Screening for Cancer with PET and PET/CT: Potential and Limitations

Heiko Schöder[1] and Mithat Gönen[2]

[1]*Department of Radiology/Nuclear Medicine, Memorial Sloan-Kettering Cancer Center, New York, New York; and*
[2]*Department of Biostatistics and Epidemiology, Memorial Sloan-Kettering Cancer Center, New York, New York*

Certainty? In this world nothing is certain but death and taxes.
Benjamin Franklin

Screening for cancer remains a very emotional and hotly debated issue in contemporary medical practice. An analysis of published data reveals a multitude of opinions based on a limited amount of reliable data. Even for breast cancer screening, which is now widely practiced in the United States and many European countries, there is continuing controversy regarding the appropriate age limits for screening mammography and, in fact, concerning the value of mammography itself. Similarly, there is no agreement as to whether screening for lung or prostate cancer is meaningful as currently practiced. Recommendations and decisions regarding cancer screening should be based on reliable data, not good intention, assumptions, or speculation. Therefore, we first explain the underlying principles and premises of screening and then briefly discuss current controversies regarding screening for breast, prostate, and lung cancers. Recently, some authors advocated CT, PET, or PET/CT for whole-body screening without support from reliable data. We discuss the potential financial, legal, and radiation safety implications associated with whole-body CT or PET cancer screening. We conclude from the available data that neither CT nor PET/CT cancer screening is currently warranted. Far from providing a desirable binary answer (presence of absence of cancer), in nonselected populations the procedures frequently yield equivocal or indeterminate findings that require further evaluation, with associated costs and potential complications. The clinical and statistical relevance of occasionally detected cancers is likely too low to justify population-wide screening efforts with these 2 imaging modalities. Ultimately, the true utility, or lack thereof, of PET and PET/CT for cancer screening can be assessed only in a prospective randomized trial. Because of prohibitive costs and the required length of follow-up, it is unlikely that such a trial will ever be conducted. Rather than spending time and resources on screening studies, medical practitioners should continue using whole-body PET/CT for diagnosing, staging, and restaging cancer and for monitoring treatment effects. Researchers should also investigate the utility of whole-body PET/CT for the surveillance of selected groups of patients who have cancer, who have completed curative treatment, but who remain at high risk for recurrent disease.

Key Words: cancer screening; PET; PET/CT

J Nucl Med 2007; 48:4S–18S

In 2005, an estimated 1,373,000 people in the United States were diagnosed with cancer, and about 570,000 died of cancer (*1*). Over the years, there has been considerable interest in screening as a means for reducing cancer-related mortality for a number of malignancies, including cancers of the breasts, colon, prostate, lungs, uterine cervix, and ovaries. In fact, screening has become popular in the United States. Recent statistics from the National Cancer Institute (NCI) demonstrated that about 70% of women aged 40 y or older in the United States had had a mammogram in the last year, more than 80% of women aged 18 y or older had had at least 1 Papanicolaou smear during the last 3 y, and 58% of men aged 50 y or older had had a prostate-specific antigen (PSA) test in the last year (*2*). The NCI estimates that 3%–35% of premature deaths from cancer could be avoided through appropriate screening (*3*). The NCI also suggests that screening might reduce cancer morbidity because treatment for earlier-stage cancers is often less aggressive than that for more advanced cancers. Nevertheless, there is as yet no convincing evidence that screening for lung, ovarian, colon, and prostate cancers translates into a reduction in mortality from these diseases.

Because screening, by definition, is undertaken in an apparently healthy population and because the fraction of cancers detected by screening is often in the range of 2%–5% (*4–6*), the vast majority of participants in screening tests derives no clear benefit from the tests, other than peace of mind. Peace of mind, however, may be misleading when the sensitivity of the test used for cancer detection is too low. At the same time, individuals who receive a false-positive diagnosis because the specificity of the test is too low may be subject to unnecessary worry and emotional trauma.

Received Mar. 8, 2006; revision accepted Jun. 8, 2006.
For correspondence or reprints contact: Heiko Schöder, MD, Department of Radiology/Nuclear Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., Box 77, New York, NY 10021.
E-mail: schoderh@mskcc.org

The use of CT for cancer screening (directed either at a single organ or at the entire body) has been debated among radiologists for at least the last 5 y. It is also the subject of passionate and apparently never-ending controversies. ^{18}F-FDG PET or PET/CT has also been proposed for screening. Many imaging specialists can quote examples from their daily practice in which imaging studies conducted for 1 purpose detected other, unexpected, abnormalities. With CT, lung lesions can be discovered during screening for coronary calcification (*7,8*), or extracolonic lesions in the abdomen can be identified in subjects undergoing CT screening for colon cancer (*9,10*). Whole-body PET may detect an unexpected second primary cancer or premalignant lesions (*11*). However, in contrast to what common sense might suggest, these incidental findings do not prove that the screening of nonselected groups of individuals is reasonable. We have tried to weigh the available evidence for and against whole-body screening studies. Findings and conclusions are presented against the background of ongoing debates regarding the usefulness of cancer screening programs.

SCREENING: DEFINITION AND PURPOSE

Screening is defined as the investigation of a group of usually asymptomatic individuals to detect those with a high probability of having or developing a given disease (*12*). To be suitable as a target disease for screening, a disease should represent a significant health problem, have a long asymptomatic natural history, and have an effective intervention that favorably influences the outcome of the disease. The disease should have a relatively high prevalence to justify the cost of the screening program. Screening should identify all or most people with the index complaint (true-positive results), identify few people without the disease as having the disease (false-positive results), and be inexpensive, safe, effective, and easy to apply to a target high-risk population (*13–16*). The potential benefit to individuals identified as having the disease by screening should offset the cost for the test as well as the inconvenience and potential harms incurred by the many participating individuals who do not have the disease. The aim of screening is to eliminate, or at least significantly delay, death from that disease. Therefore, any cancer screening technique should focus on malignancies for which earlier detection will reduce mortality or morbidity. This notion is based on the premise that cancer at an earlier stage (smaller size) is more likely to be amenable to curative treatment. Accordingly, the goal is a reduction in the absolute number of advanced (nonresectable) cancers, which should translate into a decrease in disease-specific mortality.

In the assessment of the quality of any diagnostic test, including a screening test, 3 pertinent questions arise. Does the test accurately and reproducibly detect or measure the disease? Does a new test improve on existing methods for detecting the disease and predicting mortality or other clinically relevant events? Does the test reduce mortality, improve quality of life, or lower costs without subjecting patients to unnecessary risk? However, screening is different from diagnostic or therapeutic interventions because the majority of individuals who undergo a screening test do not have the disease in question. Therefore, the costs and potential risks associated with the test are spread across a wider group of individuals. In addition, the costs and potential harms of screening generally occur in the short term, whereas any benefits are typically realized only in the long term.

STATISTICAL CONSIDERATIONS

The quality of a diagnostic test is judged by sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Sensitivity and specificity are characteristics of the test itself and are not related to the population being tested. In contrast, the predictive value of a given test is closely related to the prevalence of the disease in the population under study. Therefore, PPV and NPV should always be interpreted in the context of the disease prevalence in the study group (Bayes' theorem). For instance, when a hypothetical test with a sensitivity of 90% and a specificity of 80% is applied in a population with a disease prevalence of 5%, the PPV will be only 19%, whereas the NPV will be 99%. When the same test is applied in a population with a disease prevalence of 95%, the PPV will be 99%, and the NPV will be 30%. Accordingly, in a population with a low prevalence of disease (the usual setting for any cancer screening program), the predictive value of a positive test result will remain relatively low, and in a population with a high prevalence of disease, the predictive value of a negative test result will again be relatively low.

Given that the prevalence of individuals with cancer is generally below 5% in many screening programs (*5,14,17*), the PPV of a positive screening test result is bound to be low, even if the test is highly sensitive and specific for that disease. To detect more true-positive cases than false-positive cases in a cohort with a 5% disease prevalence, a screening test must have an exceedingly high sensitivity—greater than 95%—if the specificity is slightly below 95% and vice versa. Although desirable, in reality, most screening tests do not meet this high standard, which means that the screening program must absorb the cost of many false-positive results. It might be argued that, most importantly, a screening test should have high sensitivity. However, high sensitivity at the expense of lower specificity will cause a high rate of false-positive cases (e.g., granulomatous disease instead of cancer in a lung nodule) as well as an increased detection of "pseudodisease," that is, overdiagnosis of disease that would not have affected survival or quality of life for the affected individual (see later discussion). Conversely, a test with a high specificity will ensure the cost-effectiveness (cost per year of life saved) of the screening program. Because of referral bias (only individuals with suspected disease are referred for further evaluation), it is difficult to determine the true accuracy of a screening test.

In fact, accuracy could be determined only by monitoring all screened individuals for an appropriately long period of time. If the follow-up is too short, then some disease might be missed, and the test sensitivity might appear to be artificially high. If the follow-up is too long, then new disease might develop in the interim, and the test sensitivity might appear to be artificially low.

BIASES ASSOCIATED WITH SCREENING TESTS

Because of space limitation, we only briefly describe some potential pitfalls in designing or analyzing screening studies. Good reviews of this matter are available elsewhere (*16–18*).

Lead-time bias refers to the apparent differences in disease-specific survival (time from cancer diagnosis to death): In individuals with disease detected by screening, the time frame spans from the date of screening to death, whereas for nonscreened individuals, the time frame spans from the clinical presentation of disease to death. Because screening detects cancer in asymptomatic individuals, their survival will always be longer than that of nonscreened individuals because disease was detected at an earlier point in time. This situation remains true even if screening does not delay the ultimate time of death and if earlier treatment has no benefit.

Length bias occurs because a given disease may progress at various rates in different patients. Tumors that grow more slowly have a longer detectable preclinical phase than rapidly progressing cancers. Tumors that grow more slowly are easier to detect and more likely to be detected by screening (rapidly growing tumors may develop and appear clinically in the interim between 2 consecutive screening tests). Therefore, screening generally detects cancer with a better prognosis.

Overdiagnosis bias occurs when screening detects tumors that would otherwise have remained occult during the lifetime of that individual: the individual would have died with, rather than from, the disease. There are 2 possible scenarios: An individual may be bound to die from other diseases before the cancer becomes lethal, or screening detects a less aggressive malignancy that is not life threatening or that does not interfere seriously with the quality of life before the individual dies from other conditions (e.g., slowly growing prostate cancers in older men).

Stage shift and selection bias are other potential pitfalls in screening studies (*16*). The impact of bias on the results of a screening trial can be reduced through proper study design; a randomized controlled trial, in which study participants are randomized to a given test versus observation, generally provides data that are more stable and resistant to criticism than case–control or cohort studies. Further, mortality, rather than survival, should be recorded as the outcome measure.

CANCER SCREENING TRIAL DESIGNS

There are 5 study designs that are generally used in judging the evidence from a clinical trial, including screening studies (*3*). The highest level of statistical evidence is derived from randomized controlled trials. However, these trials are very expensive, require tens of thousands of participants, are affected by noncompliance, and take many years to complete. In imaging trials, the technology under investigation could have advanced by the time the trial is concluded (e.g., multidetector [64 or more rows] CT with true isotropic resolution instead of simple helical CT and PET/CT instead of PET alone). If a large randomized controlled trial is not feasible for financial or logistic reasons, then one has to rely on other trial designs, such as cohort studies, and indirect outcome measures, such as the earlier detection of cancer (*19,20*). In addition, one might investigate whether the test leads to a reduction in the number of interval cancers that become clinically apparent between 2 consecutive screening sessions (*21,22*). A reduction in the number of interval cancers would suggest that the time interval between sessions is appropriate and that the test itself is sufficiently sensitive for detecting rapidly growing cancers, thereby excluding length bias.

APPROPRIATE OUTCOME MEASURES

The terms "mortality" and "survival" are frequently used when reporting the outcome of screening studies. Unfortunately, both terms are oftentimes, and incorrectly, used synonymously. Survival is a case-based measure; it shows the percentage of individuals diagnosed with cancer who are still alive at a certain time point (usually 5 y) after the time of diagnosis. In this case, the denominator includes only individuals diagnosed with cancer. In contrast, mortality is a population-based measure; it shows how many people are dying of cancer within a given population (usually quoted as per 100,000 individuals). In this case, the denominator includes individuals diagnosed with cancer and all healthy individuals.

Because of lead-time bias, the 5-y survival for a given cancer will almost always improve with the introduction of a cancer screening test. However, because the incidence of cancer (number of new cases detected per 100,000 individuals) will almost always increase with screening, the following 2 prerequisites must be met for cancer mortality to decline as well: (a) more cancers must be detected at an earlier stage with screening than without, and these cases must be curable; and (b) the vast majority of screen-detected cancers must be clinically relevant (if screening only leads to overdiagnosis of cancer, this could actually increase cancer mortality if the cause of death in individuals so diagnosed were to be coded as "died of cancer," whereas another medical condition would have been assumed to be the cause of death if that individual had never undergone screening).

The gold standard parameter by which to measure the efficacy of a cancer screening test is a reduction in mortality. Disease-specific mortality has been the most widely accepted end point in randomized clinical trials. It requires that the cause of death be determined accurately and that

screening and subsequent treatment have negligible effects on other causes of death. However, some recent reviews of randomized cancer screening trials suggested that misclassification of the cause of death is a common problem, leading to an overestimation of the effectiveness (or an underestimation of the harms) of screening (*23–25*). Therefore, all-cause mortality may be a more accurate end point for screening trials (*23–25*). This parameter depends only on the accurate documentation of deaths and when they occur; that is, it is not affected by misclassification of the cause of death. Therefore, it unequivocally accounts for complications of the screening process itself and related procedures attributable to false-positive screening test results. Unfortunately, a screening trial with all-cause mortality as the sole end point would require a prohibitively large number of individuals to be enrolled (most screening participants might not die during the trial) (*26*).

If data from a randomized controlled trial are not available, then evidence obtained by other trial designs, such as stage shift or improved survival rates, compared with those of historical controls, is sometimes used to demonstrate the effectiveness of a screening program (*19*). However, these parameters are not very reliable or accurate. It is also sometimes naively assumed that current improved survival rates for patients with cancer, compared with those for historical controls, are attributable to mass screening efforts, although such improvements may reflect only improved treatment, lead-time bias, or overdiagnosis. Indeed, in a recent analysis researchers found that for many cancers, changes in 5-y survival rates are essentially unrelated to trends in disease-specific mortality, suggesting that improvements in survival were largely attributable to earlier diagnosis and detection of subclinical cases that might never have appeared clinically (*27*).

Although there is currently no universally accepted cancer screening trial design or outcome parameter, most authors would agree that the highest level of statistical evidence and the greatest benefit for screening program participants is related to mortality reduction in a randomized controlled trial. Eventually, however, the true efficacy (or lack thereof) of a screening test will be shown only once the test is applied in general practice.

CURRENT CONTROVERSIES IN CANCER SCREENING

Screening for prostate and breast cancer is widely practiced in the United States, in accordance with recommendations issued by various committees and task forces. Proponents of screening with CT or PET like to quote the apparent success of breast and prostate cancer screening programs to lend credence to their attempts to introduce CT or PET as a new screening technique for lung cancer or whole-body assessment. However, contrary to expectation, our attempt to gather data to confirm the efficacy of current cancer screening programs proved to be a sobering experience. Neither breast cancer nor prostate cancer screening is without controversy; in fact, in the eyes of some critics, both tests fail to show any benefit in terms of mortality reduction at all. Regardless of various recommendations for prostate cancer screening with PSA testing and digital rectal examination (*28–30*), it is now widely acknowledged that the effectiveness of this approach remains unproven. A recent case–control study found no evidence for a survival benefit associated with PSA testing and digital rectal examination (*31*). It is hoped that ongoing trials, such as the European Randomized Study of Screening for Prostate Cancer (*32*) and the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial (*33*), will provide more definitive answers regarding the benefits of prostate cancer screening. However, conclusive data regarding the effects of screening on prostate cancer mortality are not expected until 2008–2010. The ultimate value of lung cancer screening with CT is also uncertain at present. Here we present a summary of the current controversies in breast and lung cancer screening in the hope that it will further a realistic, evidence-based reassessment of current efforts to institute cancer screening programs with PET or PET/CT.

BREAST CANCER

About 211,000 new cases of breast cancer were diagnosed in 2005, and 40,400 patients died of this disease (*1*). Breast cancer screening has been proposed as a means of reducing mortality from breast cancer and has been practiced for more than 30 y in many developed countries. It has been estimated that cancer is detected in 5–7 of every 1,000 women on the first screening mammogram (prevalence) and in 2 or 3 of every 1,000 women who undergo regular screening mammography (incidence) (*5*). Over the years, thousands of women have been enrolled in breast cancer screening trials worldwide, but controversy on the efficacy of screening mammography continues to date. Proponents and opponents of breast cancer screening (including physicians and biostatisticians) differ in their assessment of the quality of past mammography screening trials, in the interpretation of the trial results, and in their preference for the appropriate end point (*26*). Disagreement remains regarding whether past trials proved that breast cancer screening is meaningful. For instance, Fletcher and Elmore (*34*) estimated that 4–6 lives could be saved if 1,000 women aged 50–69 y underwent yearly screening mammograms for a total of 10 y. On the basis of the average cure rate for non-screening-detected breast cancer, they calculated that screening mammograms can reduce breast cancer mortality by about 30%. In contrast, a meta-analysis of 8 randomized trials conducted by the U.S. Preventive Services Task Force in 2002 (*35*) concluded that screening mammography leads to a 16% reduction in breast cancer mortality in women aged 50 y and older. It was estimated that 1,224 women would have to undergo yearly screening mammograms over a 14-y period to save 1 life. Gotzsche and Olsen (*36*) reviewed the same 8 screening mammography trials and

arrived at a very different conclusion. These authors particularly focused on the methodological quality of the screening studies and found baseline imbalances between screening and control groups in 6 of the 8 trials and inconsistencies in the number of women randomized in 4 trials. Only in these methodologically inferior trials did mammography appear to "save lives" (the pooled relative risk for breast cancer mortality was 0.75, and the 95% confidence interval [CI] was 0.67–0.83). In contrast, the meta-analysis of the 2 trials that were considered of sufficient quality found no effect of screening on breast cancer mortality (pooled relative risk: 1.04; 95% CI: 0.84–1.27), nor was there any positive effect on all-cause mortality (pooled relative risk: 0.99; 95% CI: 0.94–1.05). These authors concluded that "screening for breast cancer with mammography is unjustified." In a subsequent analysis (*25*), the authors confirmed these findings and emphasized that screening leads to more aggressive treatment without proven benefit.

In 2003, a Swedish cohort study reported that screening reduced breast cancer mortality on the basis of lower mortality in women who had their breast cancer diagnosed during the screening period (1978–1997) than in women diagnosed with breast cancer before the introduction of mammography screening (1958–1977). More cancers were detected and treated in the screening group, leading to better survival (*37*). Others have classified the results of this trial as uninterpretable because of length and lead-time biases (*38*). Another recent study (*39*) estimated that screening reduced the mortality from breast cancer in the United States by 15% over the last 2 decades, but critics note that similar declines in breast cancer mortality have also been reported from countries without a national screening program (*40*). On March 25, 2006, the *British Medical Journal* (*41*) published a series of articles on screening mammography in which the rate of overdiagnosis of breast cancer was estimated to be 10%–30%.

Partly in recognition of the above-described controversy and trial limitations, some authors have suggested that it may be more appropriate to stream women into different screening regimens on the basis of breast characteristics or risk factors (*22*). Finally, it should be noted that the cumulative risk for having a false-positive mammogram result can approach 50% over a 10-y interval with yearly screening studies. This means that after 10 y of annual screening in the United States, 1 in 2 women will have at least 1 false-positive mammogram result (*42*).

LUNG CANCER SCREENING TRIALS

About 172,600 new cases of lung cancer were expected in 2005, and 163,500 patients were projected to die from this disease (*1*). Screening for lung cancer, originally with sputum cytology analysis and chest radiography and more recently with CT, has been proposed as a means to reduce mortality from this disease, but study results have created considerable controversy (*4,43–47*). Earlier trials showed no significant differences in lung cancer mortality between screened and control groups (*17,48*). Patients with lung cancer in the screened group were more likely to undergo surgical resection and lived longer than individuals in the control group, but equal numbers of individuals in both groups ultimately died from the disease. Thus, the apparent improvement in lung cancer survival was largely attributable to various biases (see earlier discussion), but screening did not affect the ultimate outcome of the disease.

Over the last 6 y, the controversy has focused on the role of screening CT (*14,17,49–51*). In several cohort studies (without control groups) from the United States, Europe, and Japan (*4,6,43–46,52*), low-dose CT imaging was performed for screening and was followed by immediate biopsy for suspicious lesions or high-resolution CT for further characterization of indeterminate nodules. Individuals were monitored at 1-y intervals with low-dose CT and similar management. This approach allowed for the detection of many early-stage lung cancers (*4,43–46*). At baseline scanning in these studies, lung cancer was detected with prevalences of 1.1% (*46*) to 2.7% (*4*); differences may be related to the age and risk of the screened populations. The rate of detection of lung cancer on annual follow-up scans (incidence) was about 1% (*6,43,46*). About 58%–100% of cancers on baseline CT scans and 67%–100% of cancers during follow-up scans were stage I disease. For instance, in the Early Lung Cancer Action Project study (*21*), lung cancer was diagnosed in 27 of 1,000 individuals during baseline CT (prevalence: 2.7%), and 23 of 27 cases were stage I malignancies. In the follow-up of this cohort, 1,184 CT scans were obtained and revealed a total of 30 new lung nodules, of which 7 were cancers (incidence: 0.7%). The median size of these lesions was 8 mm.

Although intuitively favorable, these results do not prove that a reduction in lung cancer mortality will occur with CT screening. Although it is better to detect lung cancer earlier than later, there may not be a linear relationship between tumor size and likelihood for metastasis (*53*) and, thus, likelihood for cure with early intervention. In fact, there is no clear cutoff in primary tumor size to predict when metastasis occurs. Otherwise, treatment with curative intent should render a patient with early lung cancer disease free for the rest of his or her life. However, even with stage I lung cancer, the average 5-y survival rate is only 47%, not 100%. Quite likely, many other biologic factors (e.g., histology, degree of neovascularity, and genetic alterations) and perhaps even random variability among primary tumors (*54*) may determine metastatic potential. Opponents of screening CT, therefore, contend that it remains unclear whether the detection of early-stage disease represents a true stage shift (earlier detection of clinically relevant disease associated with a decrease in the number of advanced lung cancers) or overdiagnosis (no decrease in lung cancer mortality; instead, only an increase in the number of detected lung cancers chiefly because of sophisticated technology, but no change in the rate of advanced cancers, i.e., no decrease in the number

of cancers that are not amenable to treatment or that are likely to fail treatment with curative intent) (*52,55*).

Because of these concerns, many epidemiologists and physicians involved in the diagnosis and treatment of lung cancer have argued that the benefits of CT screening can be proven only in a large randomized controlled trial (*17*). Indeed, several such trials are now under way in the United States, Japan, and Europe. In the meantime, the U.S. Preventive Services Task Force (*56*) has concluded that it is not possible to assess the efficacy of lung cancer screening with CT on the basis of currently available data. The American Cancer Society currently suggests that patients discuss with their physicians the potential costs and benefits of lung cancer screening with CT (*28*). At the end of 2005, a consensus statement made by the Society of Thoracic Imaging concluded that there is currently insufficient evidence to justify recommending CT screening for lung cancer to patients, including those at high risk for lung cancer (*55*).

WHOLE-BODY SCREENING WITH CT

For a while, whole-body CT was marketed aggressively as the "one-stop shop" for detecting occult cancer and cardiovascular diseases. Although malignancies and coronary artery disease were in fact detected in many participants, the overall results were disappointing. Many self-declared CT screening practices have closed their doors, sometimes ending mired in financial distress and in lawsuits. A large study conducted at the University of California, San Diego, highlighted the logistical challenges and other problems associated with whole-body screening CT (*57*). Between January and June 2000, screening CT was performed for 1,192 individuals. A total of 76% (902/1,192) of these subjects were self-referred; the others were referred by a physician for a whole-body screening test. Participants were charged $1,000 for the screening CT. A total of 3,361 findings were detected in 1,030 of the 1,192 individuals (mean of 2.8 per individual). The proportion of individuals with abnormal findings increased with age (43% if <40 y and 99% if >70 y). Most of the "abnormalities" were benign and likely without clinical consequence (e.g., parenchymal scars in the lungs, vascular calcifications, calcified mediastinal lymph nodes, and simple cysts of the liver and kidneys). CT-detected abnormalities led to recommendations for the individual or referring physician in 37% of cases; of note, the most common recommendation (69%) was that for a follow-up imaging study. It was concluded that the low prevalence of abnormal findings in individuals younger than 40 y would not justify screening CT. At the other extreme of the spectrum, screening CT may not be meaningful in individuals older than 70 y. Although the expected prevalence of cancer increases with age, the 99% prevalence of CT-detected abnormalities in older people, combined with the frequent need for further evaluation, also limits its application in this age group. Thus, screening CT may be beneficial, if at all, only in well-defined age and risk groups.

^{18}F-FDG PET FOR CANCER SCREENING

There is limited information about the true performance of whole-body PET for cancer screening. Data that might help to investigate this issue are derived from few case series analyzing the frequencies of malignancies incidentally detected during whole-body PET imaging and from PET screening studies conducted in Asian countries. These data are discussed in the following sections.

INCIDENTAL ABNORMAL ^{18}F-FDG UPTAKE DURING WHOLE-BODY PET

^{18}F-FDG PET occasionally detects previously unknown malignant or premalignant lesions that are unrelated to the disease for which the scan was performed. Although most clinicians can readily provide anecdotal evidence for this finding, Agress and Cooper (*11*) published their findings from a large study of 1,750 patients with cancer. ^{18}F-FDG PET was performed for the evaluation of a variety of malignancies, and 58 foci of abnormal but unexpected ^{18}F-FDG uptake were identified in 53 patients, that is, a frequency of 3.3%. Follow-up, available for 42 individuals, proved a malignant or premalignant condition for 30 individuals (1.7% of the entire study population). Further, 3 of 9 nonmalignant lesions were considered clinically important and required surgical or medical intervention. Although this study highlights the value of whole-body PET for the evaluation of patients with cancer, it does not provide a true estimate of the rate of detection of clinically occult malignancies, because dedicated follow-up was available only for individuals with abnormal ^{18}F-FDG uptake and because non–^{18}F-FDG-avid disease could have been missed in other individuals.

THYROID AND INTESTINAL LESIONS FOUND POSITIVE BY PET

Palpable thyroid nodules are detected in 4%–7% of the general population in the United States and at somewhat higher frequencies in areas or countries affected by iodine deficiency. With the increasing use of ultrasound and other imaging techniques, thyroid nodules are now discovered in 30%–60% of the general adult population (*58–61*). The vast majority of these nodules are benign; only 2%–5% of all thyroid nodules (*60*), 6%–9% of nonpalpable nodules (*62*), and 9%–13% of nodules selected for fine-needle aspiration represent cancer (*61*). With PET or PET/CT, the rate of such incidentally detected (hypermetabolic) thyroid nodules is 1%–3% (*63–65*). Cumulative experience in more than 20,000 PET studies has been reported. In a study by Kang et al. (*63*), 29 of 1,340 individuals (2%) showed either diffuse ($n = 8$) or focal ($n = 21$) ^{18}F-FDG uptake in the thyroid gland. Histologic analysis was available for 15 of the 21 hypermetabolic nodules and revealed papillary

carcinoma in 4 (27%). In a study of 8,800 patients with cancer, incidental focal ^{18}F-FDG uptake was noted in 101 individuals, and diffuse uptake was noted in 162 individuals. Tissue diagnosis, obtained predominantly for focal lesions, proved cancer in 24 instances (*66*). Other authors (*64,65*) have reported that up to 50% of hypermetabolic thyroid nodules are malignant. All of these studies were limited by the fact that cytologic verification was available for only two thirds of the findings or fewer. The true prevalence of cancer in hypermetabolic thyroid nodules is therefore still somewhat unclear.

Unexpected abnormal ^{18}F-FDG uptake in the abdomen has been the subject of several reports and often can be attributed to colon adenomas, which may be precursors for colon cancer, or frank malignancies. Yasuda et al. (*67*) reported abnormal focal ^{18}F-FDG uptake in 24% of 59 adenomas found at endoscopy and in 90% of all adenomas that were ≥1.3 cm. Pandit-Taskar et al. (*68*) observed focal ^{18}F-FDG uptake in the abdomen, unrelated to the disease for which the PET had been ordered, in 16 of 1,000 patients with cancer. A definitive diagnosis could be rendered for 14 lesions, and 12 of them were malignant or premalignant. Using PET/CT, Israel et al. (*69*) reported incidental abnormal ^{18}F-FDG uptake in the abdomen in 58 of 4,390 patients with cancer (1.3%). Follow-up was available for 34 patients and showed malignant or premalignant conditions for 20 (58% of verified lesions; 0.5% of the entire study population). Kamel et al. (*70*) reported abnormal abdominal ^{18}F-FDG uptake with a frequency of 3% in 98 of 3,281 patients. Follow-up was available for 69 of these 98 patients (70%); cancer was detected in 13 individuals (19%), and another 29 (42%) had precancerous lesions. Eight of the 13 patients (62%) with incidentally detected colon or esophageal carcinoma were eligible for curative surgical resection.

In conclusion, abnormal focal ^{18}F-FDG uptake in the thyroid gland or abdomen is a rare finding but, when it occurs, requires further evaluation because a significant fraction of such lesions represent either malignant or premalignant conditions, usually at a state when curative treatment is likely to succeed. It should be noted that these PET scans were performed for patients with cancer, many of whom may have an increased likelihood for developing second primary malignancies (e.g., because of the presence of certain mutations in tumor suppressor genes in patients with cancer). Therefore, it is possible that the frequency with which focal ^{18}F-FDG uptake indicates cancer is lower among healthy individuals participating in screening studies. Nevertheless, in current clinical practice, in which whole-body PET is essentially used only in the evaluation of patients with cancer, one must conclude that incidental focal ^{18}F-FDG uptake will require further evaluation.

LUNG CANCER SCREENING WITH ^{18}F-FDG PET

In 3 recent studies, the sensitivity of ^{18}F-FDG PET for the detection of T1 lung cancers ranged between 68% and 95% (*46,71,72*). Marom et al. (*72*) determined the sensitivity of ^{18}F-FDG PET in 185 patients with T1 lung cancer (192 lesions; mean size: 2.0 cm; range: 0.5–3.0 cm). A total of 95% (183/192) of all lesions showed increased ^{18}F-FDG uptake (greater than mediastinal blood-pool activity), whereas the PET findings for the remaining 9 lesions (size: 0.3–2.5 cm; mean, 1.3 cm) were negative. The rate of detection tended to be lower for carcinoid tumors and bronchoalveolar cell carcinomas (BAC; the PET findings for 5/6 and 7/11 tumors were positive, respectively). The data appeared encouraging because the sizes of the lesions studied seemed to be in the range of tumors that one would expect in a lung cancer screening study. For instance, in the Early Lung Cancer Action Project study (*4*), the diameters of cancers detected at baseline CT were between 2 and 5 mm in 1 case, 5 and 10 mm in 14 cases, 11 and 20 mm in 8 cases, and 21 and 45 mm in 4 cases. However, upon yearly follow-up (*43*), 16 of 30 additional cancers had a diameter of between 2 and 5 mm, 7 were between 6 and 10 mm, 4 were between 11 and 20 mm, and only 3 were between 21 and 25 mm.

Less optimistic data were reported from the Mayo Clinic (*71*). This institution participates in an NCI-sponsored prospective trial that assesses the role of CT in screening for lung cancer. A small subset of screened individuals with lung nodules also underwent ^{18}F-FDG PET at the discretion of their pulmonologists. At the time of publication, CT screening had detected 62 lung cancers among the 1,520 participants, apparently including both baseline and follow-up scans. Twenty of these individuals (with 22 cancers) also underwent PET. With a threshold of ^{18}F-FDG uptake of greater than mediastinal blood-pool activity or a standardized uptake value (SUV) of greater than 2.5, the PET findings for 14 of the 22 cancers (68%) were positive, the PET findings for 7 (32%) were negative, and the PET findings for 1 were considered indeterminate. The mean lesion size was 10 mm in both the positive and the negative groups and therefore smaller than that in the aforementioned study (*72*). Based on their appearance on CT, nodules were classified as solid, semisolid, or ground-glass opacity. Two of the 22 lung cancers detected by the screening program were ground-glass opacities, corresponding to BAC on histologic analysis; both had negative PET findings. Likewise, 6 of the 22 cancers were semisolid nodules, and only 3 of these 6 were detected by PET. Indeed, ground-glass opacities ($n = 2$) and semisolid nodules ($n = 3$) accounted for the majority of the 7 cancers with negative PET findings. The relatively lower rate of positive PET findings among T1 cancers in this study was likely related to differences in tumor histology and lung nodule composition. Although the study had selection bias, it confirmed a lower rate of detection of BAC and adenocarcinomas with BAC features by PET (*72–74*). Moreover, as one should expect, among malignant lesions, the probability for positive PET results is inversely related to the number and density of viable tumor cells within the lesion; that is, the probability for cancer detection in solid nodules is greater

than that in semisolid nodules, which is greater than that in ground-glass opacities. Therefore, the use of ^{18}F-FDG PET for the evaluation of ground-glass opacities was discouraged to reduce the number of false-negative results.

In a prospective study from Italy, researchers combined CT and ^{18}F-FDG PET to screen for lung cancer (*46*). They enrolled 1,035 individuals who were older than 50 y and who had smoked for at least 20 y. All patients underwent baseline and annual low-dose CT for 5 y. Calcified nodules or lesions with maximum diameters of less than 5 mm were considered benign, and the patients were scheduled to undergo follow-up with CT 1 y later. Dedicated spiral CT was performed for suspicious, noncalcified nodules with diameters of greater than 5 mm, with measurements of contrast enhancement on CT. Noncalcified nodules with diameters of greater than 5 mm were further characterized by their contrast enhancement on CT, and those that demonstrated an enhancement of greater than 30 Hounsfield units were biopsied. At baseline, lung cancer was detected in 11 individuals (prevalence: 1.1%); at the 1-y follow-up, lung cancer was detected (incidence) in another 1.1%. Fifty-five percent of lung tumors detected at baseline and all 100% of those identified at follow-up were stage I cancers. ^{18}F-FDG PET was performed for all noncalcified nodules with diameters of greater than 7 mm. An SUV of greater than 2.0 was considered suggestive of malignancy, requiring biopsy. At baseline, PET was performed for 29 individuals with indeterminate lung nodules and identified lung cancer with an accuracy of 86% (8 true-positive results, 3 false-positive results, 17 true-negative results, and 1 false-negative result). Three of 4 stage I cancers (<2 cm) and all 5 stage II or III cancers were found positive by PET, with mean SUVs of 2.0 and 13.4, respectively. PET contributed to establishing the correct diagnosis in 43% (6/14) of cases with indeterminate findings on high-resolution CT. On the other hand, 3 of 5 biopsies for benign nodules were triggered by false-positive PET findings (caused by bronchiectasis, inflammatory pseudotumor, and lymphocytic infiltrates). Two well-differentiated adenocarcinomas of 8 and 11 mm were false negative on PET. At the 1-y follow-up, PET was performed for 13 individuals with indeterminate nodules. Eleven of these 13 were eventually diagnosed with cancer. PET had an accuracy of 85% (10 true-positive results, 1 false-positive result, 1 false-negative result, and 1 true-negative result). The authors suggested that the combination of low-dose CT and ^{18}F-FDG PET for the evaluation of selected patients with indeterminate nodules might be a reasonable approach to lung cancer screening.

However, uncertainty remains. Screening detects mainly slowly growing cancers, but ^{18}F-FDG uptake in lung cancer is directly related to tumor aggressiveness and proliferation rate (*75*). Further, the SUV for ^{18}F-FDG accumulation in lung cancer is inversely related to prognosis. Does this mean that lung lesions with negative PET findings do not require immediate intervention? Which patient (or physician) would want to live with the uncertainty that a lung lesion might be malignant, even if the risk for sudden growth or metastasis remains low? In any event, because negative PET findings cannot exclude malignancy (sensitivity may be as low as 67% (*71*)), continued follow-up for that lesion will still be necessary. In addition, the problem of false-positive PET findings in a cancer screening program will need to be addressed.

^{18}F-FDG PET FOR WHOLE-BODY CANCER SCREENING

"More bang for the buck" is a commonly used idiom in American English and has sometimes been applied to describe the expected major benefits from cancer screening with whole-body ^{18}F-FDG PET. But could it be that people are asked to pay "a lot of bucks" for "little bang"?

Proponents of PET for cancer screening (*76*) tend to refer to the intense ^{18}F-FDG uptake in many primary malignancies, thereby suggesting high sensitivity for tumor detection. Moreover, because PET is generally offered as a whole-body imaging study, it has the potential to reveal 1 or several malignancies anywhere in the body. In contrast, in current screening studies, efforts are focused on a particular organ (mammography for breast cancer, colonoscopy for colorectal cancer, and PSA measurements for prostate cancer). ^{18}F-FDG PET is a standard diagnostic test and is already in use for cancer screening in at least some institutions in the United States and on a more widespread basis in Japan (*77*) and Taiwan (*78*). It is now hoped that PET/CT will add both sensitivity and specificity to the PET interpretation by identifying physiologic tracer uptake as such and delineating cancerous lesions with low or no ^{18}F-FDG uptake.

Opponents of screening PET (*79*) refer to the unproven benefits and high costs. They also criticize published PET screening studies for their poorly defined inclusion criteria, unsatisfactory gold standard, and lack of cost-effectiveness data. There are also some concerns about creating a false sense of security from negative PET results and about the potential risks associated with unnecessary radiation.

Following is a summary of the relevant data.

Chen et al (*78*) described a cancer screening program in Taiwan that includes PET or PET/CT, ultrasound, and assessment of tumor markers. Individuals with abnormal findings undergo further evaluation; all others are monitored clinically for at least 1 y. Among a group of 3,631 individuals, this program detected 47 malignant tumors (1.3% of the population). Thirty-eight of these 47 cancers had true-positive PET results (sensitivity: 80%). For a subset of 32 individuals eventually diagnosed with cancer, screening PET was performed in the form of PET/CT, which led to the detection of 28 of 32 malignancies by the PET component of PET/CT, whereas only 15 of 32 lesions were identified by the CT component of PET/CT. Data on false-positive PET results and technical details were not reported.

In the imaging center at Lake Yamanaka, Japan (*77*), members of a health club undergo screening for cancer with blood tests, ultrasound of the neck and abdomen, chest CT, and whole-body PET or PET/CT. A total of 3,165 individuals

were studied between 1994 and 1999, and follow-up was at least 10 months. Within 1 y after screening, malignant tumors were discovered in 67 individuals (2.1%). Thirty-six cases had true-positive PET results (sensitivity: 54%), and most of these malignancies detected by screening were potentially curable. Thirty-one cases had false-negative PET results; 22 of the malignancies were detected by other imaging studies or PSA measurements. About one half of the false-negative PET findings occurred in patients with urologic malignancies, possibly related to urinary excretion of ^{18}F-FDG and low ^{18}F-FDG uptake in many primary prostate cancers. The total number of false-positive cases was not reported, but 5 individuals underwent surgery because of false-positive PET results; their final diagnoses were thyroiditis, tuberculoma, organizing pneumonia, and chronic maxillary sinusitis. The authors noted that 10 of the cancers detected by screening were found only by ^{18}F-FDG PET (1 lung, 1 breast [6 mm], 1 thyroid, 4 colorectal, 1 lymphoma, 1 parapharyngeal, and 1 chronic myelogenous leukemia). It should be noted that CT of the abdomen or pelvis was not part of the screening program. It is possible that the 4 colorectal cancers would have been found otherwise. The authors admitted that their data do not provide justification for public funding of PET cancer screening. Therefore, members of the health club pay the cost for the screening program. The authors noted that some false-positive findings, such as thyroiditis, can now be avoided because of the knowledge that diffuse thyroid uptake is essentially always benign. There was bias insofar as the results of conventional imaging studies were known at the time of interpretation of the PET scans.

These initial data were recently updated as part of a survey among 11 PET centers in Japan (*76*). Approximately 40,000 individuals underwent "sophisticated cancer screening" with ^{18}F-FDG PET and other imaging modalities, including ultrasound of the neck, breast, and abdomen or pelvis; whole-body CT; and abdominal MRI. Cancer was detected in 526 cases (1.32%). The most commonly detected tumors were cancers of the thyroid, lungs, colon, prostate, and breasts. About two thirds of the malignancies detected by screening showed recognizable ^{18}F-FDG uptake. The percentage of cancers detected by PET as a fraction of all cancers identified in this nationwide effort was highest for colon cancer (89%; PET findings for 91/102 detected cancers were positive), followed by thyroid cancer (PET findings for 87% of detected cancers were positive), breast cancer (80%), lung cancer (72%), and cancer of the stomach, esophagus, and pancreas (about 66% each). We are surprised by the high rate of detection of gastric and pancreatic cancers by PET. As one would expect, malignancies with low rates of detection included ovarian and renal cancers (PET findings for 33% were positive), prostate cancer (PET findings for 18% were positive), and bladder cancer (PET findings for 0% were positive). Hence, lower rates of detection for certain tumors were related to urinary excretion of ^{18}F-FDG (kidneys and bladder), low cell density (signet ring cancer of the stomach or scirrhous tumor of the breast), low ^{18}F-FDG metabolism (some lung adenocarcinomas, especially BAC; hepatomas; and most primary prostate cancers), or small lesion size. The authors admitted that lesions with diameters of less than 1 cm will be detected only occasionally, because partial-volume effects and lack of count recovery significantly lower the target-to-background ratios for these small tumors.

In summary, although interesting, none of these data permits determination of the efficacy of PET for cancer screening. There is no information regarding the cost-effectiveness of PET in the screening setting. These questions can be answered only in a prospective randomized trial that analyzes disease-specific mortality rates in the screened population and a control group.

VALUE OF PET/CT

PET/CT is more accurate in detecting cancer and provides fewer equivocal findings than PET alone (*80–83*), CT alone, or separately acquired PET and CT studies in a head-to-head comparison (*84*). For cancer staging, PET/CT is also more accurate than either modality alone, as shown for lung cancer (*85,86*), colorectal cancer (*83*), and lymphoma (*87*). Antoch et al. investigated the TNM staging accuracy of PET/CT in 260 patients with a variety of malignancies (*88*). Histopathologic and clinical follow-up at 311 ± 125 d (mean ± SD) served as a standard of reference. PET/CT had a significantly higher TNM staging accuracy (84%) than side-by-side PET plus CT (75%), CT alone (63%), or PET alone (64%). Values were slightly different for T, N, and M staging, but the same general trend toward superior accuracy of PET/CT was observed.

Although these studies suggested that PET/CT might be more sensitive and specific for cancer detection than either modality alone, none of them proves that this new imaging technology should be used for cancer screening attempts.

FINANCIAL CONSIDERATIONS

Affordability and availability are critical issues when a screening test is introduced. Affordability, like everything in life, is a measure of assets and worry. Whole-body cancer screening studies with either CT or PET (now perhaps with PET/CT) are currently not covered by insurance companies but are offered "at market price" to interested individuals in the United States and Japan. For the participating individuals, the cost of the test is usually not a matter of major concern. Some may be motivated by true concern about their elevated risk for cancer (e.g., strong family history of breast or colon cancer or greater than 20 pack-year history of cigarette smoking), whereas others may be driven by curiosity and the desire to obtain a routine examination (with the thinking that "my body deserves at least the same level of attention as my car"). This small fraction of the population has sometimes been characterized as "the worried well" (*89*). However, regardless of the

immediate cost of the screening imaging study, downstream costs resulting from further evaluation of true-positive or false-positive findings, which will usually burden the health care system as a whole (rather than being charged to the screened individual), must also be considered. Some lessons for screening PET can be learned from recent screening CT studies.

LESSONS FROM WHOLE-BODY SCREENING CT

Because there is no reliable information on the eventual costs of whole-body screening CT, which could be derived only from a randomized trial, Beinfeld et al. (*90*) used Monte Carlo decision analysis to estimate the potential effect of this test on health outcome and health care costs in a hypothetical cohort of 500,000 asymptomatic individuals. Potential benefits (from earlier detection of disease) and complications (from unnecessary intervention for false-positive screening findings) were compared for individuals undergoing 1-time whole-body CT and those who had no screening. The costs and effectiveness of the screening program (years of life gained from early detection and treatment of disease) were modeled. The model considered 8 conditions likely to be detected by whole-body CT: cancer of the ovaries, lungs, liver, kidneys, colon, and pancreas; aortic aneurysms; and coronary artery disease. On the basis of prior publications (*57*), the model considered that 90% of participants had at least 1 positive finding but that only 2% had any of the aforementioned diseases detected. This analysis showed that screening CT was associated with a minimal gain in life expectancy of only 6 days (in an effort to adjust for lead-time bias, the authors assumed that only 50% of the expected gain in survival was real and that 50% was attributable to lead-time bias). The average cost per screened individual was $2,513, and the incremental cost-effectiveness ratio (dollar amount spent to improve outcome) was $151,000 per year of life gained. The evaluation of false-positive or equivocal findings accounted for more than 30% of the total costs. Whereas these results depend on the prevalence of the disease in the population studied and on the diagnostic performance (sensitivity or specificity) of the test itself, even under the most favorable assumptions (similar sensitivity, specificity higher than that published, and CT scan cost that is 50% of the published cost), 1-time whole-body screening CT would not be cost-effective compared with currently accepted medical interventions. Moreover, a large burden to the health care system would result from the definitive assessment of false-positive or equivocal CT findings. Therefore, CT screening does not appear to be appropriate in a population with an average risk for any of the 8 conditions. Like any model or study, this one also has some limitations, but it presents an honest effort to assess the effectiveness of CT screening. The sobering news is that, despite heated propaganda, the test may be nothing more than an expensive exercise in futility.

ARGUMENTS AGAINST WHOLE-BODY SCREENING WITH ^{18}F-FDG PET

To place the debate over screening PET in the proper context, it is worthwhile to recall some facts. The current Medicare reimbursement for whole-body ^{18}F-FDG PET is about $2,000; free-market rates are somewhat higher. The median household income in the United States in 2004 was $44,389 (*91*). Therefore, we would expect that spending money on screening PET is not a priority and would not be considered reasonable for the majority of households in the United States. Modeling studies such as the aforementioned study for screening CT are not available for PET imaging.

All of the above-described financial considerations should also be placed in the larger context of health care spending in society as a whole. For instance, President Bush is currently promoting plans for "consumer-directed health care," which would enable families to make annual, tax-deductible deposits into a personal health savings account. The official goal is to put "consumers" in charge of their own health care, thereby promoting both quality control and cost control in the health care business. We find it entirely conceivable that individuals motivated by true concern about their elevated risk for cancer, but also those driven by curiosity, might want to undergo whole-body screening tests. It may be overly optimistic to expect that the average consumer could fully grasp the intricacies of current debates on cancer screening.

Accordingly, a large number of unnecessary and expensive screening tests might be done if individuals were subjected to irrational and misleading advertisements for screening PET or CT. Further, in 2006, the U.S. health sector will absorb about one sixth of the gross domestic product, a share projected to reach 18.7% by 2014 (*92,93*). Although whole-body screening studies with CT or PET may be paid for by consumers, subsequent evaluation of false-positive and false-negative findings will likely burden the health care system as a whole. Consider, then, that about 21% of adults and 12% of children in the United States are now without health insurance of any kind (*94*). Given this background, we consider it unjustified to spend the limited financial resources of the health care system for the wrong purpose by conducting whole-body cancer screening examinations of unproven benefit.

RADIATION DOSIMETRY CONCERNS

One of the criteria for a successful screening test is little morbidity for nondiseased individuals. For CT or PET, this criterion requires consideration of the radiation dose. The biologic effect of radiation will vary with the specific kind of radiation used and the distribution of the dose among healthy organs. These factors are accounted for by calculating the effective dose (ED), Σ(radiation dose to organ $i \times$ relative biological effectiveness $\times$ tissue i weighting factor); the unit is millisieverts.

The radiation dose from CT depends largely on 4 factors: the exposure time (s), x-ray tube current (mA), tube voltage

(kV), and table increment (or pitch). The absorbed dose, as well as the ED, is proportional to the milliampere × seconds (i.e., the product of the exposure time and the tube current) and to the square of kilovolts. Most diagnostic studies will be performed at 120–140 kV, whereas the tube current will be adjusted according to the clinical question and the body region. For instance, at many institutions, chest CT is performed with a tube current of between 200 and 300 mA. Low-dose CT for attenuation correction and basic anatomic information (140 kV, 80 mA, tube rotation of 0.8 s per rotation, pitch of 3:1) can be performed with an ED of 9 mSv (*95*). The ED for ^{18}F-FDG is 0.029 mSv/MBq, or 10 mSv from 370 MBq of ^{18}F-FDG (*96*). Accordingly, with the aforementioned CT parameters and injection of 370 MBq (10 mCi) of ^{18}F-FDG, the ED equivalent for the entire study will be about 19 mSv. Depending on the specific CT protocol and the ^{18}F-FDG activity, the ED equivalent for whole-body PET/CT may range between 10 mSv (scout view, low-dose CT with 120 kVp, 60 mA, and 370 MBq of ^{18}F-FDG) and 25 mSv (same procedure but followed by a diagnostic CT scan at 120 kVp and 200 mA) (*97*).

These doses can be compared with those for other radiologic tests that are used for screening purposes. For an average coronary calcium scoring study with electron-beam CT, the ED is between 0.7 mSv (*98*) and 1.3 mSv (*99*). The ED is slightly higher when CT coronary angiography is performed, variably estimated at 1.1 mSv (*98*) or at 1.5 mSv for men and 2.0 mSv for women (*99*). The radiation dose for cardiac studies is somewhat higher with multidetector CT than with electron-beam CT, approaching 1.5–5.2 mSv for men and 1.8–6.2 mSv for women for the purpose of calcium scoring and 6.7–10.9 mSv for men and 8.1–13.0 mSv for women for the purpose of coronary angiography (*99*). The typical dose for chest CT is in the range of 5–7 mSv (*98*), but a range of 3–27 mSv has been reported (*100*). The typical dose for CT of the abdomen and pelvis is in the range of 8–11 mSv (*98*). The estimated doses from whole-body screening CT with multidetector CT are 11.6 mSv for men and 13.5 mSv for women (*101*).

All of the above-described data should be interpreted in the context of natural (nonmedical) background radiation. According to NCRP (1987b) (http://www.ncrponline.org/Publications/93press.html), the average natural radiation dose in the United States is 3.6 mSv/y. Incidentally, the ED for 1 round-trip transatlantic flight between New York and Paris can be estimated at about 0.12 mSv. Man-made radiation is generally believed not to be significantly harmful as long as it does not exceed the average background radiation level.

To place things in perspective, the International Commission on Radiological Protection has suggested that there is a real (stochastic) risk of 5% per sievert for inducing malignancy from radiation exposure (*102*). This means that 5 of 100 individuals exposed to an ED of 1 Sv would develop cancer. If this concept could be applied to lower-level radiation exposure (a notion that is currently not proven), then one would have to assume an additional 5 radiation-induced malignancies among 100,000 individuals exposed to an ED equivalent of 1 mSv/y. In our view, radiation from an ever-increasing number of medical imaging studies is clearly a concern, but in the overall debate about screening CT and PET, it is only a minor contributing factor. If the efficacy of these studies for reducing cancer mortality could be proven, then concerns about radiation dose might be of lesser importance as long as the principle of "as low as reasonably achievable" is upheld. However, because there is currently no such evidence, dosimetry concerns remain an additional factor in cautioning against indiscriminate screening efforts.

LEGAL IMPLICATIONS

Marketing PET or CT as a screening tool for cancer detection may have considerable legal ramifications (*103–105*). Apart from misdiagnosis and oversight of findings in the screening scan, such procedures may also include complications as part of follow-up studies, which may prove unnecessary, or the lack of recommendation for follow-up (*106*); technical parameters of how the PET or PET/CT study was acquired may also be considerations (*107*). Therefore, it would appear wise for institutions offering screening PET or PET/CT to obtain at least comprehensive informed consent from interested individuals.

BELIEFS VERSUS FACTUAL EVIDENCE

In a recent survey in the United States, 87% of participants stated their belief that routine cancer screening is almost always a good idea and that earlier cancer detection saves lives (*108*). Similarly, 68% of women believe that screening prevents or reduces the risk of contracting breast cancer (*109*). In preparation for writing this article, we conducted a (nonscientific) survey among residents, fellows, technologists, and pharmacists within the Nuclear Medicine Service at Memorial Sloan-Kettering Cancer Center, asking the following questions: Do you think that whole-body PET screening is effective in detecting cancer at an early, potentially curable state? Should whole-body ^{18}F-FDG PET be marketed as a screening study to healthy, asymptomatic individuals? Would you be willing to have a whole-body ^{18}F-FDG PET screening examination? All 20 participants answered the first question with "yes." Although nobody seemed to favor marketing PET or PET/CT as a screening tool to the public, at least 14 individuals were curious enough to undergo a screening PET examination if it were offered to them at no cost (1 additional fellow stated "yes, if I were over the age of 50"). It is likely that similar results would be obtained if this survey were presented to a larger group of health care professionals.

Although curiosity can enhance the quest for diagnosis and innovation, it is often not recognized that subjecting patients (or asymptomatic individuals) to unnecessary testing and treatment carries its own risk. Apart from the initial costs, testing may result in further expense and harm as an

explanation for false-positive results is pursued, producing a cascade effect resembling a "chain of events (which) tends to proceed with increasing momentum, so that the further it progresses, the more difficult it is to stop" (*110*). Physicians sometimes pursue equivocal or simply unclear findings in the hope of finding the "right answer." Yet, as noted by the previous editor of the *New England Journal of Medicine*, "absolute certainty in diagnosis is unattainable, no matter how much information we gather, how many observations we make, or how many tests we perform" (*111*). Although this statement was made in reference to excessive diagnostic testing, it applies just as well to screening efforts. Underlying motives for excessive testing (screening) may include pressure from peers and supervisors, the convenience with which a test can be ordered, demands by the patient or family, and the desire to avoid malpractice claims. Physicians themselves may be curious about test results or ignorant about the test (screening) characteristics; some may simply have financial interests (advertisement of screening CT or PET in the news media). In many cases, excessive testing, including unnecessary screening, may detect abnormalities, the majority of which will have no bearing on the patient's health status (e.g., lung granuloma) but which will trigger a number of subsequent (imaging) studies. Above all, it must be realized that "however large the risk reduction [from screening], risk will remain" (*112*).

SIMPLE FINAL MESSAGE CONCERNING PET IN CANCER SCREENING

It is clear that PET and PET/CT can detect subclinical cancers as well as a number of other clinically important or potentially important conditions, such as an abdominal aortic aneurysm. Negative ^{18}F-FDG PET results may reassure curious healthy individuals that no obvious, clinically relevant cancer is present, as long as the malignancy in question is known to be ^{18}F-FDG avid. However, negative ^{18}F-FDG PET results cannot exclude small malignancies of any kind (but those may be clinically irrelevant at the time of the test) and cannot exclude the presence of certain malignancies with known low ^{18}F-FDG uptake (e.g., BAC, small primary prostate cancers with a low Gleason score, and mucinous pancreatic or ovarian neoplasms). Stated simply, it is probably better to have negative rather than positive PET screening test results. Positive or equivocal PET screening test results will require further evaluation, and many findings will in fact be false-positive findings. It is possible that PET/CT would perform better than either imaging modality alone in the screening setting; for instance, PET might demonstrate lesions in bone marrow or small lesions overlooked by CT; conversely, CT might identify abnormalities not seen on PET because of low ^{18}F-FDG uptake or high background activity. Nevertheless, small lesions or those limited to the mucosa might still be undetected. Neither whole-body CT nor whole-body PET or PET/CT can be applied in a cost-effective manner to the general population. Whether either test can be effective and cost-effective for cancer screening in certain high-risk groups remains to be determined. However, at present it is largely unclear which subgroup of individuals might benefit from these tests. Moreover, far from being the ultimate screening test, screening PET or PET/CT may prove to be a treacherous endeavor and open a Pandora's box of undesirable issues.

PET AND PET/CT IN SURVEILLANCE OF PATIENTS WITH CANCER

Different from the application of PET for screening is its use in the surveillance of patients with cancer after successful treatment of the primary disease with curative intent. The results of such efforts, if published at all, usually are based on a retrospective analysis of clinical imaging studies. Unless a clear algorithm has been established, these studies are often ordered at an arbitrary schedule, sometimes on the basis of symptoms and sometimes not. However, limited evidence suggests that PET imaging for surveillance may be more sensitive and perhaps more accurate than either clinical examination or other imaging studies. For instance, Lowe et al. used ^{18}F-FDG PET in the surveillance of patients who had head and neck squamous cell carcinomas and who were considered to be at high risk for recurrence on the basis of the biological factors of the primary tumors (*113*). Sixteen of 30 patients developed recurrence in the first year after therapy; all recurrences were identified by ^{18}F-FDG PET, and for 5 patients, PET was the only test to show the recurrent disease. A similar application of PET or PET/CT would likely also be useful in the surveillance of patients with aggressive lymphoma (*114*) and bone and soft-tissue sarcomas.

CONCLUSION

^{18}F-FDG PET and PET/CT can detect subclinical cancers in some individuals, but many pertinent questions remain unanswered. On the basis of the limited reliable data available, it is impossible to assess the efficacy of PET and PET/CT for cancer screening. No firm recommendation can be given, but it is unlikely that these tests can be used in a meaningful and cost-effective manner for population-wide cancer screening. Future studies will have to investigate the potential use of PET as a screening tool in well-defined populations and in a disease-specific manner. In a sometimes emotional debate, it is important to remember that the real benefit from screening is derived from earlier initiation of treatment, not simply earlier detection of cancer. To avoid biases inherent in many screening studies, the desired outcome from earlier treatment should be a measurable decrease in cancer mortality. Because it is difficult to convey the risks and potentially misleading comforts associated with screening tests to the general population, it is even more important to demand reliable data before recommending a new, expensive screening modality. For now, it would

seem appropriate that institutions offering screening PET or PET/CT counsel participating individuals regarding the limitations and potential risks (limited sensitivity, detection of false-positive findings requiring further evaluation, and radiation dose) of the test. Despite limited data, we foresee a potential role for PET/CT as a surveillance tool in well-defined, high-risk patients with cancer; this test may prove effective and, by eliminating other imaging studies, perhaps also cost-effective in the early detection of recurrent malignancies.

ACKNOWLEDGMENTS

We thank Pat Zanzonico, PhD, for his critical review of the radiation dosimetry section of the article. We thank residents, fellows, technologists, and pharmacists within the Nuclear Medicine Service at Memorial Sloan-Kettering Cancer Center for their participation in the survey.

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