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Myocardial perfusion scans: projected population cancer risks from current levels of use in the U.S

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Abstract

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

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 based on the National Research Council Biologic 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 (UI) were estimated using Monte Carlo simulations. Estimated risks for a scan performed at age 50 years ranged from 2 cancers/10,000 scans (95%UI:1–15) for a positron emission tomography ammonia-13 test to 25 (95%UI:9–58) cancers/10,000 scans for a dual-isotope (thallium-201+technetium-99m) scan. Risks were 50% lower at age 70 years, but were similar for males and females. Combination of cancer risk estimates with data on frequency of use suggested that the 9.1 million myocardial perfusion scans performed annually in the U.S. could result in 7400 (95%UI:3300–13700) 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 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.

Keywords

nuclear medicine; perfusion; radioisotopes; cancer risks; computed tomography

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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 (U.S.), approximately double the number performed in 1996.[1] The level of radiation exposure from a myocardial perfusion scan is comparable with or higher than 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 U.S. population received from diagnostic procedures.[3]

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 U.S. using estimates of the frequency of test utilization by test types 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's Biological Effects of Ionizing Radiation Committee report (BEIR VII).[8] Using similar methodology, cancer risks for other commonly used diagnostic cardiac tests that involve ionizing radiation (cardiac CT angiography and coronary artery calcification scores) were also calculated. 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 depend on the type of radiopharmaceutical, level of administered activity and protocol used. Technetium-99m (Tc-99m) and thallium-201 (Tl-201) are currently the most commonly used for cardiac perfusion studies.[1] Organ doses and effective dose were calculated using standard dose conversion coefficients derived from dosimetry models of the International Commission on Radiological Protection (ICRP)[9] for the median, minimum and maximum recommended administered activity levels as described in the guidelines from the American Society of Nuclear Cardiology (ASNC).[7] Radiation doses for cardiac positron emission tomography (PET) using Rubidium (Rb)-82 and ammonia (N)-13 were estimated using ASNC imaging guidelines and ICRP dosimetry models.[10,11]

Radiation doses were calculated for coronary artery calcification CT and cardiac CT coronary angiography using 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 using 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+thallium-201)) and protocol (1 or 2 day).[1] Estimates of the age distribution of myocardial perfusion scans were taken from a recent report, which used a

large National Commercial Insurance Database.[18] These estimates were cross-checked for consistency with other national data including Medicare and the Veteran's Association.

The latency period between radiation exposure and cancer development is thought to be at least five years for solid cancers, and at least two 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 multi-center prognostic study of myocardial perfusion scans to estimate the proportion of scans performed in patients that die within five years of undergoing testing.[19] After 2.5 years about 5% of patients had died and so using a linear extrapolation we estimated that 10% of patients would have died by five 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 fifty years after radiation exposure, the total detriment following 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 commonly referred to as risk projections. The BEIR VII committee recently conducted a comprehensive review of the literature on health risks from low-level radiation exposure (<100 milli-Gray (mGy)), and used it to develop cancer risk projection models for the U.S. population.[8] All models (except breast and thyroid) were developed using data from the latest follow-up of the Japanese atomic bomb survivors because this is the most comprehensive dataset 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 and for leukemia the dose-response model was linear-quadratic. A minimum latency period of five years for solid cancers and two years for leukemia was also included.[8] We used the Japanese atomic bomb survivors and the BEIR methodology to develop additional models for six organs not included in the original report (oral cavity, esophagus, pancreas, brain, kidney and rectum; see Appendix A for further details). These organ-specific risk models were combined with the dose estimates described above 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] using Monte Carlo simulation methods to estimate risks with uncertainty intervals, accounting for statistical uncertainties in the risk parameters, and subjective uncertainties in the transfer of risks from the Japanese to U.S. population and other assumptions.[8] We report mean estimates with 95% uncertainty limits (Ul) from these simulations. The impact of additional uncertainties in the data and assumptions were investigated in sensitivity analyses.

Results

The estimated effective dose for each myocardial perfusion scan ranged from 9 milli-Sievert (mSv) for a stress only technetium-99m test to 35mSv for a dual isotope study (assuming median level of administered activity, Table 1). The effective dose for a PET scan with RB-82 was similar to a technetium-99m test (15mSv) but for N-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 (42mGy) and colon (30mGy) and in the dual isotope test the highest doses were to the ovaries (97mGy) and kidneys (86mGy) (Appendix B).

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% Uncertainty Interval:5–19; Table 2). A PET ammonia-13

scan had the lowest risk: 2 (1–5) cancers per 10,000 tests and a dual isotope study had the highest risk (25 (9–58) 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 lung cancer in females. Although organ-specific risks varied somewhat by gender, the total cancer risk was similar in men and women when summed across all organs regardless of age at exposure (Figure 2).

A number of sensitivity analyzes examined the impact of varying the assumptions in these calculations. As risk is approximately proportional to dose, higher or lower administered activity levels (e.g. ±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 about 20% of annual cancer incidence in the U.S. If these had been included, then the risk estimates could have been approximately 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 about 20%.

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 U.S. population. If life-expectancy is shorter than average, then this will reduce the radiation-related cancer risk. For example, a five-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 about 25%. Similarly a five-year increase in life-expectancy would increase cancer risk by a comparable percentage.

In the U.S., 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 using only thallium-201 make up only 2% of the annual tests. Combination of the cancer risk estimates described above with the data on frequency of use suggested that the 9.1 million annual myocardial perfusion scans in the U.S. could result in 7400 (95% UI: 3300–13700) additional future cancers, assuming use of median radionuclide activity (Table 2). About 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 other diagnostic cardiac tests (e.g. CT angiography) according to age at exposure (Figure 2). For the specific protocols considered, the effective dose per test ranged from 35mSv for a dual isotope study to 3mSv for a coronary artery calcification CT. In women, cardiac CT angiography had the second highest risk before age 50 years, primarily due to the relatively high breast cancer risk before this age (Appendix A), but had a similar level of risk to a technetium-99m rest-stress test after age 50 years. 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 about 18 cancers per 10,000 tests.

Discussion

This paper provides comprehensive estimates of the potential population future cancer risks related to current levels of myocardial perfusion scanning in the U.S. The results suggest

that the 9.1 million tests performed each year in the U.S. could result in approximately 7400 [95% UI: 3,300–13,700] additional future cancers. Nearly 70% of these projected cancers were from the most commonly used technetium-99m rest-stress tests and about 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, as no data are currently available on actual activity levels that are administered in practice, our estimates were based on doses recommended in the ASNC guidelines, which are similar to other guidelines.[27,28] The results for cancer risks assumed that the mid-point 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 about 20% higher if the maximum rather than the median dose was used. Conversely, if tests were performed routinely using the minimum recommended activity, radiation exposure could be reduced by about 20% (compared to the mid-point of the recommended range). However, reduction of dose to minimum activity could adversely affect image quality and diagnostic accuracy.[29]

There are other factors that 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 has a radiation dose that is typically two-fold higher than technetium-99m because of its longer half-life. Use of thallium-201 has already nearly halved from three 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. At current radiation doses, Rubidium-82 for cardiac PET has a radiation exposure profile similar to 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. Alternatively, more efficient single photon emission computed tomography (SPECT) 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 more than three times higher than the number of CT coronary angiograms.[18] Therefore, they make a greater contribution to the collective radiation exposure to the U.S. population and also to the potential future cancer risks from diagnostic cardiac procedures. Using similar methods to those presented here, we recently estimated that these 2.6 million CT coronary angiograms performed in the U.S. in 2007 could result in about 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[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). Similarly, although the estimated effective dose for a PET scan with Rubidium-82 is slightly higher (15mSv) than for a technetium-99 rest-stress test

(12mSv) the risk estimates are lower 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 Appendix B). 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 which 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 supported also 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 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 one of the key assumptions in these risk projections. The risk estimates in table 1 which summarize the risk per 10,000 tests therefore are most appropriate for asymptomatic individuals, i.e. 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 less straightforward 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 address this issue indirectly. For example, we excluded from the calculations the 10% of scans that were estimated to be performed in the sickest individuals, i.e. those who die within five years of undergoing testing. Prognostic studies using myocardial perfusion scans generally report that subjects with normal test results have lower cardiac death rates than the general population (i.e. 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 U.S., results from a number of surveys in specific settings (e.g. academic medical centers) find that about 40–60% 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 the Veterans Association, and showed good concordance.[18] As the risk estimates per test were

very similar for males and females, 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, as at low dose levels the risks are approximately additive. For example, if 4.5 million individuals each underwent two 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 multi-center study using these criteria found that about 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 paper 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 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 performed, for example, by performing 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 (MRI) could be considered dependent on cost, availability, and adequate sensitivity and specificity. Alternatively, newer generation SPECT 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 account of all potential risks, being mindful of guidelines for radiation safety and appropriateness criteria for the test.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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This paper provides population-based estimates of lifetime cancer risk from nuclear myocardial perfusion scans and other cardiac imaging tests for comparison. Positron emission tomography (PET) and dual isotope scans have the lowest and highest radiation exposures respectively. Cancer risks are low, ranging from 2 cancers/10,000 scans (95% uncertainty intervals (Ul) 1–15) for ammonia-13 cardiac PET to 25 cancers/10,000 scans (95% UI 9–58) for dual isotope studies. However, because of widespread use of nuclear myocardial perfusion studies (9.1 million scans/year in the U.S.), 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 AHA/ACC appropriateness criteria guidelines. In the future, newer technologies with lower radiation exposure and adequate sensitivity and specificity for disease detection may be preferred.

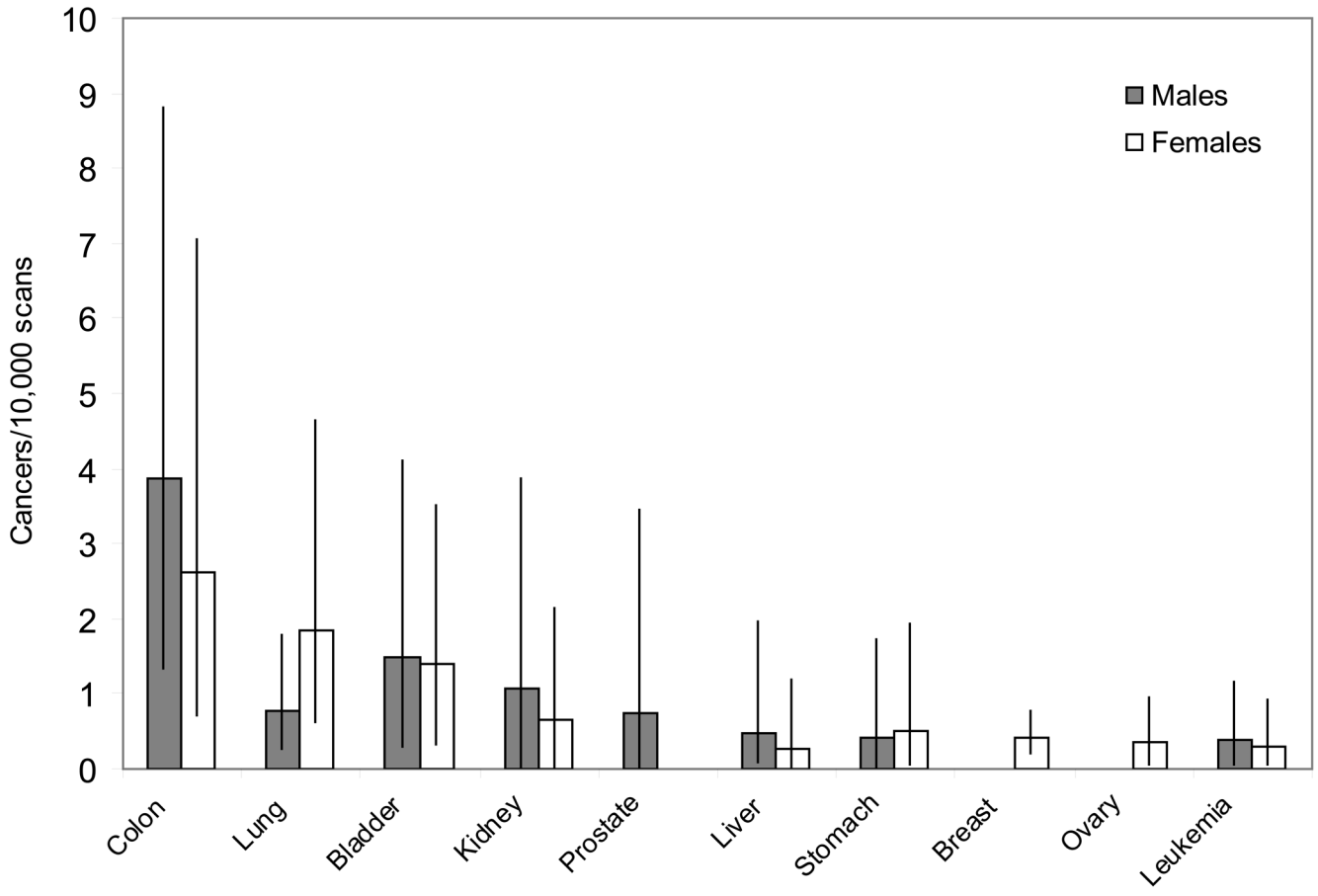

Figure 1.
Estimated radiation-related cancer risk for a technetium-99m rest-stress myocardial perfusion scan at age 50 years (per 10,000 scans): breakdown in risk according to cancer site

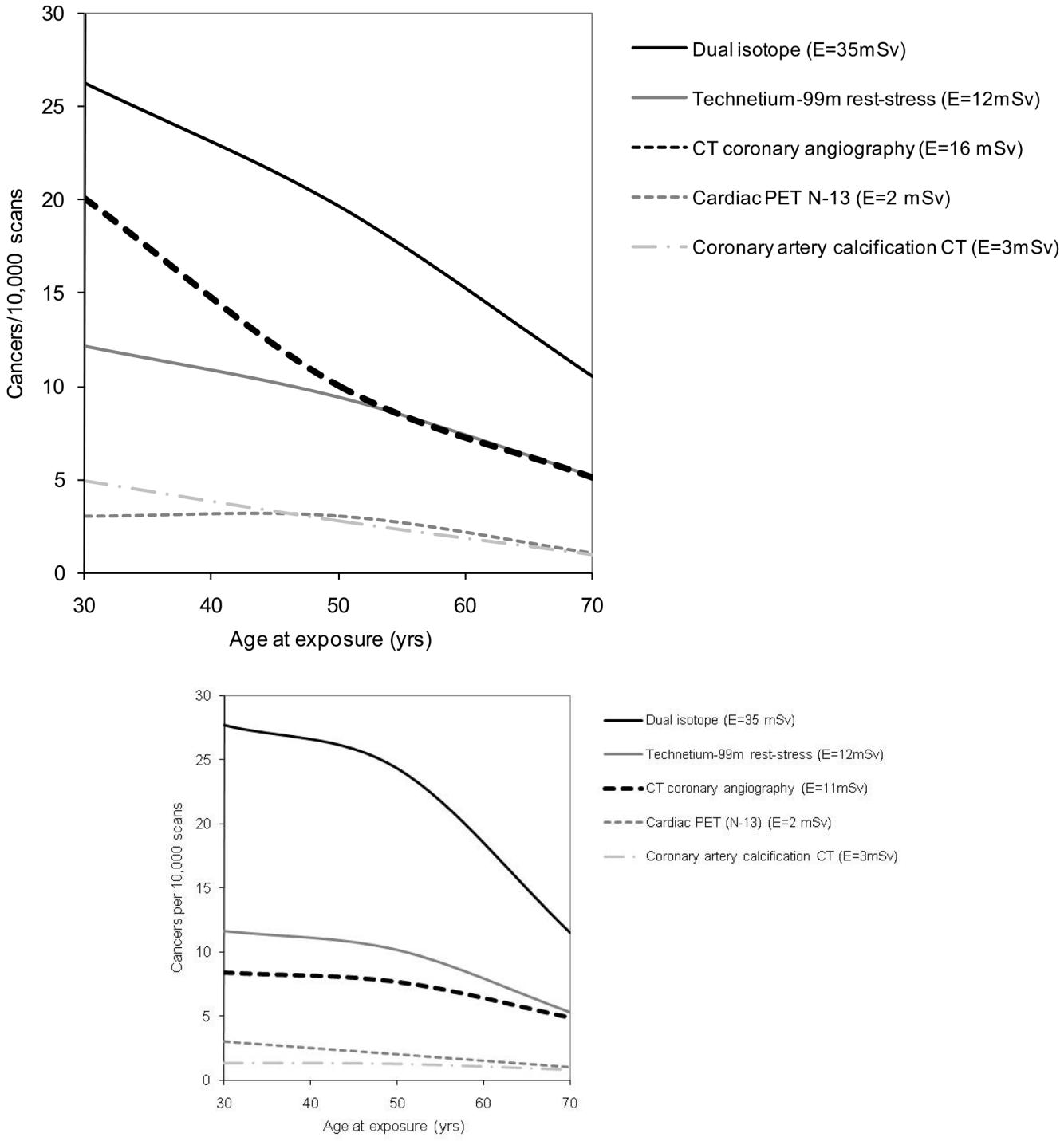

Figure 2.
Projected number of future cancers per 10,000 scans: comparison of myocardial perfusion and cardiac CT scans according to age at exposure
a) Females
b) Males

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

		Administered activity	Effective dose	*Radiation-related cancers*† (per 10,000 tests at age 50)
Radiopharmaceutical	**Test type**	**Range (MBq)***	**Mid-point (range)**	**N cancers (95% UI)**
Technetium-99m	Rest/stress	296–444 and 888–1332	12 (10–15) mSv	10 (5–19)
	Stress/rest	888–1332 and 888–1332	19 (15–23) mSv	16 (7–29)
	Stress only	888–1332	9 (7–11) mSv	8 (3–13)
Thallium-201	Stress/redistribution	93–148	26 (12–33) mSv	18 (6–46)
	Viability	111–148	29 (24–33) mSv	19 (6–50)
Dual isotope	Rest/stress	Tl-201:93–148 Tc-99m:888–1332	35 (28–43) mSv	25 (9–58)
Rubidium-82	Rest/stress	1480–2250	15 (11–18) mSv	7 (3–13)
Ammonia-13	Rest/stress	370–740	2 (1–3) mSv	2 (1–5)

*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 mid-point of the recommended range of administered activity.

‡Thallium-201 and Technetium-99m

MBq, megabecquerel; N, number; mSv, milli-Sievert; UI, uncertainty interval

Table 2

Projected number of future cancers related to the annual number of myocardial perfusion scans performed in the U.S. in 2008

		Annual scans		*Radiation-related cancers*‡		
Radiopharmaceutical	**Scan type**	**N**†	**%**	**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	[3300–13700]	100%

†10% of these scans were excluded in estimating the projected number of cancers (see methods for more details).

‡Assuming the mid-point of the recommended administered activity range (Table 1).

*Dual isotope - Thallium-201 and Technetium-99m

N, number; UI, uncertainty interval.