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Low-dose lung CT screening before age 55: estimates of the mortality reduction required to outweigh the radiation-induced cancer risk

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Abstract

Objectives—To estimate the risk of radiation-induced lung cancer mortality from three annual low-dose lung CT screens before age 55 years and the mortality reduction from screening (i.e. the efficacy) needed to outweigh these risks for never and current-smokers. The risk of radiation-induced breast cancer was also estimated for women.

Methods—The Biological Effectiveness of Ionizing Radiation VII committee's risk models were used to estimate radiation risk. Lung cancer mortality rates (based on the Bach model for current and the Cancer Prevention Study for never-smokers) were used to estimate the mortality reduction needed to outweigh this risk.

Results—For never-smokers the estimated excess lifetime risk of radiation-induced lung cancer mortality from annual screening age 40-42 was 1/10,000 (90% credibility interval:0.4-3) for males and 3/10,000 (2-6) for females. For current-smokers the estimated risks were approximately 2-fold higher, with wider credibility intervals. Risks from screening age 30-32 or 50-52 years were of similar magnitude. The mortality reduction required to outweigh these risks was, for male never-smokers: 125% (40%-300%) age 30-32 years, 70% (30%-190%) age 40-42 years and 25% (10%-70%) age 50-52 years, and for male current-smokers: 70% (20%-120%) age 30-32 years, 10% (3%-20%) age 40-42 years and 2% (1%-4%) age 50-52 years. These figures were 2-3 times higher for females because of the higher radiation risks. The risk of radiation-induced breast cancer was in the range of 3-6 cases/10,000 females screened.

Conclusions—Before age 50 the mortality reduction from lung CT screening that is required to outweigh the radiation risk may be substantial, and in some cases unattainable (i.e.>100%).

Introduction

The risk of radiation-induced cancer from lung CT screening is frequently described as small, for example by comparison with the typical spontaneous fatal cancer risk of about 1 in 4.¹ The most relevant comparison though is the magnitude of the potential absolute benefit from such screening. Brenner previously estimated the risk of radiation-induced lung cancer mortality for smokers aged 50+ and suggested that lung cancer mortality would need to be reduced by at least 5% to outweigh these risks.² It is not widely appreciated though that this figure is likely to be higher for screening at younger ages because the radiation risks will be higher, due to the

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longer time available to develop a radiation-induced cancer,³ whilst the absolute benefit will be lower because lung cancer incidence rates are lower.

A recent US survey found that a high proportion of never-smokers would be willing to consider lung CT screening.⁴ Screening studies of low-dose lung CT are already recruiting smokers and non-smokers as young as age 40.^{5,6} Radiation-induced cancer risk estimates from lung CT screening are not currently available for never-smokers, or for screening before age 50.

There are no empirical data at present from which to estimate the cancer risks from CT scans directly and generally such studies are considered infeasible,⁷ but the risks can be estimated by extrapolating risk models from studies of subjects exposed to a wider range of radiation doses, such as the Japanese atomic bomb survivors.³ In this paper we estimate the potential risk of radiation-induced lung cancer from three annual lung CT screens for asymptomatic individuals starting at age 30, 40 and 50 years. As the efficacy of lung CT screening is also not yet established we then estimated the level of screening efficacy that would be required to outweigh these risks. For women we also estimated the risk of radiation-induced breast cancer. The risk estimates were developed for never smokers and for current smokers.

Materials and Methods

A synopsis of the methods is presented here and further details are provided in the online supplement.

Radiation risk models

We used the Biological Effects of Ionizing Radiation (BEIR) VII committee's risk model for radiation-induced incident lung cancer to estimate risks according to smoking status. The model was based on the data from the study of the Japanese atomic bomb survivors.³ There is considerable uncertainty surrounding the form of the joint effect of smoking and radiation, hence the BEIR VII committee recommended the use of a risk model that was a weighted average of the estimate from an excess relative risk model (equivalent to assuming a multiplicative effect of radiation and smoking on lung cancer risk) and an excess absolute risk model (equivalent to assuming an additive effect of radiation and smoking on lung cancer risk). The BEIR VII committee recommended that greater weight be given to the excess absolute risk model (weight=0.7) than to the excess relative risk model (weight=0.3) because a detailed analysis of smoking and radiation in the Japanese atomic bomb survivors found evidence that the effects appeared to be additive rather than multiplicative.⁸ These weights were allowed to vary in the uncertainty analysis (see below).

Background lung cancer rates

We estimated lung cancer rates for never smokers using recent results from the Cancer Prevention Study II (Appendix Table A).⁹ For current smokers we used the Bach lung cancer risk model,¹⁰ assuming a 40 cigarettes per day smoking history (Appendix Table A). The Bach lung cancer risk model, which predicts one-year lung cancer probabilities according to age, smoking status, amount and duration of smoking was developed using data from the Carotene and Retinol Efficacy Trial, and has been recently validated using data from the Alpha-Tocopherol, Beta-Carotene trial.¹¹

Lifetime risk of radiation-induced lung cancer mortality and radiation dose

CT-Expo software was used to calculate age- and sex-specific organ doses and effective doses based on the screening protocol used in the National Lung Screening Trial.¹² This protocol was optimised to ensure minimum radiation dose whilst maintaining appropriate image quality with a target CTDI_{vol} range of 2-3 mGy for regular size patients.¹³ The protocol specifies the

use of multi-detector CT scanners with four or more channels, gantry rotation times of ≤ 0.8 seconds, pitch range from 0.98-2.0, nominal reconstruction thickness of ≤ 3.2 mm, X-ray tube potential of 120 kVp and tube current-time product in the range 25-80 mAs depending on the scanner type and patient size. The mean radiation dose to the lung from a helical low-dose lung CT was estimated to be 3.9 mGy (range 2.7-6.1 mGy) for females and 3.8 mGy (range 2.6-5.9 mGy) for males, and the mean effective doses were 1.3mSv and 1.0mSv, respectively.

The risk of radiation-induced lung cancer remains elevated indefinitely after radiation exposure.³ Therefore, the total excess risk of radiation-induced lung cancer mortality was calculated as a cumulative lifetime risk starting from ten years after exposure, which was the assumed lag period. To estimate radiation-induced lung cancer mortality the cumulative risk of lung cancer incidence was multiplied by 90% (the estimated probability of dying from lung cancer in the absence of screening).¹⁴ Adjustments for competing causes of death were based on US all cause mortality rates and survival probabilities, which were adjusted for smoking status by assuming that current smokers will have a median survival of approximately five years less than the general population and never smokers will have a median survival of approximately five years more than the general population.^{15,16}

Risk estimation for other cancer sites

The doses to other organs were also estimated using CT-Expo and assuming the same CT parameter settings described above. The estimated breast dose was 4 mGy and the thymus, stomach, liver and red bone marrow were all estimated to receive doses of 1 mGy from a low-dose helical lung CT scan. We used the BEIR VII risk models combined with the site-specific cancer incidence rates for the US general population from the Surveillance Epidemiology and End Results cancer registries data for 2000-04 to estimate the risk of radiation-induced cancer for each of these additional sites.^{3,14} All the risk models, except breast cancer, were based on the data from the Japanese atomic bomb survivors. The BEIR VII breast cancer risk model was based on the pooled analysis of breast cancer cohorts by Preston et al.¹⁷ All other aspects of the calculations were the same as for lung cancer.

Lung cancer mortality reduction required to outweigh the radiation risk

Direct estimates of the relative or absolute reduction in lung cancer mortality from lung CT screening are not yet available. Therefore, we used an indirect approach based on incidence-based mortality rates (mortality rates that are partitioned according to the age when the cancer was diagnosed) to estimate the absolute reduction in lung cancer mortality required to outweigh the radiation risk.¹⁸ Incidence-based mortality rates were estimated using the smoking and age-specific incidence rates for the relevant screening period (e.g. age 30-32 years) multiplied by 90% (the estimated probability of dying from lung cancer in the absence of screening).¹⁴ A two-year (range 1-4 years) mean sojourn time (the period during which the disease is pre-clinical but detectable by screening) was assumed based on the findings from a recent study that estimated this parameter using data from six published lung CT screening studies.¹⁹ Hence, the cumulative incidence-based mortality rate for each three year screening period was the sum of the rates for the screening ages plus rates for the following two years. The mean sojourn time was allowed to vary from one to four years in the uncertainty analysis (see below). The percentage reduction in this cumulated incidence-based mortality that would be necessary to outweigh the risk of radiation-induced lung cancer mortality was then calculated by dividing the estimated risk of radiation-induced lung cancer mortality by the cumulative incidence-based mortality rate for each screening period.

Uncertainty analysis

Monte Carlo simulation was used to quantify the effects of the uncertainty in the weights applied to the excess relative and excess absolute risk models, the radiation risk model

parameters,³ the dose estimates,^{12,13} and the mean sojourn time.¹⁹ Distributions for the parameters were specified (Appendix Table B) and Latin-hypercube sampling was conducted using Crystal Ball software to estimate the 5th and 95th percentile of the distribution of results, which is referred to as the 90% credibility interval.²⁰

Results

For never smokers the excess lifetime risk of radiation-induced lung cancer mortality from annual lung CT screening from age 30-32 was estimated to be 3 deaths (90% credibility interval: 2-5) per 10,000 women screened and 1 (0.3-2) death per 10,000 men screened (Tables 1a and 1b). For current smokers the risks were approximately two-fold higher: 5 deaths (2-12) per 10,000 women and 2 deaths (1-4) per 10,000 men screened. For annual screening from ages 40-42 or 50-52 the estimates were similar in magnitude to those for screening age 30-32 because of the relatively low background lung cancer rates before age 50.

The estimated cumulative risk of lung cancer mortality without screening was relatively low for each screening period because lung cancer incidence rates are still low at these ages, even for current heavy smokers (Table 1). Hence, the potential number of lung cancer deaths that could be prevented by screening at these younger ages was also relatively low and the mortality reduction required to outweigh the radiation risks was high. For male never-smokers the estimates were: 125% (40%-300%) age 30-32 years, 70% (30%-190%) age 40-42 years and 25% (10%-70%) age 50-52 years, and for male current-smokers: 70% (20%-120%) age 30-32 years, 10% (3%-20%) age 40-42 years and 2% (1%-4%) age 50-52 years. These figures were 2-3 times higher for females because of the higher radiation risks.

For annual screening of never smokers from ages 30-32 the estimated risk of radiation-induced breast cancer incidence was 6 (90% CI: 3-9) cases per 10,000 women screened (Table 2). The risk was slightly lower for current smokers because of their higher competing risks, and the estimated risks decreased with age at screening to 4 (2-6) cases per 10,000 screened from age 50-52. The estimated radiation-induced risks for all other cancers were much lower than for lung or breast cancer (<0.5 cases for three annual screens per 10,000 females or males) (data not shown).

Discussion

These estimates suggest that before age 50 the mortality reduction required to outweigh the radiation risk from lung CT screening may be substantial, or in some cases unattainable (>100%). For smokers aged about 50 the required mortality reduction is considerably lower, but until results from the randomized screening trials are available it is uncertain what the net benefit could be. The trials are powered to detect about a 20% reduction in lung cancer mortality due to screening. Estimates of the mortality reduction from observational studies depend upon the use of models to generate a theoretical control group of unscreened individuals. In an analysis of this type of the Mayo study McMahon et al estimated that five annual screens with low-dose CT reduced lung cancer mortality by 28% at six years. No confidence bounds were provided, but given the small number of deaths in the study they are likely to be wide.²¹ A pooled analysis of three observational studies (which included the Mayo study), found no evidence overall for a reduction in lung cancer mortality (RR=1.0) but with a wide confidence interval (0.7-1.3).²²

Our calculations involve a number of assumptions. One of the most important in the radiation risk estimate is the assumed form of the joint effect of smoking and radiation. A recent analysis of the data from the Japanese atomic bomb survivors found that the joint effect of radiation and smoking appeared to be closer to additive than to multiplicative.⁸ Several previous studies

of cancer patients treated with radiotherapy, however, found that the joint effect of the two exposures was consistent with a multiplicative model.²³⁻²⁵ It is possible that the two exposures interact differently at low and at high doses of radiation exposure and further work is currently ongoing to try to understand these differences. We took account of this uncertainty by using a weighted average approach and allowed these weights to vary in the calculation of the credibility intervals.³ This source of uncertainty was one of the key determinants of the width of the credibility intervals. However, in general the conclusions would not be altered materially even at the extremes of the credibility intervals. This suggests that the difference in the results for current and never smokers is due to factors other than the assumed joint effect of radiation exposure and smoking. In particular the fact that lung cancer rates appear to increase more rapidly with increasing age in current than in never smokers (Appendix Table A).

Concern has been raised about the appropriateness of transferring risk estimates from the Japanese atomic bomb survivors to other populations exposed to fractionated low-dose exposures.³ These concerns are particularly relevant for lung cancer because the rates have been very low in Japan in comparison with the US. If the excess relative risk model were not the correct biological model for radiation-induced lung cancer then using it to transfer risk estimates from the Japanese to the US could result in over-estimation of the risk. This is an additional reason that the BEIR VII committee recommended that a weighted average of the excess relative and excess absolute risk models be used for estimating risks for the US population rather than using only the excess relative risk.³

The use of this weighted average risk model is one of the explanations for why our risk estimates of the radiation-induced lung cancer mortality for a single lung CT screen at age 50 are approximately three times lower than estimates from an earlier publication.² Brenner used only the excess relative risk component of the risk model from the Japanese atomic bomb survivors for his calculations.²⁶ Another reason that our risk estimates are lower is because our estimated absorbed lung dose was lower (3.9 compared to 5.2 mGy per screen) presumably due to the use of a more recent, optimised screening protocol.¹³

In the current paper we assumed a linear no-threshold dose-response relationship for estimating radiation risk estimates at low doses. The BEIR VII committee recommended that these risk estimates be reduced by a dose and dose reduction effectiveness factor (DDREF) of 1.5 for exposures of 0.1 Gy or lower.³ There are considerable uncertainties surrounding the application of a DDREF though, and because there is also radiobiological evidence that supports downturned dose-response curves at low doses we have not applied a DDREF to the current risk estimates.²⁷ Preston et al concluded that there was no evidence of departure from linearity at low doses for radiation-induced breast cancer, and so did not recommend that a DDREF should be applied to estimate breast cancer risk from fractionated radiation exposures.¹⁷ The evidence for the effects of dose fractionation on radiation-induced lung cancer risk is limited to the studies of patients with tuberculosis who received multiple fluoroscopies.^{28,29} The risk per unit dose was lower in these studies than in the Japanese atomic bomb survivors. This could be due to the effect of dose fractionation, but could also be due to confounding with the underlying disease or smoking. If we had applied a DDREF to our calculations then it would have reduced our risk estimates for radiation-induced lung cancer by about 33%, but this would not have had a material impact upon our conclusions.

The radiation-induced lung cancer risks were about three times higher for females than for males because the radiation risk parameters in the Japanese atomic bomb survivors are estimated to be higher for females.³ This is also true for several other cancer sites, but the difference is larger for lung cancer, and does not seem to be explained by differences in smoking patterns.⁸ It is uncertain whether these differences reflect real biological variability in radiation

sensitivity. Further research into this question is warranted as it has important implications for radiation protection.

Smoking specific lung cancer rates are also uncertain. However, the estimated rates used here were broadly similar to those available from other populations.^{9,10,30,31} Furthermore, because the lung cancer rates were used in both the calculation of the radiation risk and the estimation of the mortality rate in the absence of screening, increases or decreases in the rates would impact both estimates in a similar direction and hence the mortality reduction required to outweigh the risk (which is the ratio of these two estimates) should not be materially altered by this source of uncertainty.

The relatively short screening period of three years used in our calculations was chosen so that the strong age-dependence of the risk-benefit comparison would be evident. Also the results from lung CT screening trials such as the National Lung Screening Trial will provide estimates of the relative and absolute reduction in lung cancer mortality from similar periods of lung CT screening (3 screens) for smokers aged about 50 and older. Indirect methods will still have to be used though to estimate the absolute reduction in lung cancer mortality for never or younger smokers. We used the method of incidence-based mortality rates previously to estimate the absolute reduction in breast cancer mortality from mammographic screening before age 50 in the UK. Assuming a 17% mortality reduction from screening our estimate of 0.6 deaths prevented per 1000 women screened from age 40-49 was similar to the observed reduction of 0.4 deaths per 1000 women screened from age 40-47 in the UK Age trial.^{32,33}

Although we developed risk estimates for the general category of never-smokers our results should be broadly applicable to never-smokers who have been exposed to other risk factors such as second-hand tobacco and asbestos. Typically these factors are associated with about a two-fold higher risk of lung cancer than for a never smoker,³⁴ and this would double the potential absolute benefit from screening but would also slightly increase the radiation risk. Similarly, although we conducted our calculations for current smokers of 40 cigarettes per day the balance of the risks and benefits would be similar for current smokers with different smoking histories.

As far as we are aware this is the first paper to estimate and highlight the risk of radiation-induced breast cancer incidence from lung CT screening. The radiation dose to the breast from a lung CT screen is similar in magnitude to the average dose from a two-view mammogram.³⁵ The risk of radiation-induced breast cancer is higher for pre-menopausal women and increases with decreasing age at exposure and so becomes comparatively more important for screening of younger women. Even if not fatal, a radiation-induced breast cancer is an important detrimental effect of radiation exposure and so these potential risks should also be taken into account in the decision making process.

Our calculations are based on the radiation exposure received from the screening scans. Studies suggest that up to 20% of lung CT screens for current older smokers will reveal abnormalities suspicious for cancer, and these subjects are usually referred to receive additional follow-up CT scans.³⁶ The additional radiation dose will be highly dependent on the type and number of follow-up scans, in particular whether they are further low-dose or full diagnostic CT scans. Inclusion of these additional scans in the current estimates would have further increased radiation risks and therefore further increased the mortality reduction required to outweigh the risks. We are currently conducting additional research to evaluate the patterns of follow-up CT scans after lung CT screening and this will be the topic of a future publication.

Although the calculations depend on a number of uncertain assumptions we have based the assumptions on the best data that are currently available. We also calculated credibility intervals to quantify the effect of the uncertainties in the parameters and the assumptions; even when

the extremes of these intervals are considered the conclusions are generally unaltered. The results suggest that before age 50 the mortality reduction from lung CT screening required to outweigh the radiation risk may be substantial, and in some cases unattainable (i.e. >100%). In the absence of direct data these indirect approaches for comparing the risks and the benefits of screening provide valuable evidence to help inform those making screening decisions.

Appendix: Example of calculations for a lung CT screen at age 40 years

The risk at each attained age (a_j) is proportional to the cumulative radiation dose to the lung up to age $j-10$ (D_{j-10}), assuming a ten-year lag period. For the excess relative risk model (ERR) the risk is estimated relative to the age-specific lung cancer rates for smokers (λ_j) (Appendix Table A). For both models the risk is per Gray (Gy) and for the excess absolute risk (EAR) model the risk is per 10,000 persons. The BEIR VII committee radiation risks models for lung cancer are for males:

$$ERR_j = 0.32 D_{j-10} (a_j/60)^{-1.4} \quad EAR_j = 2.3 D_{j-10} (a_j/60)^{5.2}$$

and for females:

$$ERR_j = 1.4 D_{j-10} (a_j/60)^{-1.4} \quad EAR_j = 3.4 D_{j-10} (a_j/60)^{5.2}$$

The radiation-induced cumulative risk (CLR) of lung cancer up to age 100 is the sum of the ERR or EAR from age 50 (10 years after the exposure) to age 99 inclusive. The risk is adjusted for competing causes of death based on all cause survival probabilities for smokers (S_j). The weighted average (WAR) of the ERR and EAR risk is then calculated on the log scale with the weights of 0.3 and 0.7, respectively.

Appendix Table A

Annual lung cancer rates according to smoking status and age (per 10,000)

Age (yrs)	Females		Males	
	Never smoker	Current	Never smoker	Current
30-34	0.1	1	0.1	1
35-39	0.2	2	0.2	2
40-44	0.3	4	0.3	4
45-49	0.4	10	0.4	10
50-54	0.6	23	0.6	24
55-59	0.9	50	0.9	53
60-64	1	89	1	94
65-69	2	135	2	143
70-74	3	195	3	207
75-79	4	281	5	298
80+	5	404	8	428

Current smoker rates estimated using the Bach lung cancer risk model, assuming smoking of 40 cigarettes per day starting at age 17.

* Never smoker rates are for lung cancer mortality and are based on Thun et al (2006).

Appendix Table B

Parameter values and distributions used in the uncertainty analysis (calculation of the 90% credibility intervals)

Source of uncertainty	Distribution and parameters	Females	Males
Lung cancer risk model (ERR/Sv)	Normal, mean (s.e.)	0.34 (0.20)	-1.14 (0.40)
Lung cancer risk model (EAR/Sv)	Normal, mean (s.e.)	1.22 (0.20)	0.83 (0.40)

Source of uncertainty	Distribution and parameters	Females	Males
Lung cancer risk model (weighting for ERR)	Triangular, pinnacle (range)	0.3 (0-1)	0.3 (0-1)
Mean sojourn time for lung cancer (years)	Triangular, pinnacle (range)	2 (1-4)	2(1-4)
Radiation dose - absorbed lung (mGy)	Normal, mean (s.e.)	3.9 (1.0)	3.8 (1.0)
Breast cancer risk model (EAR/Sv)	Normal, mean (s.e.)	2.24 (0.18)	n.a.
Radiation dose - absorbed breast (mGy)	Normal, mean (s.e.)	4.1 (1.0)	n.a.

ERR — Excess Relative Risk

EAR — Excess Absolute Risk

s.e. — standard error

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Table 1

Cumulative radiation-induced lung cancer mortality (and 90% CI), cumulative risk of lung cancer mortality without screening and reduction in lung cancer mortality (%) required to outweigh radiation risk following three annual lung CT screens

a) females							
Annual screening period	Smoking status	Radiation-induced lung cancer mortality		Cumulative risk of lung cancer mortality without screening		Reduction in lung cancer mortality to outweigh radiation risks	
		n (per 10,000)	(90% CI)	n (per 10,000)	(90% CI)	%	(90% CI)
Age 30-32 yrs	Never *	3	(2-5)	0.8	(0.6 - 1.0)	375%	(200%-800%)
	Current	5	(2-12)	3	(2-4)	170%	(100%-500%)
Age 40-42 yrs	Never *	3	(2-6)	1.8	(1.5 - 2.3)	170%	(100%-300%)
	Current	5	(2-12)	17	(13-24)	30%	(10% - 70%)
Age 50-52 yrs	Never *	3	(1-5)	4	(3-5)	75%	(30%-130%)
	Current	5	(2-12)	100	(80-140)	4%	(2% - 10%)
b) males							
Annual screening period	Smoking status	Radiation-induced lung cancer mortality		Cumulative risk of lung cancer mortality without screening		Reduction in lung cancer mortality to outweigh radiation risks	
		n (per 10,000)	(90% CI)	n (per 10,000)	(90% CI)	%	(90% CI)
Age 30-32 yrs	Never *	1	(0.3-2)	0.8	(0.6-1.0)	125%	(40%-300%)
	Current	2	(1-4)	3	(2-4)	70%	(20%-120%)
Age 40-42 yrs	Never *	1	(0.4-3)	1.5	(1-2)	70%	(30%-190%)
	Current	2	(1-4)	19	(15-26)	10%	(3%-20%)
Age 50-52 yrs	Never *	1	(0.4-3)	4	(3-5)	25%	(10%-70%)
	Current	2	(1-4)	110	(90-160)	2%	(1%-4%)

* 40 cigarettes per day

Table 2

Estimated lifetime risk of radiation-induced breast cancer incidence (and 90% CI) per 10,000 women screened annually with lung CT: according to age at screening and smoking status

Annual screening period	Smoking status	Cases	(90% CI)
Age 30-32 yrs	Never	6	(3-9)
	Current *	4	(2-6)
Age 40-42 yrs	Never	5	(3-8)
	Current *	4	(2-5)
Age 50-52 yrs	Never	4	(2-6)
	Current *	3	(1-4)

*
40 cigarettes per day