinical cardiovascular disease. The apparent gain may be due to lead-time bias (earlier detection and therefore a longer period in which disease is known but there is no survival advantage), overdiagnosis/pseudodisease (detection of clinically irrelevant disease), length bias (preferential detection of very slowly progressing disease), and/or pseudo–stage shift bias (advanced disease-stage shifted to early stage but within this stage a more aggressive tumor or, in the case of atherosclerosis, a vulnerable plaque).

The combination of prevalence of disease, sensitivity, and specificity determines the number of true- and false-positive and true- and false-negative outcomes of a screening test. To illustrate how the prevalence of a disease, and the sensitivity and specificity of the screening test, drive the trade-offs, consider the following hypothetical example. A disease has a prevalence of 1%. A screening test designed to detect this disease has a sensitivity of 95% and a specificity of 90%. If 100,000 individuals are screened, we can expect 950 true-positive outcomes and 9,900 false-positive outcomes. The ratio of true- to false-positive outcomes is 1:10, which implies that for every case detected, ten subjects will undergo further unnecessary testing, experience associated anxiety, and induce costs to the health care system and society.

These calculations are for one disease. In screening for more than one disease, the possibility of a false-positive test result applies to each disease and/or organ screened, which dramatically increases the likelihood that an individual will have at least one false-positive result. Analogously, the false-negative rate applies to each disease too, which increases the likelihood that an individual will have at least one false-negative result. For example, assume that the same hypothetical screening test, with the same sensitivity and specificity, is designed to simultaneously detect another disease with the same prevalence. The overall sensitivity becomes 90% (95% × 95%) and the overall specificity 81% (90% × 90%). With this screening program there will be 1,800 true-positive outcomes and 18,600 false-positive outcomes.

Evaluation of CT screening

Bearing in mind the possible positive and negative outcomes of screening, we can now list the prerequisites for a cost-effective screening program (see "Prerequisites for screening") and the parameters that should be considered in evaluating a screening program (Table 1).

Whereas RCTs are absolutely crucial in defining the benefits of screening, a preliminary estimate of the costs and benefits that can be expected with screening can be derived by simulation models. Models are also very useful adjuncts to RCTs in extrapolating long-term outcomes from short-term results and in estimating the associated costs of the diagnostic workup, therapeutic procedures, follow-up, and caregiving. Such models for screening generally demonstrate a very small mean gain in effectiveness, but one should keep

Prerequisites for screening

- The disease must be common and have substantial morbidity and/or mortality
- The screening test must be acceptable, feasible, and accurate for the detection of subclinical disease
- Curative potential must exist primarily at early disease stages
- Early detection must result in improved patient outcomes
- Sufficient resources must exist for screening, diagnosis, and therapy
- In screening a (selected) population, there must be a favorable trade-off between risks, benefits, and costs

in mind that whereas the majority of the cohort studied will experience no difference in effectiveness, a very small proportion of the cohort will experience a large gain. Simulation models are necessarily based on simplifying assumptions to make the problem tractable. Nevertheless, they synthesize and integrate the currently available evidence into one consistent whole, which can guide decision making. In addition, they provide the opportunity to explore the effect of uncertainty in the estimated parameters and variability in the screened population by performing sensitivity analysis. Furthermore, such analyses can help define research priorities by estimating the value of performing another study to obtain more information.

Screening for coronary calcium

Coronary calcification can be considered the cumulative effect of exposure to cardiovascular risk factors and therefore an overall indicator of atherosclerotic disease. The prevalence and incidence of atherosclerotic disease are high, especially in the elderly. Approximately 35% of all deaths in the Western world are due to cardiovascular disease, and in a prospective cohort study in The Netherlands, more than half of all subjects over 55 had calcified coronary arteries, an indication of atherosclerotic disease (2).

Published evidence suggests that coronary calcium detected by EBCT is predictive of CHD events in asymptomatic populations. The relative risk for a CHD event in the presence of calcified coronary arteries is substantial. A systematic review (3) demonstrated an increased risk for the combined outcome of nonfatal MI, death, or revascularization in individuals with calcium levels above the population median level. The studies published to date, however, are limited by various methodological issues, making it difficult to assess whether the use of EBCT has incremental value compared to using the traditional risk indicators only. Well-performed prospective studies are required to determine the real value of CT screening of coronary calcium.

Imaging technology is constantly advancing. In the last 2–3 years MDCT has become available, and it is virtually replacing EBCT for fast scanning. MDCT is responsible for stimulating the marketing of CT screening. Sensitivity, specificity, and reproducibility of MDCT for the detection of coronary calcium have been shown to be higher than those for EBCT (4, 5), implying that MDCT is a promising technique, but its effectiveness in screening programs has not yet been proven.

One problem with the use of CT for the identification of coronary calcifications is the presence of incidental findings. With cardiac CT, only 30% of the lungs is imaged, and the population is not restricted to current or former smokers. Therefore, the prevalence of malignant lung nodules is much lower than in CT lung cancer screening cohorts. One study reported that 53% of 1,812 patients who underwent cardiac CT had noncoronary and extracoronary incidental findings but only 0.2% had malignant disease (6).

There are many alternative screening methods for the identification of subjects at high risk for atherosclerotic disease. These methods determine traditional risk indicators including blood pressure, smoking history, lipid levels, body weight, and family history, as well as less traditional indicators such as homocysteine; ankle-brachial index (the ratio of the systolic blood pressure measured at the ankle to that measured at the arm); evidence of prior infarction or ischemia, measured by ECG; C-reactive protein; and carotid intima thickness, measured with ultrasound. Since this is an area of active research, it is highly likely that new risk indicators will be found in the future.

Patients identified with atherosclerotic disease and at high risk for a cardiovascular event can be treated effectively with aspirin therapy, cholesterol-lowering agents, and, if the patient is hypertensive, with antihypertensive drugs. Findings in a CT scan may also motivate lifestyle changes. Aspirin, at a dosage of 75 mg/d, has been evaluated for primary prevention and shown to significantly reduce the number of MIs and all-cause mortality (7). Aspirin use is, however, associated with an increased risk of hemorrhagic stroke and an increased risk of major gastrointestinal bleeding. Of all the cholesterol-lowering agents, statins are currently the most used. A meta-analysis of five large randomized trials of long-term statin treatment compared with placebo, involving 30,817 participants with a mean duration of treatment of 5.4 years, demonstrated that statins reduced major coronary events (i.e., MI and CHD-associated death) as well as all-cause mortality (8). A systematic review and meta-analysis of antihypertensive therapy (9) demonstrated that initial low-dose thiazide therapy was the most effective. Compared with placebo, low-dose thiazide therapy reduced CHD events, stroke, and all-cause mortality.

A number of RCTs of coronary calcium screening with EBCT are underway that will assess the impact of EBCT information (10) and the effect of atorvastatin plus vita-

mins C and E therapy on patients with EBCT-detectable coronary calcification (11). In the meantime, we have to base our judgments on published cost-effectiveness analyses. One cost-effectiveness analysis of EBCT screening for the identification of patients with coronary calcification suggests that statin therapy is highly cost-effective and that EBCT screening may be helpful in defining which subjects should receive statins (12) (Table 2). The analysis was, however, based on the assumption that coronary calcification on EBCT is correlated with arteriographic luminal narrowing and that luminal narrowing predicts coronary events. This ignores the fact that many coronary events are caused by noncalcified vulnerable plaque, which will not be identified by either CT or arteriography. A more convincing argument could be made if the cost-effectiveness of screening were to be modeled based on the results of prospective studies predicting coronary events in relation to the calcium score and with an RCT of CT screening. Furthermore, if advances in CT technology permit vulnerable plaques to be reliably identified, the prediction of future events could potentially be improved. Finally, programs designed to encourage lifestyle changes, interventions for smoking cessation, monitoring and treatment of blood pressure and lipid levels, and perhaps even universal treatment with statins and/or aspirin above a certain age may be more cost-effective than CT screening and should be considered as alternatives when CT screening programs are evaluated.

Screening for lung cancer

The prevalence of lung cancer is a little over 1% in current and former smokers, and the annual incidence lies between 0.4% and 0.7% (13, 14). The overall 5-year survival of patients diagnosed with lung cancer is 13%. Five-year survival of treated localized disease is higher, and screening has therefore focused on attempting to diagnose lung cancer in its localized stage.

Published prospective uncontrolled cohort studies of high-risk current or former smokers suggest that helical CT can diagnose lung cancer in an early stage, which would advance the time of diagnosis to a time when the cancer is potentially curable (13). All studies were performed in high-risk populations of current or former smokers. In all studies, indeterminate nodules that required additional diagnostic procedures and follow-up were detected in a large number of individuals (12–51% of individuals in the base-line screening examinations, and 2–13% in the annual repeat examinations). As the distinction between benign and malignant nodules is not reliable based on CT imaging criteria alone, additional follow-up CT scans are required to monitor the growth of such nodules. A biopsy is commonly required to determine the nature of the lesion, and a wedge resection is sometimes necessary to rule out cancer.

The primary treatment is surgical resection of the lung cancer. Five-year survival, if the disease is localized, has been reported to be between 67% and 80%. Only 10–15% of patients currently present with localized disease. Advocates of CT screening assume that early detection with screening implies a stage shift from advanced to localized disease. They further assume that localized disease is curable. These assumptions ignore the bias introduced by pseudo–stage shift, lead time, and length time, as explained earlier.

At present, there are no published RCTs on CT screening for lung cancer. RCTs have been published that evaluated screening with chest x-rays, with or without sputum cytology, but no benefit was demonstrated (15).

Table 1
Parameters for evaluating screening programs

Disease	Prevalence of disease, probability of disease in selected populations at high risk
	Annual incidence of disease
	Natural history of disease
Screening test	Sensitivity and specificity of the screening examination
	Radiation-associated risk
	Loss in quality of life due to screening test and possible further workup
	Complication rate of further diagnostic workup
	Proportion of nonadherence to screening program
	Alternative screening tests
Treatment	Available therapy
	Proportion of diagnosed patients that are treatable
	Benefit from early treatment, curability, efficacy, quality of life
	Complication rate of treatment
RCTs	Size
	Screening program
	Duration of follow-up
	Mortality and morbidity reduction
Costs and cost-effectiveness	Costs of screening test and further workup
	Costs of treatment and follow-up medical care, risk factor modification, lifestyle changes
	Costs of informal caregiving, travel and time costs, lost productivity
	Evaluation of different screening programs and alternatives to screening
	Perspective (societal perspective should be considered)
	Effectiveness gained: composite measure that integrates risks, benefits, and quality of life
	Incremental costs of screening program
	Trade-off of costs and effectiveness: incremental costs per effectiveness gained

Several RCTs are ongoing or planned, including the USA National Lung Screening Trial, in which 50,000 subjects are to be randomized; the French Depiscan trial, randomizing 21,000 subjects; the NELSON trial in The Netherlands, randomizing 24,000 subjects; and the LUCAS trial in the United Kingdom, randomizing 40,000 subjects (16). These studies will take 5–10 years to recruit subjects and to complete necessary follow-ups, and they are all multimillion-dollar endeavors.

Three cost-effectiveness analyses have recently been published based on simulation modeling (13, 14, 17). All three analyses have important limitations. For example, Marshall et al.'s model (17) included no costs related to other diseases or to complications resulting from biopsies, and it excluded increased risk of death and associated costs from the numerous diseases common in older smokers, such as cardiovascular disease and other cancers. Chirikos et al.'s analysis (14) took a national payers group perspective, used the results from only one study for sensitivity and specificity estimates of the screening program, did not adjust for quality of life, and discounted only costs but not effects (thus favoring screening). Furthermore, Chirikos et al. (14) did not adjust for any form of bias, and Marshall et al. (17) provided only a crude estimate of the effect of lead-time bias. Mahadevia et al. (13) did take possible lead-time and length bias into account, though only to a limited extent, and they performed a sensitivity analysis for pseudo–stage shift bias.

Overall, the analysis by Mahadevia et al. (13) was the most comprehensive and the most consistent with recommended standards for cost-effectiveness analyses (13, 18) (Table 2). The analysis evaluated a screening program with 20 annual helical CT scan screens starting at the age of 60 in current, quitting, and former smokers and considered a 20-year time frame. Mahadevia et al. took a societal perspective (as is recommended), used pooled estimates from four published prospective cohort studies of CT screening for lung cancer, adjusted for quality of life, and discounted for both costs and effects (as recommended by the US Panel on Cost Effectiveness in Health and Medicine; ref. 18). The results demonstrated that CT screening is not cost-effective. The authors concluded, and we agree, that major hurdles — in particular the incidence of false-positive outcomes — would need to be overcome before CT screening for lung cancer could be cost-effective. In fact, it may be more effective to search for another screening method, such as biomarkers in sputum (possibly combined with CT as the second step), or to invest in antismoking programs. The US Preventive Task Force currently does not recommend the use of CT to screen for lung cancer in asymptomatic individuals without a history of cancer.

Screening for colorectal cancer

The lifetime risk of colorectal cancer in the US is 5.6% (19). An important distinguishing feature of colorectal cancer in the context of screening for disease is the existence of a precancerous lesion, namely the polyp.

The fecal occult blood test (FOBT) is commonly used as the first step in screening for colon cancer, because it is simple and inexpensive, but it has a low degree of sensitivity. The double-contrast barium enema has long been used as the standard imaging screening test for colorectal cancer. Although earlier studies reported reasonable sensitivity and specificity, a recent study of the double-contrast barium enema reported a sensitivity of 48% for lesions over 1 cm and a specificity of 85% (20) . This study was, however, based on a patient population presenting with symptoms rather than a screening population and had methodological problems; it probably yielded an overly pessimistic estimate of the sensitivity of the double-contrast barium enema. The barium enema is associated with a low risk of bowel perforation and a low radiation dose. Colonoscopy has a sensitivity of 95% and, when combined with histological verification of any lesions found, an assumed specificity of 100%. It is associated with a risk of bowel perforation of 1 in 1,000 individuals (19). Sigmoidoscopy is similar but examines only a limited part of the colon, which has the highest incidence of cancer. Both double-contrast barium enema and colonoscopy/sigmoidoscopy are uncomfortable to the patient, and compliance with these tests for screening is low.

CT colonography is currently under development. The reported sensitivity is in the range of 90–94% with a reported specificity of 72%, and the procedure has virtually no associated risk of bowel perforation (19). Of note, CT colonography is not part of a regular CT scan; the patient requires extensive preparation with purgatives to cleanse the colon, and retrograde insufflation with air or carbon dioxide is necessary to distend the colon. Thus, CT colonography requires more time and expense than a regular CT scan and is somewhat more uncomfortable for the patient. Another new, but as-yet unproven, screening method is a test for colorectal cancer biomarkers in patient feces.

Polyps found during screening are precancerous and need to be removed. Polypectomy can conveniently and safely be performed during colonoscopy, which is an advantage of using it as a screening method. If histology demonstrates a high-risk polyp, a more intensive surveillance scheme with colonoscopy is advised. Colorectal cancer is surgically resected, and adjuvant chemotherapy may be given.

Published RCTs of screening for colorectal cancer have evaluated the FOBT and demonstrated that annual screening reduces cancer incidence and mortality by 20% and 33%, respectively (21). Sigmoidoscopy screening has also been demonstrated to result in a decrease in colorectal cancer mortality rates (21). As yet, no RCTs have been published evaluating colonoscopy, double-contrast barium enema, or CT colonography.

McMahon et al. compared and reanalyzed the results of three often cited cost-effectiveness analyses of colorectal cancer screening in average-risk populations (22). In spite of differences across these studies, when

standardized methods were used to reevaluate the studies, a concordant optimal screening strategy emerged: double-contrast barium enema every 3 years, or every 5 years accompanied by the FOBT. The incremental cost-effectiveness ratio was less than $56,000 (US dollars) per life year saved, which is generally considered cost-effective. These cost-effectiveness analyses, however, were performed before publication of the more recent study of double-contrast barium enema in which sensitivity was reported to be 48% (20). Furthermore, the authors of these cost-effectiveness analyses did not consider CT colonography. Another cost-effectiveness analysis, performed from the perspective of the third-party payer, compared CT colonography to colonoscopy and to no screening (23) (Table 2). The results demonstrated that CT colonography was cost-effective compared with no screening, but not cost-effective compared to screening with colonoscopy. This analysis, however, failed to include relevant strategies that use double-contrast barium enema and the FOBT, and it used preliminary results of CT colonography; therefore the reported results may not be meaningful.

All published cost-effectiveness analyses suggest that screening for colon polyps to prevent colorectal cancer is cost-effective when compared with no screening (24). No one strategy, however, can be shown to be consistently better than the others given the currently available evidence. CT colonography could potentially play a role, but the high incidence of false-positive outcomes is still a major hurdle.

Table 2
Parameters to consider in the evaluation of CT screening programs

Parameters to consider	Coronary calcium (2, 3, 7–12)	Lung cancer (13, 14)	Colorectal cancer (19, 21, 23)	AAA (25–27, 29)
Disease				
Prevalence	Depends on definition of disease	1–2%	High-risk polyps: 2%	5%
Incidence	CHD events: 1–2% annually	0.4–0.7%	0.05%	Not available
Age of cohort	55–85	Current and former smokers, age-independent	50	65–74, male only
Screening test				
Test positive	50%	20%	30%	5%
Sensitivity/specificity	55%/94%	First scan: 93%/80% Repeat scan: 85%/92%	90–94%/72%	~100%/~100%
Risk	Radiation (1–6 mSv)	Radiation	Radiation. Very low risk of perforation	Radiation
Further workup	None	Repeat CTs, biopsy	Colonoscopy, biopsy	Repeat CT/Ultrasound for growth
Nonadherence	5%	6.5%	35%	20%
Alternative tests	Blood pressure, lipid levels, smoking history, ankle-brachial index, other cardiovascular risk indicators	Biomarkers in sputum	Barium enema, FOBT, sigmoidoscopy, colonoscopy, biomarkers in feces	Ultrasound
Treatment				
Available therapy	Statins, aspirin, antihypertensives	Surgical resection	Polypectomy, surgery	Surgery for AAA ≥ 5.5 cm
Proportion treatable	100%	50–60%	Polyps: 100%	~100%
Curability/efficacy	Risk reduction ~30%	Assumption: stage shift	Localized: 5-yr survival 90%; Metastasized: 5-yr survival 8%	Relative risk of AAA-related death 0.58
Complications	Hemorrhage with aspirin	Surgical complications	Colon perforation	Mortality 4%
Randomized screening trials	PACC, St. Francis Heart Study	USA, France, The Netherlands, United Kingdom	None on CT colonography	Multicentre Aneurysm ScreeningStudy, United Kingdom,using ultrasound
Costs (estimates)				
Screening test	200–300	300	500	200–300
Further workup	None	300–5,000	1,000	200–300
Treatment	500/yr	44,000–67,000	1,500–22,000	11,000
Cost-effectiveness				
Program	EBCT screening + statins	Annual CT, 20 yr, current smokers	Screen every 10 yr	(One-time ultrasound, 65–74 yr; time frame 10 yr)
Perspective	Health care system	Societal	Health care system	Health care system
Effectiveness gained	4 events less/1,000 pers-yr	0.04 QALYs	0.05 LYs	0.002 LYs
Incremental costs pp.	1,000	4,600	600	100
Trade-off	200/CHD event avoided	116,300/QALY	11,500/LY	13,000/LY

All costs are shown in US dollars. mSv, millisievert; PACC, Prospective Army Coronary Calcium study; pers-yr, person years of follow-up; pp., per person screened; LY, life year; QALY, quality-adjusted life year.

Screening for AAA

In a large randomized study evaluating screening for AAA, aneurysms of more than 3 cm were detected with ultrasound in 5% of men aged 65–74 who were undergoing screening (25). The rupture rate of aneurysms smaller than 5.5 cm is 1% per year, and the risk of rupture increases with the diameter of the aneurysm (26). Aneurysm rupture can sometimes be treated with emergency surgery but is generally associated with a high mortality and morbidity rate.

Ultrasound is a reliable and inexpensive screening test for detecting AAA. In the majority of individuals, the aorta can be identified and measured, but some individuals are very obese or have overlying bowel gas that precludes adequate ultrasonographic imaging. CT scanning virtually always provides adequate images and a reliable measurement of the aorta. Furthermore, CT, in contrast to ultrasound, is operator independent.

Open elective surgery is indicated for aneurysms measuring 5.5 cm or more. A larger diameter is used as a threshold for patients at high risk for perioperative complications due to comorbidity. Perioperative mortality is, on average, 4–7%, and systemic or remote complications occur in up to 44% of patients (27). A new, but unproven, therapy — endovascular treatment — in which a stent graft is placed using a catheter technique via the common femoral arteries is associated with lower mortality and complication rates (27) and is potentially cost-effective (28), but the results during long-term follow-up are still uncertain.

The Multicentre Aneurysm Screening Study in the United Kingdom (25) was a population-based randomized controlled screening trial in which 67,800 men aged 65–74 years were randomized to be invited for abdominal ultrasound for the detection of AAA or to receive usual care. Aneurysms of 3–4.5 cm were followed annually with ultrasound. Aneurysms of 4.5–5.4 cm were subject to ultrasound analysis in 3-month intervals. Surgery was performed if an AAA of 5.5 cm or more was detected, if expansion of 1 cm or more per year occurred, or if the patient developed symptoms. During follow-up, the risk of aneurysm-related death in the invited group compared with the control group was substantially reduced. The benefit of this screening trial can be extrapolated to screening with CT, as CT would diagnose AAA with even greater accuracy. The only disadvantages of using CT would be a very small risk associated with radiation exposure and a slight increase in the costs of the screening test.

A cost-effectiveness analysis was performed based on the results of the Multicentre Aneurysm Screening Study (29). Over the 4-year period observed, the associated costs were $45,000 per life year gained and $57,000 per quality-adjusted life year gained, which is considered cost-effective. When extrapolated to 10 years, the incremental cost-effectiveness ratio was $13,000 per life year gained, which is even more favorable.

Although these results apply to ultrasound, screening for AAA can be done more easily, accurately, and reliably with CT scanning. The major benefit of CT scanning compared with ultrasound is its operator-independence and the superior image quality, especially in obese patients. If the abdominal aorta were to be scanned (even if only over a limited part) as part of a more comprehensive CT scan screening examination, the screening test's marginal cost would be very low. To avoid high follow-up costs, serial follow-up examinations could be performed with ultrasound.

Additional considerations

In this article we have discussed CT screening for the identification of patients with coronary calcification, lung cancer, colorectal polyps or cancer, and AAAs. CT screening has also been advocated to detect tumors of the liver, kidney, ovary, and other abdominal organs. Prevalence of clinically relevant cancer in the abdominal organs is extremely low and the proportion of false positives high. On unenhanced CT, masses are commonly found that require follow-up with enhanced CT, MRI, and, in some cases, biopsy. Most masses turn out to be cysts or hemangiomas, which are benign lesions of no consequence. Furthermore, if one looks very carefully in the kidney with microsection pathology, one will invariably find cancer cells (30), but most of these would never develop into clinically relevant cancers. This implies that overdiagnosis bias is likely to influence reports on screening for these cancers. Furthermore, there is no evidence that abdominal tumors can be diagnosed using CT screening at a curable stage, and no evidence of the cost-effectiveness of CT screening for abdominal tumors in general.

Although the radiation dosage with MDCT is a concern, the radiation risk from performing a single study is low. A dose of 100 millisieverts (mSv) is estimated to cause only 0.004 long-term mutations per cell, a trivial addition to the one mutation per cell per day that results from natural processes (31). Biological defense mechanisms ensure an adaptive response of cells to low-level radiation by stimulating production of repair enzymes and an increased immune response. Monitoring of 96,000 radiation workers in the US, the United Kingdom, and Canada found no indication of excess risk for doses less than 400 mSv (31). The incidence of breast cancer in Canadian women exposed to x-ray fluoroscopy for tuberculosis suggests no excess risk for doses less than 200 mSv, and data on the incidence of lung cancer in these women suggests that there is no excess risk for doses less than 1,000 mSv (31). Assuming that a CT scan is associated with a radiation dose of between 2 and 6 mSv, we can safely conclude that if a scan were to be performed every 5 years starting at, for example, age 50, we would not need to worry about the radiation risk. If, on the other hand, a scan were to be performed every year and additional follow-up scans were performed in a large proportion of patients with abnormal findings, the radiation dose is a cause for concern.

Conclusions

To date, it remains unproven that CT screening is beneficial, especially in the low-risk population. RCTs coupled with cost-effectiveness analyses are needed. The evidence available thus far suggests that the mean gain in life expectancy is very small, that the cost to the health care system and society is enormous, and that the potential harm to the individual is real.

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