Myocardial Perfusion Scans

Projected Population Cancer Risks From Current Levels of Use in the United States

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Background—Myocardial perfusion scans contribute up to 20% of the estimated annual collective radiation dose to the US population. We estimated potential future cancer risk from these scans by age at exposure and current frequency of use in the United States.

Methods and Results—Usage patterns were determined from national survey data, and radionuclide dosage was based on current guidelines. Cancer risk projection models were generated on the basis of the National Research Council Biological Effects of Ionizing Radiation VII report, under the assumption that risk has a linear relationship with radiation exposure even at low doses. The mean projected number of radiation-related incident cancers and 95% uncertainty intervals were estimated with the use of Monte Carlo simulations. Estimated risks for a scan performed at age 50 years ranged from 2 cancers per 10 000 scans (95% uncertainty interval, 1 to 5) for a positron emission tomography ammonia-13 test to 25 cancers per 10 000 scans (95% uncertainty interval, 9 to 58) for a dual-isotope (thallium-201 plus technetium-99m) scan. Risks were 50% lower at age 70 years but were similar for men and women. The combination of cancer risk estimates and data on frequency of use suggests that the 9.1 million myocardial perfusion scans performed annually in the United States could result in 7400 (95% uncertainty interval, 3300 to 13 700) additional future cancers.

Conclusions—The lifetime cancer risk from a single myocardial perfusion scan is small and should be balanced against likely benefit and appropriateness of the test. The estimates depend on a number of assumptions, including life expectancy. They apply directly to asymptomatic individuals with life expectancies similar to those of the general population. For individuals with a symptomatic clinical profile, on whom such scans are typically performed, the risks will be lower because of shorter life expectancy. **(*Circulation*. 2010;122:2403-2410.)**

Key Words: cancer risks ■ computed tomography ■ nuclear medicine ■ perfusion ■ radioisotopes

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Myocardial perfusion scans are a key tool for the diagnosis and risk assessment of coronary artery disease. The expansion of imaging technology and interest in early disease detection have led to an estimated 9.1 million tests being performed annually in the United States, approximately double the number performed in 1996.[1] The level of radiation exposure from a myocardial perfusion scan is comparable to or higher than that of many computed tomography (CT) scans.[2] The combination of high frequency of use and relatively high radiation doses means that perfusion scans are now estimated to contribute 20% of the annual collective radiation dose to the US population received from diagnostic procedures.[3]

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Increasing use of CT scanning and the potential cancer risks from these exposures have been the subject of a number of recent publications.[3–6] To date, the radiation-related cancer risks from nuclear medicine procedures such as myocardial perfusion scans have not been assessed. Risks will vary by age at exposure, life expectancy, radionuclide type, and administered dosage. Population cancer risks will also depend on the patterns of utilization. The purpose of this study was to project future cancer risks for current levels of perfusion scans in the United States. We used estimates of the frequency of test utilization by test type from a large national survey of nuclear medicine facilities[1] combined with radiation doses from national guidelines[7] and cancer risk models from the National Research Council Biological Effects of Ionizing Radiation VII committee report.[8] Cancer risks for other commonly used diagnostic cardiac tests that involve ionizing radiation (cardiac CT angiography and coronary artery calcification scores) were also calculated with the use

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of similar methods. Thus, it becomes possible to compare risks across test types and to estimate the total potential public health risk from this increasing source of radiation exposure.

Methods

Organ-Specific Doses

Radiation dose from nuclear medicine procedures depends on the type of radiopharmaceutical, level of administered activity, and protocol used. Technetium-99m and thallium-201 are currently the most commonly used for cardiac perfusion studies.[1] Organ doses and effective dose were calculated with standard dose conversion coefficients derived from dosimetry models of the International Commission on Radiological Protection[9] for the midpoint, minimum, and maximum of recommended administered activity levels as described in the guidelines from the American Society of Nuclear Cardiology.[7] Radiation doses for cardiac positron emission tomography (PET) with rubidium-82 and ammonia-13 were estimated with the use of American Society of Nuclear Cardiology imaging guidelines and International Commission on Radiological Protection dosimetry models.[10,11]

Radiation doses were calculated for coronary artery calcification CT and cardiac CT coronary angiography with the use of CT-Expo and CT Dosimetry programs.[12,13] These programs use organ dose databases based on Monte Carlo radiation transport modeling and calculate doses according to CT setting parameters.[14–16] The parameters were obtained from protocols described in recently published literature.[2,5]

Procedure Frequency

The frequency of different types of myocardial perfusion scans performed in the United States in 2008 was estimated with data from the IMV surveys of nuclear medicine and PET facilities.[1,17] The nuclear medicine survey provides estimates of the annual number of tests according to radionuclide used (technetium-99m, thallium-201, or dual isotope [technetium-99m plus thallium-201]) and protocol (1 or 2 days).[1] Estimates of the age distribution of myocardial perfusion scans were taken from a recent report that used a large national commercial insurance database.[18] These estimates were cross-checked for consistency with other national data including those from Medicare and Veterans Affairs.

The latency period between radiation exposure and cancer development is thought to be at least 5 years for solid cancers and at least 2 years for leukemia.[8] Therefore, patients who die within a few years of undergoing these tests are very unlikely to develop a radiation-related cancer. To take account of this in our calculations, we used results from a large multicenter prognostic study of myocardial perfusion scans to estimate the proportion of scans performed in patients who die within 5 years of undergoing testing.[19] After 2.5 years, ≈5% of patients had died, and therefore, using a linear extrapolation, we estimated that 10% of patients would have died by 5 years. Hence, 10% of the annual number of scans were excluded from the calculations of radiation-related cancer risks.

Statistical Analysis

Because cancer risks have been shown to remain elevated for at least 50 years after radiation exposure, the total detriment after an exposure is estimated by the cumulative lifetime risk, which is the sum of the risks across the remainder of the individual's lifetime.[20] These lifetime risks are also referred to as risk projections. The Biological Effects of Ionizing Radiation VII committee recently conducted a comprehensive review of the literature on health risks from low-level radiation exposure (<100 mGy) and used it to develop cancer risk projection models for the US population.[8] All models (except breast and thyroid) were developed with the use of data from the latest follow-up of the Japanese atomic bomb survivors because this is the most comprehensive data set currently available for most cancer sites.[21] The models for breast and thyroid cancer were based on pooled analyses of Japanese and other medically exposed cohorts.[22,23] For solid cancers, the risk was assumed to have a linear relation with dose, and for leukemia, the dose-response model was linear-quadratic. A minimum latency period of 5 years for solid cancers and 2 years for leukemia was also included.[8] We used the Japanese atomic bomb survivors and the Biological Effects of Ionizing Radiation methodology to develop additional models for 6 organs not included in the original report (oral cavity, esophagus, pancreas, brain, kidney, and rectum; see Table I in the online-only Data Supplement for further details). These organ-specific risk models were combined with the aforementioned dose estimates to estimate the lifetime risk of radiation-related cancer per 10 000 tests. The total cancer risk was calculated by summing risks across all exposed organs.

The risk calculations were performed with Analytica software (version 4.1)[24] with the use of Monte Carlo simulation methods to estimate risks with uncertainty intervals (UIs), accounting for statistical uncertainties in the risk parameters, subjective uncertainties in the transfer of risks from the Japanese to US population, and other assumptions.[8] We report mean estimates with 95% UIs from these simulations. The impact of additional uncertainties in the data and assumptions was investigated in sensitivity analyses.

Results

The estimated effective dose for each myocardial perfusion scan ranged from 9 mSv for a stress-only technetium-99m test to 35 mSv for a dual-isotope study (with the assumption of the midpoint of administered activity level; Table 1). The effective dose for a PET scan with rubidium-82 was similar to that for a technetium-99m test (15 mSv), but for ammonia-13 it was much lower (2 mSv) (Table 1). In a technetium-99m rest-stress test, the organs that received the highest estimated doses were the kidneys (42 mGy) and colon (30 mGy); in the dual-isotope test, the highest doses were to the ovaries (97 mGy) and kidneys (86 mGy) (Table II in the online-only Data Supplement).

A technetium-99m rest-stress test at age 50 years was estimated to result in a lifetime risk of 10 cancers per 10 000 tests (95% UI, 5 to 19; Table 2). A PET ammonia-13 scan had the lowest risk at 2 (95% UI, 1 to 5) cancers per 10 000 tests, and a dual-isotope study had the highest risk (25 [95% UI, 9 to 58] cancers per 10 000 tests). The breakdown of total cancer risk according to cancer site is shown for a technetium-99m rest-stress test in Figure 1. The largest component of total cancer risk was from colon cancer, followed by bladder cancer and by lung cancer in women. Although organ-specific risks varied somewhat by gender, the total cancer risk was similar in men and women when summed across all organs.

A number of sensitivity analyzes examined the impact of varying the assumptions in these calculations. Because risk is approximately proportional to dose, higher or lower administered activity levels (eg, ±20%) would increase or lower the risk estimates by a similar amount. It was not possible to develop risk projection models for a number of rarer cancer sites that collectively account for ≈20% of annual cancer incidence in the United States. If these had been included, then the risk estimates could have been ≈20% higher (assuming similar dose-response relationships to the cancer sites that were included). Conversely, several cancer sites that were included have not been confirmed as radiation inducible (oral, pancreatic, kidney, and prostate cancer).[8] Exclusion of these sites would have reduced the risk estimates by ≈20%.

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Table 1. Estimated Effective Dose and Radiation-Related Cancer Risk From Exposure to Age 50 Years for Myocardial Perfusion Scans, According to Radiopharmaceutical and Protocol

Radiopharmaceutical and Test Type	Administered Activity Range, MBq*	Effective Dose Midpoint (Range), mSv	Radiation-Related Cancers† (per 10 000 Tests at Age 50 y), No. of Cancers (95% UI)
Technetium-99m			
Rest/stress	296–444 and 888-1332	12 (10–15)	10 (5–19)
Stress/rest	888–1332 and 888–1332	19 (15–23)	16 (7–29)
Stress only	888–1332	9 (7–11)	8 (3–13)
Thallium-201			
Stress/redistribution	93–148	26 (12–33)	18 (6–46)
Viability	111–148	29 (24–33)	19 (6–50)
Dual isotope‡			
Rest/stress	Tl–201: 93–148; Tc–99m: 888–1332	35 (28–43)	25 (9–58)
Rubidium-82			
Rest/stress	1480–2250	15 (11–18)	7 (3–13)
Ammonia-13			
Rest/stress	370–740	2 (1–3)	2 (1–5)

Tl-201 indicates thallium-201; Tc-99m, technetium-99m.

*Based on the American Society of Nuclear Cardiology guidelines.[7] Ranges are given for the administered level for both rest and stress studies.

†Assuming the midpoint of the recommended range of administered activity.

‡Thallium-201 and technetium-99m.

Another uncertain factor is the life expectancy of the patients undergoing the tests. The lifetime risk is estimated by summing across all ages after exposure, with adjustment for the probability of surviving to that age. These probabilities are based on all-cause mortality rates for the general US population. If life expectancy is shorter than average, this will reduce the radiation-related cancer risk. For example, a 5-year reduction in life expectancy (the average reduction for a lifelong smoker)[25] was estimated to reduce the lifetime cancer risk from a test at age 50 years by ≈25%. Similarly, a 5-year increase in life expectancy would increase the lifetime cancer risk by about the same amount.

Table 2. Projected Number of Future Cancers Related to the Annual Number of Myocardial Perfusion Scans Performed in the United States in 2008

Radiopharmaceutical and Scan Type	Annual Scans		Radiation-Related Cancers†		
	No.*	%	Mean	95% UI	%
Technetium-99m					
Rest/stress	6 000 000	66	3800	1800–6800	51
Stress/rest	1 100 000	12	1200	500–2100	16
Stress only	300 000	3	130	60–300	2
Thallium-201					
Stress/redistribution	100 000	1	90	40–200	1
Viability	100 000	1	90	40–200	1
Dual isotope‡					
Rest/stress	1 500 000	16	2100	800–4100	28
Rubidium-82					
Rest/stress	45 000	<1	20	10–40	<1
Total	9 100 000	100	7400	3300–13 700	100

*Ten percent of these scans were excluded in estimating the projected number of cancers (see Methods for more details).

†Assuming the midpoint of the recommended administered activity range (see Table 1).

‡Thallium-201 and technetium-99m.

In the United States, two thirds of the 9.1 million myocardial perfusion scans performed annually are technetium-99m rest-stress tests (Table 2). The second most common test is a dual-isotope study (1.5 million tests annually). Studies in which only thallium-201 is used comprise only 2% of the annual tests. The combination of the aforementioned cancer risk estimates and the data on frequency of use suggests that the 9.1 million annual myocardial perfusion scans in the United States could result in 7400 (95% UI, 3300 to 13 700) additional future cancers, assuming use of the midpoint radionuclide activity level (Table 2). Approximately half of these projected cancers were from technetium-99m rest-stress tests, and 28% were from dual-isotope studies.

The radiation-related cancer risks for myocardial perfusion scans were compared with those for other diagnostic cardiac tests (eg, CT angiography) according to age at exposure (Figure 2). For the specific protocols considered, the effective dose per test ranged from 35 mSv for a dual-isotope study to 3 mSv for a coronary artery calcification CT. In women, cardiac CT angiography had the second highest risk before age 50 years, primarily because of the relatively high breast cancer risk before this age (Table I in the online-only Data Supplement), but after age 50 they had a level of risk similar to that for a technetium-99m rest-stress test. Coronary artery calcification CT had the lowest risk at all ages. If multiple types of tests are performed, the risks are approximately additive. For example, if a 50-year-old man undergoes both a technetium-99m rest-stress test and a cardiac CT angiography, then the lifetime risk would be ≈18 cancers per 10 000 tests.

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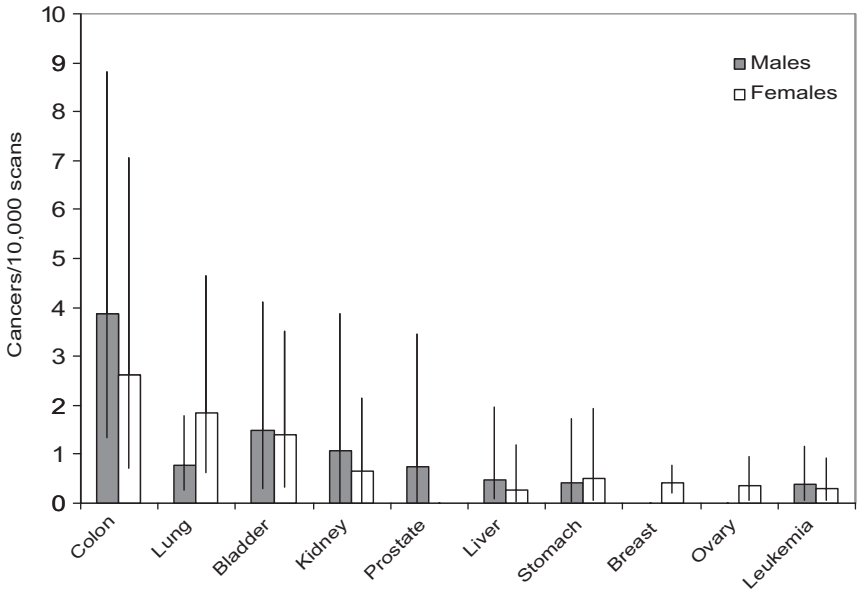

Figure 1. Estimated radiation-related cancer risk for a technetium-99m rest-stress myocardial perfusion scan at age 50 years (per 10 000 scans), showing breakdown in risk according to cancer site.

Discussion

This article provides comprehensive estimates of the potential population future cancer risks related to current levels of myocardial perfusion scanning in the United States. The results suggest that the 9.1 million tests performed each year in the United States could result in ≈7400 (95% UI, 3300 to 13 700) additional future cancers. Nearly 70% of these projected cancers were from the most commonly used technetium-99m rest-stress tests, and ≈30% were from the higher-dose dual-isotope studies.

Radiation dose from myocardial perfusion scans varies widely, depending primarily on the radiopharmaceutical used but also on the protocol and administered activity. Previous studies have provided estimates of the radiation doses or frequency of myocardial perfusion scans but have not estimated the potential cancer risks.[3,4,26] The dose estimates from these previous studies are in broad agreement with those presented here. National survey data on the frequency of different radiopharmaceuticals provided key information on one of the sources of variation in dose (Table 1). However, because no data are currently available on actual activity levels that are administered in practice, our estimates were based on activity levels recommended in the American Society of Nuclear Cardiology guidelines, which are similar to other guidelines.[27,28] The results for cancer risks assumed that the midpoint of the recommended activity range was used. There is anecdotal evidence that the typical administration levels may be nearer the maximum of the recommended values.[18] Sensitivity analysis showed that cancer risks would be ≈20% higher if the maximum rather than the midpoint was used. Conversely, if tests were performed routinely with the minimum recommended activity, radiation exposure could be reduced by ≈20% (compared with the midpoint of the recommended range). However, reduction of dose to minimum activity could adversely affect image quality and diagnostic accuracy.[29]

Other factors could reduce radiation exposure from myocardial perfusion scans, such as the properties of the radionuclide itself. For example, use of thallium-201 in dual-isotope studies has improved efficiency and throughput in high-volume laboratories.[30,31] However, thallium-201 results in a radiation dose that is typically 2-fold higher than that of technetium-99m because of its longer half-life. Use of thallium-201 has already nearly halved from 3 million injections in 2002 to 1.7 million injections in 2008[1]; probable reasons include the enhanced image quality of technetium-99m and also concerns about the radiation risks. In current practice, rubidium-82 for cardiac PET has a radiation exposure profile similar to that of technetium-99m, whereas ammonia-13 has a lower radiation exposure (Table 1). Unfortunately, ammonia-13 is not widely used because there is limited availability of cyclotrons necessary for its production. More efficient single photon emission computed tomography cameras or new-generation CT scanners with prospective gating could substantially reduce the radiation dose and hence cancer risk from cardiac imaging.[32,33]

Although the effective radiation dose from a technetium-99m rest-stress test is slightly lower than that for a typical CT coronary angiogram, the number of cardiac perfusion tests currently performed annually is >3 times higher than the number of CT coronary angiograms.[18] Therefore, they make a greater contribution to the collective radiation exposure to the US population and also to the potential future cancer risks from diagnostic cardiac procedures. Using methods similar to those presented here, we recently estimated that these 2.6 million CT coronary angiograms performed in the United States in 2007 could result in ≈2300 future cancers.[5] The comparison of the cancer risks across the different types of cardiac tests by age at exposure highlights the fact that although the effective radiation dose gives a broad indication of cancer risk, it does not take account of the age dependence of radiation-related cancer risks. In particular, because radiation-related breast cancer risk declines for exposures after age 50 years,[23] the higher effective dose for a CT coronary angiogram does not necessarily translate into a correspondingly high cancer risk after this age (Figure 2).

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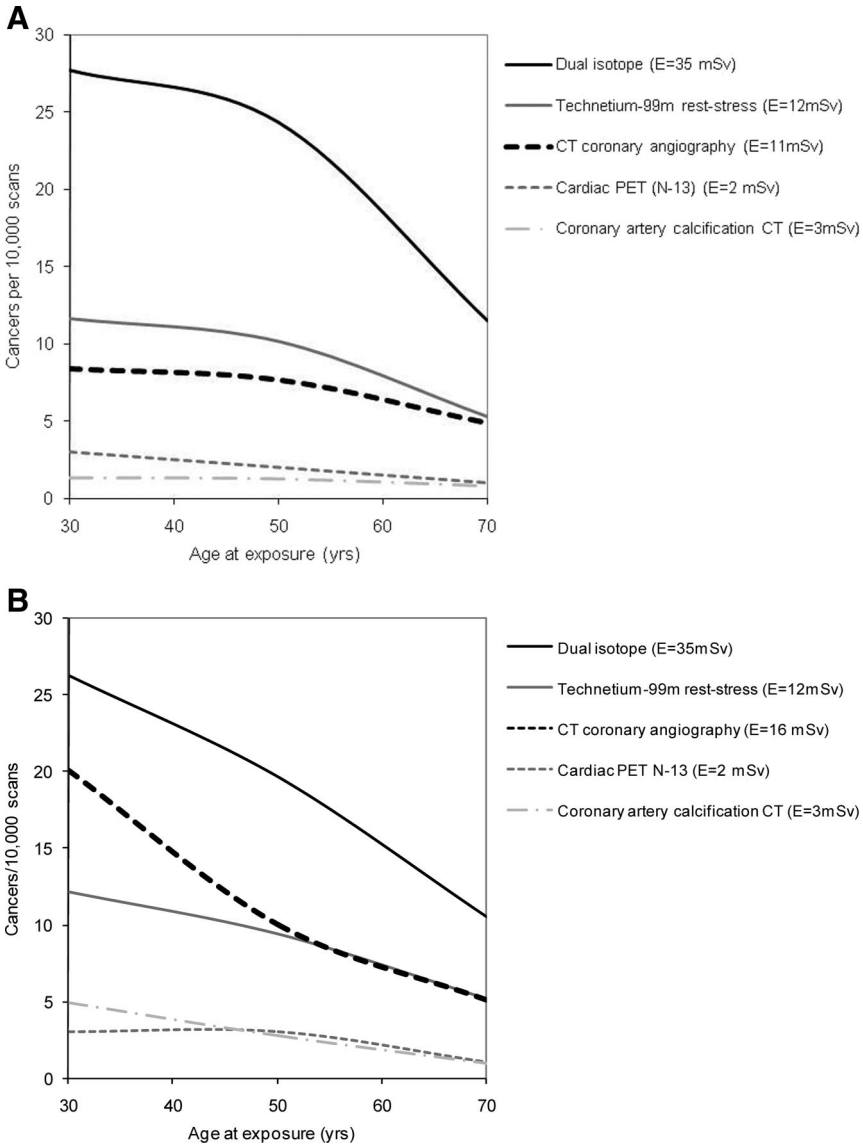

Figure 2. Projected number of future cancers per 10 000 scans, showing comparison of myocardial perfusion and cardiac CT scans according to age at exposure in men (A) and women (B).

Similarly, although the estimated effective dose for a PET scan with rubidium-82 is slightly higher (15 mSv) than for a technetium-99 rest-stress test (12 mSv), the risk estimates are lower. This is because the higher effective dose is largely due to the high thyroid dose from rubidium-82, but in adults the risk of radiation-related thyroid cancer is very small (Table 1 and Table II in the online-only Data Supplement). It should be noted that the dose and risk comparisons for different cardiac tests in Figure 2 were for specific protocols and that exposure levels are likely to vary considerably in practice.

To study the long-term cancer risks from myocardial perfusion scans directly would require a very large sample size (hundreds of thousands of subjects) with long-term follow-up.[34] Risk projection studies with allowance for the major modeling uncertainties provide a more feasible approach and a more timely assessment of the potential risks. These projections depend on a number of assumptions. A key assumption is the linear no-threshold assumption, which states that radiation-related cancer risks are proportional to dose and that there is no low-dose threshold below which there is no cancer risk.[35] There is a large body of data to support this assumption, including evidence of significantly increased cancer risks in populations exposed to low levels of radiation such as nuclear workers and the Japanese atomic bomb survivors.[36,37] There is also biological evidence that suggests that it is unlikely that there is a threshold for radiation-related cancer induction.[35] Linear risk models fit the available epidemiological data well at these low doses, and this model is also supported by experimental evidence.[35] As a result, most national and international committees support use of the linear no-threshold assumption for radiation protection.[8,38,39] However, there is a minority opinion that carcinogenesis has a threshold below which low-dose radiation may not be harmful through stimulation of multiple DNA repair mechanisms.[40]

Because there is evidence that cancer risks from low-dose rate exposures, like nuclear medicine tests, are lower per unit dose than the high-dose rate exposures received by the Japanese atomic bomb survivors, we reduced the risk per unit dose in our calculations by an uncertain factor with a mean

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estimate of 1.5 (known as a dose and dose rate reduction effectiveness factor).[8] Where possible, uncertainties in the calculations were incorporated into the estimates via the use of Monte Carlo simulations.

The life expectancy of the exposed individuals is another key assumption in these risk projections. The risk estimates in Table 1 that summarize the risk per 10 000 tests therefore are most appropriate for asymptomatic individuals (ie, for a group of individuals who will likely have the life expectancy of the general population). The impact of the assumed life expectancy on the number of projected cancers from current levels of use (Table 2) is difficult to assess because some of the required data on the life expectancy of those currently undergoing testing are, by definition, not available. However, we can use a number of sources to assess its impact. For example, we excluded from the calculations the 10% of scans that were estimated to be performed in the sickest individuals (ie, those who die within 5 years of undergoing testing). Prognostic studies in which myocardial perfusion scans are used generally report that subjects with normal test results have lower cardiac death rates than the general population (ie, longer than average life expectancy), whereas those with abnormal test results have higher cardiac death rates.[41] Although there are no nationally representative data on the current proportion of tests that are normal in the United States, results from a number of surveys in specific settings (eg, academic medical centers) find that ≈40% to 60% of the patients have normal test results.[42–44] Therefore, the impact of the underestimation of projected cancers in those with normal tests and the overestimation in those with abnormal tests may approximately cancel each other out.

Although there was no single data source that included the information required on the current frequency of tests according to age, sex, and test type, the data on age and test type have previously been cross-checked with other sources, including Medicare and Veterans Affairs, and showed good concordance.[18] Because the risk estimates per myocardial perfusion scan were very similar for men and women, it was not necessary to have data on the distribution of tests by sex for our calculations. Similarly, although we did not have data on the number of individuals who underwent tests, only the total number of tests, this will not have affected the estimated potential cancer risks because at low-dose levels the risks are approximately additive. For example, if 4.5 million individuals each underwent 2 tests, the total future projected cancers would be the same as for 9 million individuals who underwent a single test.

Given the multiple indications for cardiac perfusion studies and the lack of clinical trial data, it has not been possible thus far to estimate the absolute benefits in terms of the number of deaths that may be prevented by these tests.[45] However, appropriateness criteria for myocardial perfusion scans have been published by the American College of Cardiology Foundation with support of several organizations.[46] In general, perfusion tests were indicated to assess intermediate- and high-risk patients with likely coronary artery disease, but they were considered inappropriate or of uncertain appropriateness for low-risk patients or for general screening. A recent multicenter study in which these criteria were used found that ≈14% of tests were classified as inappropriate.[47]

In summary, myocardial perfusion scans are a key tool in the assessment of patients with known or suspected heart disease. For most patients, the risks from not performing the myocardial perfusion scan will be greater than the small radiation-related cancer risks. However, this article highlights the fact that even when individual risks are small, significant numbers of future cancers can accumulate when large numbers of people are exposed. The estimates depend on a number of assumptions, including life expectancy. They apply directly to asymptomatic individuals with life expectancies similar to those of the general population. For individuals with a symptomatic clinical profile, on whom such scans are typically performed, the risks will be lower because of shorter life expectancy.

The risks could be reduced by decreasing the number of tests, by performing lower dose tests, for example, stress-only technetium-99m studies or by decreasing the radiation dose per test. Other modalities that do not involve ionizing radiation such as stress echocardiography or cardiac magnetic resonance imaging could be considered, depending on cost, availability, and adequate sensitivity and specificity. Alternatively, newer-generation single photon emission computed tomography or CT scanners and hybrid systems may allow improved detection of disease with lower radiation exposure. For the individual subject, the physician should balance the need for diagnostic testing and the risk-benefit ratio, taking into account all potential risks and being mindful of guidelines for radiation safety and appropriateness criteria for the test.

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Disclosures

None.

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CLINICAL PERSPECTIVE

This article provides population-based estimates of lifetime cancer risk from nuclear myocardial perfusion scans and other cardiac imaging tests for comparison. Positron emission tomography and dual-isotope scans have the lowest and highest radiation exposures, respectively. Cancer risks are low, ranging from 2 cancers per 10 000 scans (95% uncertainty interval, 1 to 5) for ammonia-13 cardiac positron emission tomography to 25 cancers per 10 000 scans (95% uncertainty interval, 9 to 58) for dual-isotope studies. However, because of widespread use of nuclear myocardial perfusion studies (9.1 million scans per year in the United States), it is possible that 7400 additional future cancers could be related to these scans. These risk estimates depend on several assumptions, including the assumption that the cancer risk and radiation dose have a linear no-threshold relationship even at low doses and that the life expectancy for individuals undergoing the scans is similar to that of the general population. The clinician should be familiar with the indications for nuclear myocardial perfusion studies and order scans in accordance with the American Heart Association/American College of Cardiology appropriateness criteria guidelines. In the future, newer technologies with lower radiation exposure and adequate sensitivity and specificity for disease detection may be preferred.

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