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Abbreviation:
CI = credibility interval

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Radiation Risks Potentially Associated with Low-Dose CT Screening of Adult Smokers for Lung Cancer[1]

PURPOSE: To estimate the radiation-related lung cancer risks associated with annual low-dose computed tomographic (CT) lung screening in adult smokers and former smokers, and to establish a baseline risk that the potential benefits of such screening should exceed.

MATERIALS AND METHODS: The estimated lung radiation dose from low-dose CT lung examinations corresponds to a dose range for which there is direct evidence of increased cancer risk in atomic bomb survivors. Estimated dose-, sex-, and smoking status–dependent excess relative risks of lung cancer were derived from cancer incidence data for atomic bomb survivors and used to calculate the excess lung cancer risks associated with a single CT lung examination at a given age in a U.S. population. From these, the overall radiation risks associated with annual CT lung screening were estimated.

RESULTS: A 50-year-old female smoker who undergoes annual CT lung screening until age 75 would incur an estimated radiation-related lung cancer risk of 0.85%, in addition to her otherwise expected lung cancer risk of approximately 17%. The radiation-associated cancer risk to other organs would be far lower. If 50% of all current and former smokers in the U.S. population aged 50–75 years received annual CT screening, the estimated number of lung cancers associated with radiation from screening would be approximately 36,000, a 1.8% (95% credibility interval: 0.5%, 5.5%) increase over the otherwise expected number.

CONCLUSION: Given the estimated upper limit of a 5.5% increase in lung cancer risk attributable to annual CT-related radiation exposure, a mortality benefit of considerably more than 5% may be necessary to outweigh the potential radiation risks.

There is increasing interest in the possibility of using low-dose computed tomography (CT) for annual screening of smokers and former smokers for early-stage lung cancer. The results of several pilot studies (1–7) have shown an increased capability for detecting small malignant nodules, and a National Lung Screening Trial is now under way (8,9).

The potential benefits of lung cancer screening have been much discussed (9–13), as have the potential risks of invasive procedures ensuing from false-positive findings (14). Less attention has been paid to the potential radiation risks—specifically, radiation-induced lung cancer—associated with CT lung screening. In part this is because the screening technique involves “low-dose” rather than standard CT lung scans, and in part it is because excess relative risks of radiation-induced cancer generally decrease markedly with increasing age (15).

There are, however, several indications that radiation risk to the lung associated with this screening technique may not be negligible:

1. Cancer risks from radiation are generally multiplicative of the background cancer risk (16), which is, of course, high for lung cancer in the target population of smokers and nonsmokers. This general observation has been borne out by the results of assessments of

the interaction between radiation and smoking, which most authors have suggested is near multiplicative (17–24), although an intermediate interaction, between additive and multiplicative, has been suggested for radon exposure (25) and there is one report of an additive interaction (26).

2. While radiation-related cancer risks generally decrease markedly with increasing age at exposure (Figs 1, 2), risks of radiation-induced lung cancer apparently do not show this pattern (15,16).

3. The lung doses of interest in low-dose CT lung screening are in the range for which there is direct evidence of increased risk in atomic bomb survivors. As we discuss below, the lung dose from a single low-dose CT lung screening examination is 2.5–9.0 mGy, with correspondingly increased total doses for repeat examinations. So, for example, 10 low-dose CT lung screening examinations would produce lung doses in the range of 25 to 90 mGy. Among approximately 30,000 individuals in the cancer incidence cohort of atomic bomb survivors who received doses between 5 and 100 mSv (mean dose, 29 mSv), there was a statistically significant increase in cancer risk (77 excess cancers, $P = .05$) compared to that in the control population (27).

These observations suggest that the risk of radiation-induced lung cancer associated with repeated low-dose CT lung screening in smokers may not be negligible. Thus, the purpose of this study was to estimate the radiation-related lung cancer risks from annual low-dose CT lung screening in adult smokers and former smokers, to establish a baseline risk that the potential benefits of such screening should exceed.

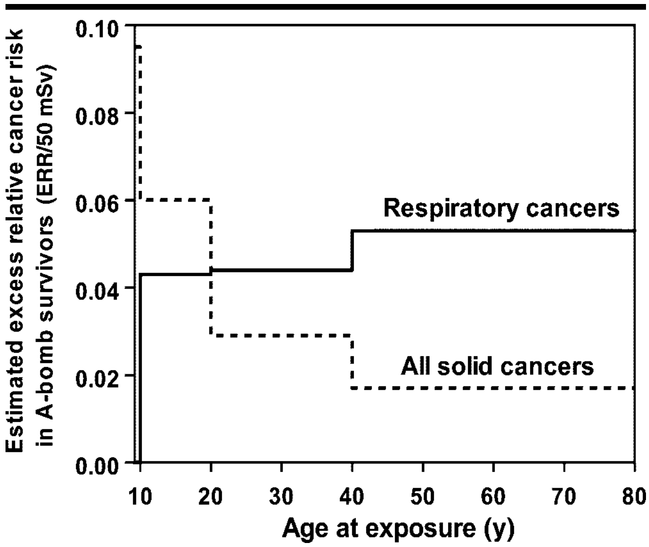

Figure 1. Graph shows estimated excess relative risks for respiratory cancer (trachea, bronchus, and lung) and for all solid tumors in atomic bomb survivors exposed to a radiation dose of 50 mSv, according to age at exposure (15). Unlike the estimated relative risks for most solid cancers, that for respiratory cancer does not show evidence of decreasing with increasing age at exposure, though the mechanisms underlying this observation are not yet clear.

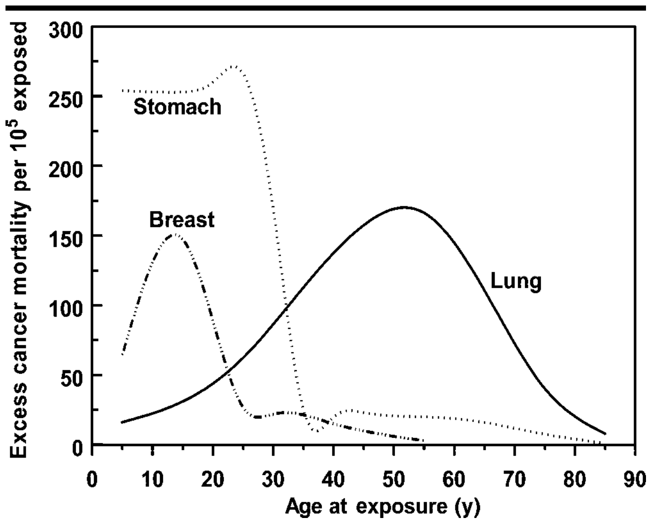

Figure 2. Graph shows estimated excess cancer mortality by age at exposure in a stationary population that has U.S. mortality rates and that is exposed to a radiation dose of 50 mSv (16). Estimates are shown for respiratory cancers, digestive cancers, and female breast cancers. Note the different age dependence for lung cancer incidence.

MATERIALS AND METHODS

Risk Estimation

To generate risk estimates for radiation-induced lung cancer that are applicable to the U.S. population, we used as a basis the excess relative risks for radiation-induced lung cancer in Japanese atomic bomb survivors (15). The atomic bomb survivor cohort was used as the basis for predicting radiation-related lung cancer risks in a general population because it is the most thoroughly studied large exposed population, because its members were not selected for disease, and because a substantial subcohort received lung radiation doses comparable with those from CT lung screening, as discussed above.

Standard methods of analysis (16,28,29) were applied to the atomic bomb survivor data, to generate estimates of the lifetime excess relative risk (ERR_L) for lung cancer induction. These methods, which take into account generally accepted sources of bias and uncertainty, result in risk estimates that are applicable to repeated low-dose radiation exposures in U.S. populations. These ERR_L estimates depend on the radiation dose to the lung (D_L), as well as on sex (G) and smoking status (S): The estimated ERR_L at a radiation dose to the lung of 5.2 mGy (see below) in current smokers older than 50 years is 0.0037 for women and 0.0012 for men. The estimated ERR_L at this same radiation dose in former smokers older than 50 years is 0.0047 for women and 0.0015 for men.

By using these estimated $ERR_L(D_L,G,S)$ values and an estimated lung radiation dose (${}_{CT}D_L$) from a single low-dose CT

TABLE 1
Estimated Background Lung Cancer Risks, *B*(*A*,*G*,*S*), by Age, Sex, and Smoking Status

	Women		Men	
Age (y)	Current Smoker	Former Smoker	Current Smoker	Former Smoker
50	0.169	0.095	0.158	0.089
55	0.163	0.092	0.156	0.088
60	0.157	0.088	0.149	0.084
65	0.148	0.084	0.133	0.075
70	0.127	0.073	0.108	0.061
75	0.086	0.051	0.073	0.043
80	0.042	0.028	0.039	0.025
85	0.013	0.012	0.016	0.013

Sources.—References 30, 31.

TABLE 2
Probabilities of Surviving 10 Years, $P_{10}(A,G)$ Derived from U.S. Life Tables for 2000

Age (y)	Women	Men
50	0.96	0.93
55	0.94	0.90
60	0.90	0.86
65	0.86	0.81
70	0.81	0.76
75	0.75	0.72

Source.—Reference 32.

TABLE 3
Smoking Prevalences for 1999–2001, by Age and Sex

	Women		Men	
Age (y)	Current Smoker	Former Smoker*	Current Smoker	Former Smoker*
50–64	0.23 (0.17, 0.29)	0.24 (0.19, 0.28)	0.22 (0.18, 0.27)	0.46 (0.39, 0.52)
65–74	0.083 (0.058, 0.11)	0.30 (0.23, 0.37)	0.13 (0.074, 0.18)	0.50 (0.42, 0.58)

Source.—Reference 38.
Note.—Data are for Pennsylvania and are close to the median for all states. Data in parentheses are 95% confidence intervals.
* A former smoker is defined here as an individual who has smoked at least 100 cigarettes and no longer smokes.

lung examination, it is possible to estimate the excess relative risk for lung cancer associated with a single examination at a given age in an individual of a given sex and smoking status. This approach is based on the assumptions *(a)* that the radiation-associated lung cancer risk can be scaled from the background lung cancer risk by the excess relative risk, and *(b)* that there is a latency period of 10 years after each radiation exposure before any lung cancer is manifest (16). Thus, the excess lung cancer risk (R_{CT}) associated with a single CT lung examination at a given age A in an individual of sex G and smoking status S is

$$R_{CT}(A,G,S) = \mathrm{ERR_L}({}_{CT}D_L,G,S) \cdot B[(A+10),G,S] \cdot P_{10}(A,G),$$

where $B(A,G,S)$ is the lifetime lung-cancer risk for a person of age A, which is estimated from U.S. tumor registries data (30), with adjustments (31) for smoking status (Table 1). $P_{10}(A,G)$ is the probability of living at least 10 years from age A, which is generated (Table 2) from U.S. population-wide life tables (32). Recent smoking-dependent life-table information is not readily available, but on the basis of earlier data (33), $P_{10}(A,G)$ for adults aged 50–75 years may be expected to vary between smokers and nonsmokers by no more than about 10%. The Equation, or similar variants, has been used in most national and international radiation risk estimation studies for solid-tumor risks (16,29,34–36).

As an example, for a single CT lung examination in a 50-year-old female smoker, the estimated $\mathrm{ERR_L}$ for a lung radiation dose of 5.2 mGy, which is typical for a single low-dose examination (see Radiation Doses to the Lung from Low-Dose CT Lung Screening), is 0.0037; the estimated age-shifted background lifetime lung-cancer risk $B(A = 60, G = \text{female}, S = \text{smoker})$ is 0.16; the estimated probability $P_{10}(A = 50, G = \text{female})$ of surviving at least 10 years is 0.96; and, thus, the estimated lifetime excess lung-cancer risk due to the single CT examination is 0.00057.

The current CT lung screening trials are designed to facilitate the evaluation of routine annual lung screening (37). Therefore, using the estimated risks for a single examination, we also calculated lifetime risks for a series of annual examinations. Assuming that annual screening is recommended from age A_B to age 75, the age-dependent risks are summed for each of the $76 - A_B$ examinations that an individual would undergo. Because the underlying $\mathrm{ERR_L}$ values are estimated for low doses, simple summing of the risks is appropriate (36).

Finally, we estimated the number of deaths that might be attributed to annual CT lung screening in the current U.S. population of smokers and former smokers (ie, ever-smokers). Calculations were performed for different values of A_B, the recommended age at which annual screening begins. For these calculations, we used recent U.S. population census data, categorized by age and sex, and supplemented this information with age- and sex-specific smoking prevalence data for 1999–2001 from the Behavioral Risk Factor Surveillance System (38). The smoking prevalence data (Table 3) are for Pennsylvania but approximate the median for all states.

Using the methodology described previously (28,29), we also estimated the 95% credibility interval (CI), the range of risks that has a 95% probability of containing the true risk. This was done by using Monte Carlo simulation software (Crystal Ball; Decisioneering, Denver, Colo) to combine estimates of the various individual sources of uncertainty that contribute to the overall CI, with the source of the greatest uncertainty being the transfer from Japanese to U.S. populations.

Radiation Doses to the Lung from Low-Dose CT Lung Screening

It is important to note that the doses under consideration here for risk estimation are organ doses (eg, doses to the lung), and not effective doses (36), the latter being weighted averages of the doses to all radiogenic organs. This is because we are primarily concerned with radiation-induced lung cancer.

The radiation dose to the lung from a low-dose CT lung examination depends strongly on the protocol used for the examination, and primarily on the product of the current and exposure time (the mAs setting). For low-dose CT lung examinations, current–exposure-time settings typically range from 30 to 100 mAs (1–7); the National Lung Screening Trial protocol (8) recommends 60 mAs. In the calculations that follow, we have used a direct measurement by Nishizawa et al (39), scaled to a current–exposure-time setting of 60 mAs, which yields a dose of 5.2 mGy ± 0.9 to the lung.

We also have calculated the lung doses that would be expected from the various techniques that have been reported in

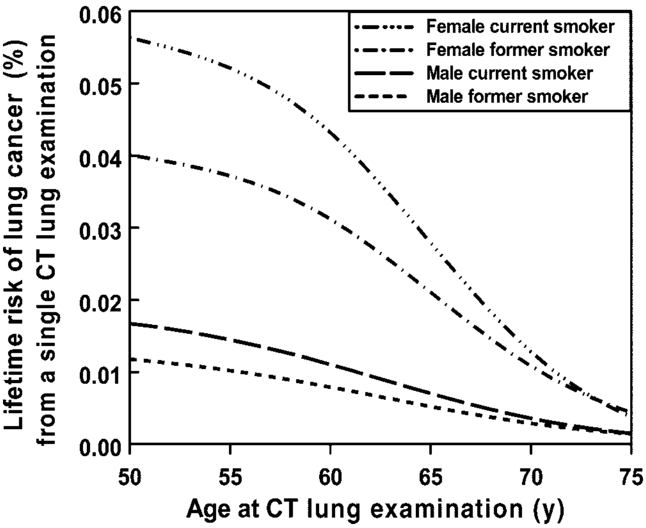

Figure 3. Graph shows estimated age-dependent risks, R_{CT}, of lung cancer associated with the radiation from a single low-dose CT lung examination. The risks decrease with age at exposure because of the decreasing background lung cancer risk. Risks were estimated by using a lung radiation dose of 5.2 mSv; risks for other doses can be proportionately scaled according to the dose.

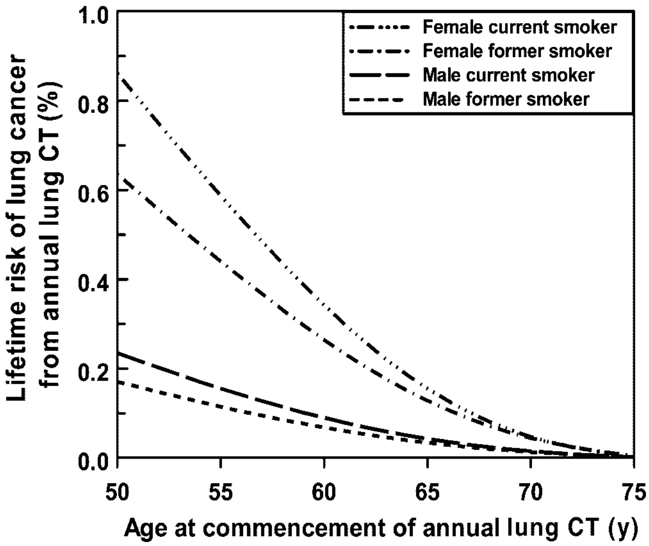

Figure 4. Graph shows estimated risks, R_{CT}, of lung cancer associated with the radiation from annual low-dose CT lung screening, as a function of the age at which annual CT screening commences. Annual examinations are assumed to commence at the specified age and continue until age 75. The risks decrease with age, both because the risks of examination decrease (Fig 3) and because fewer examinations take place. Estimated 95% CIs are approximately a factor of 3 in both directions. Risks were estimated by using a lung dose of 5.2 mSv; risks for other doses can be proportionately scaled according to the dose.

the literature for low-dose CT lung screening examinations (1–7). With the use of calculation techniques described by Jones and Shrimpton (40), estimated lung doses vary from approximately 2.5 to 9.0 mGy, so the value that we estimated (5.2 mGy) is quite typical. Estimated risks for any other lung radiation dose can be linearly scaled on the basis of the risks for this value.

Other Cancer Sites

Corresponding cancer risk estimates were also made for sites proximal to the lung, by using the same methodology. The sites considered were those, other than the lung, that receive the highest doses from a CT lung examination: the female breast, the esophagus, the liver, the stomach, and the thyroid, which receive organ doses that are approximately 1.1, 1.0, 0.6, 0.5, and 0.4 times the lung dose, respectively (39).

RESULTS

Figure 3 shows the estimated lifetime lung-cancer risks, R_{CT}, associated with the radiation from a single low-dose CT lung screening examination. The corresponding estimated risks for all other organs (the highest risk being that for the stomach) are at least an order of magnitude lower and, thus, are unlikely to play any role in risk-benefit analyses. A notable feature of lung cancer risks is the major difference between men and women, which reflects the large sex-related difference in excess relative risk for lung cancer among Japanese atomic bomb survivors (15).

Figure 4 shows the estimated lifetime radiation-related lung-cancer risks for smokers and former smokers who undergo a series of annual low-dose CT examinations starting at a given age and ending at age 75. For example, a 50-year-old female smoker who undergoes annual low-dose CT lung screening starting in 2003 would accrue an estimated excess lung cancer risk of about 0.85% (95% CI: 0.28%, 2.2%) associated with total radiation exposure, in addition to her otherwise expected lung cancer risk of about 16.9%. The corresponding estimated radiation-related excess lung cancer risk for a 50-year-old male smoker who undergoes annual low-dose CT screening starting in 2003 is 0.23% (95% CI: 0.06%, 0.63%), in addition to his otherwise expected lung cancer risk of about 15.8%.

Figure 5 shows the predicted numbers of radiation-related lung cancers that would occur in the current (stationary) U.S. population, assuming that 50% (41) of smokers and former smokers older than a given age underwent annual low-dose CT lung screening starting in 2003 and continuing until age 75. Thus, for example, if the entire U.S. population of current and former smokers aged 50–75 years—approximately 36 million people (38)—were offered annual CT lung screening until age 75, with a 50% compliance rate the estimated number of lung cancers associated with the radiation from these examinations would be about 36,000 (95% CI: 11,300, 93,600). Of the approximately 18 million people older than 50 years who would undergo annual screening until age 75, about 1.9 million would be expected to contract lung cancer independent of the CT-related lung radiation dose (30,31); thus, the radiation exposure from annual CT lung examinations would increase this number by approximately 1.8% (95% CI: 0.5%, 5.5%).

Correspondingly, if screening were recommended to start at age 60 rather than 50 years, annual screening of the 16.6 million people (38) in the U.S. population who are smokers or former smokers aged 60–75, with a compliance rate of 50%, would be predicted to result in approximately 6,000 radiation-associated lung cancers (Fig 5). Of the 8.3 million ever-smokers aged over 60 who would undergo annual low-dose CT screening until age 75, about 0.74 million would be expected to contract lung cancer independent of the CT-related radiation exposure (30,31); thus, the radiation exposure from annual CT lung examinations

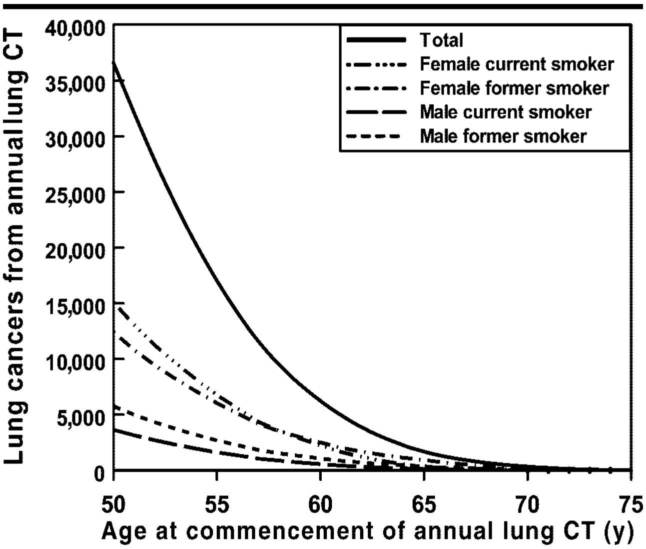

Figure 5. Graph shows predicted numbers of lung cancers associated with the radiation from annual low-dose CT lung examinations in the current U.S. population. The ordering of these population risks is different from that of the individual risks (Figs 3, 4) because of the different sizes of the four subpopulations (see Table 3). Numbers are based on the assumption that 50% of all smokers and former smokers receive annual low-dose CT examinations, beginning at the specified age (or their current age, whichever is greater) and continuing until age 75. Estimated 95% CIs are approximately a factor of 3 in either direction. These results can be linearly scaled for different doses, different compliance rates, and, approximately in North American and Western European populations, different numbers in the four smoking categories.

would be predicted to increase this number by approximately 0.8% (95% CI: 0.2%, 2.5%).

DISCUSSION

The only important radiation-related hazard from low-dose CT lung screening is radiation-induced lung cancer. Although the dose to the lung from a single low-dose CT lung examination is low (typically 2.5–9.0 mGy), the associated lung cancer risks are not negligible, for two related reasons: First, the excess risk for radiation-induced lung cancer is highest in those aged approximately 55 years at exposure, in contrast to the radiation-associated cancer risks for most other sites, which are highest at much younger exposure ages. Thus, for example, routine screening mammography, while delivering a similar dose to the breast (typically about 3 mGy [42,43]), probably results in a substantially lower risk, because the radiation-associated cancer risk to the breast at ages above 40 or 50 is much lower than that at younger ages (44,45).

The second reason for concern regarding CT lung examinations in adult ever-smokers is the evidence that radiation damage and smoking damage interact synergistically. Although this interaction is hard to quantify, the results of most studies suggest that the interaction is near multiplicative (17–24). An intermediate interaction, between additive and multiplicative, has also been suggested for radon exposure (25), and there is at least one report of an additive interaction (26).

The estimates described here suggest that a single baseline CT screening examination for lung cancer would result in a fairly low risk (<0.06%) for radiation-induced lung cancer, and negligible risks for other cancers. The estimated risks are higher for current smokers than for former smokers, and the risks would be expected to be higher for heavy ever-smokers compared with light ever-smokers.

Although the risks from a single baseline CT lung screening examination are comparatively small, yearly screening from age 50 would add about 0.85% (95% CI: 0.28%, 2.2%) to the 16.9% lung cancer risk faced by a 50-year-old female smoker—a 5% increase in risk. For a 50-year-old male smoker, annual screening would add about 0.23% (95% CI: 0.06%, 0.63%) to his 15.8% lung cancer risk—a 1.5% increase in risk.

For the current U.S. population of smokers and former smokers (approximately 36 million people between ages 50 and 75), these results suggest that, with a compliance rate of 50%, annual screening from age 50 (or current age, if higher) to age 75 could result in approximately 36,000 radiation-associated lung cancers. For reference, of the approximately 18 million adult smokers or former smokers older than 50 years who would be assumed to undergo annual CT lung screening until age 75, about 1.9 million would be expected to contract lung cancer independent of the radiation dose from annual screening (30,31). Thus, the radiation exposure from annual CT lung examinations could increase this number by approximately 1.8% (95% CI: 0.5%, 5.5%).

The radiation risks estimated are for radiation-induced lung-cancer incidence rather than mortality; however, because of the high mortality-to-morbidity ratio associated with lung cancer (46), it seems reasonable to use these incidence risks as a baseline for a minimum requirement in the reduction in lung cancer mortality through CT lung screening. Given the estimated upper limit of a 5.5% increase in lung cancer risk due to annual CT-related radiation exposure, a mortality benefit of considerably more than 5% may be necessary to outweigh the potential radiation risks.

These risk estimates are based on data from the study of Japanese atomic bomb survivors (15,27). However, they do not involve major extrapolations from higher dose levels: The dose ranges for low-dose CT lung examinations are comparable with the radiation dose range for which an increase in cancer risk is seen in the atomic bomb survivors (27).

Our risk estimates, which correspond to a lung dose of about 5 mGy for a single low-dose CT examination, apply to a particular technique performed with a particular scanner. This dose is in the middle range of current usage. A decrease in radiation dose through changes in technique would be expected to result in a corresponding decrease in risk, and the lowest settings possible in screening CT have yet to be definitively established (1–7).

It is clear that the radiation-related risks decrease rapidly with increasing age at commencement of screening. If the radiation risks prove to be a concern, an increase in the minimum age at which screening is recommended, from 50 to 60

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years, would reduce the risks considerably. Another alternative would be to screen every 2 years, which would reduce the radiation risk by about 50%.

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