Radiation-induced Cancer Risk from Annual Computed Tomography for Patients with Cystic Fibrosis

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Rationale: Computed tomography (CT) is being considered as a tool for routine monitoring of lung damage in people with cystic fibrosis. Concern has been raised, however, about the associated risk of radiation-induced cancer. Objectives: To estimate the risk of radiation-induced cancer from annual lung CT for patients with cystic fibrosis, assuming annual monitoring starting at age 2 years. Methods: Radiation risk models (derived primarily from the study of Japanese atomic bomb survivors) were used to estimate the excess risk of radiation-induced cancer for the organs that receive measurable doses from lung CT. Two scenarios were considered: median survival to age 36 years (approximate current median survival) and median survival to age 50 years (projected median survival by 2030). Measurements and Main Results: The estimated risk of radiation-induced cancer from annual lung CT was 0.02% for males and 0.07% for females assuming median survival to age 36 years. The estimated risks increased to 0.08% for males and 0.46% for females assuming median survival increases to age 50 years. The risks are higher for females because of the risk of radiation-induced breast cancer (50% of total risk) and higher risk of thyroid cancer. Conclusions: The cumulative risk of radiation-induced cancer from repeated lung CT scans for patients with cystic fibrosis is relatively small (less than 0.5%). However, routine monitoring should not be recommended until there is a demonstrated benefit that will outweigh these risks.

Keywords: computed tomography; cancer; radiation; cystic fibrosis; risk

Computed tomography (CT) is being considered as a tool for routine monitoring of lung damage in people with cystic fibrosis. Concern has been raised, however, about the associated risk of radiation-induced cancer from repeated CT scans, and there are particular concerns about the magnitude of the risks from childhood exposures (1). It is impractical to estimate the risk of radiation-induced cancer from CT scans directly through an observational study, because this would require follow-up of hundreds of thousands of patients for their entire lifetime. The magnitude of the risks can be estimated indirectly by extrapolating risk models from existing long-term studies of the effects of radiation exposure, such as the Life Span Study of the Japanese atomic bomb survivors (2). In one article in the Journal, de Jong and coworkers (3) used this approach and estimated that the cumulative risk of radiation-induced cancer mortality from annual lung CT monitoring for patients with cystic fibrosis was approximately 2% (3). Assuming that by 2030 median survival had improved to approximately 50 years the risk of radiation-induced cancer mortality was estimated to increase to 13%. We suggested in our accompanying editorial to their article that these risk estimates were surprisingly high as the effective dose from each annual scan was only 1 mSv (4). In this article, we use the radiation risk models from the same report by the National Research Council BEIR VII committee (Biological Effects of Ionizing Radiation) (5) and also use the same data sources but estimate that the risks are considerably smaller than those calculated by de Jong and coworkers (3).

METHODS

An outline of the methods is presented here; see the online supplement for further details.

Organ-specific radiation doses were estimated with CT-Expo version 1.5 (Dr. Georg Stamm and Dr. Hans Dieter Nagel, Medizinische Hochschule Hannover, Hannover, Germany) (6), in accordance with the CT protocol used by de Jong and coworkers (3). The software calculates organ-specific radiation doses for male and female adults, children (age, 7 yr) and babies (age, 2 mo). We used linear interpolation to estimate doses for children aged 2–17 years. The organs that were estimated to receive measurable radiation doses were (in approximate order of magnitude) the breast, lung, thymus, esophagus, liver, thyroid, stomach, bone marrow, pancreas, and kidneys (see the online supplement). The effective dose for a child aged 7 years was estimated to be 0.98 mSv for females and 0.82 mSv for males; the effective dose for adults was 0.67 mSv for females and 0.57 mSv for males.

We used the radiation risk models for sex- and organ-specific cancer incidence that were developed by the BEIR VII committee (5). Site-specific models were not available for cancers of the thymus, esophagus, kidney, or pancreas and so these sites were estimated with the risk model for "other solid cancers." For most cancer sites, the committee’s risk models were estimated on the basis of data from the Life Span Study of the Japanese atomic bomb survivors; exceptions were the risk models for thyroid cancer, which was based on a pooled analysis of seven studies by Ron and coworkers (7), and for breast cancer, which was based on an excess relative risk model from a pooled analysis of eight cohort studies by Preston and coworkers (8). Cancer incidence rates for patients with cystic fibrosis were assumed to be the same as those in the general U.S. population, and were estimated on the basis...
of rates for all races from the Surveillance, Epidemiology, and End Results (SEER) Program cancer registries for 2000–2003 (9).

After an initial lag period (assumed to be 10 yr for solid cancers and 2 yr for leukemia) the risk of radiation-induced cancer remains elevated for the remainder of a person’s lifetime (5). Therefore, the total risk of radiation-induced cancer was calculated by life table methods as a cumulative lifetime risk and adjustment for competing causes of death was made using all-cause mortality rates from a prospective study of patients with cystic fibrosis in France (10). Median survival in this cohort was 36 years, which is similar to the current median survival in the United States (11). However, children born now with cystic fibrosis are expected to survive considerably longer because of continuing medical advances (12). Therefore, the calculations were repeated assuming that median survival will have increased by 2030 to approximately 50 years (12). In accordance with de Jong and coworkers (3), we calculated cumulative risks to age 40 years for current survival and to age 65 years for the scenario assuming median survival to age 50 years.

The differences between our methods and those used by de Jong and coworkers (3) are summarized here, and the impact of these differences on the results is described subsequently (see DISCUSSION). We both used risk models from the BEIR VII committee report. However, because a lung CT scan does not deliver a uniform radiation dose to the whole body we used organ-specific radiation doses and risk models. de Jong and coworkers used only two risk models, one for all solid cancers and one for hematological cancers, and assumed that the radiation exposure from a lung CT scan is uniform to all organs. Although we used different software to estimate the radiation doses we used the same CT protocol and the effective dose estimates for children were similar (see the online supplement). Our calculations were performed using life table methodology, whereas de Jong and coworkers used Markov models; however, these two computational methods should produce the same results with the same inputs. One final difference is that we estimated radiation-induced cancer incidence whereas de Jong and coworkers estimated radiation-induced cancer mortality.

RESULTS

Table 1 shows the estimated cumulative risk of radiation-induced cancer incidence according to cancer site. The estimated radiation risk for all cancer sites combined was 15.3 per 100,000 for males (0.02%) and 72.7 per 100,000 for females (0.07%). The estimated risks were higher for females than for males because of the contribution from radiation-induced breast cancer and also because the risk of radiation-induced thyroid cancer was 10 times higher for females than for males. For the second scenario, assuming that median survival increases to age 50 years, the estimated risks for all cancer sites combined were approximately four times greater for both males (83.5 per 100,000 or 0.08%) and females (459.2 per 100,000 or 0.46%). The risks were higher for the second scenario because of the longer time to cumulative risk and because “background cancer rates” and hence radiation risks increase with increasing age.

Figure 1 shows the cumulative risk of radiation-induced cancer according to age at exposure for all cancer sites combined (for the scenario assuming median survival to age 50 yr). The risks decreased considerably with increasing age at exposure. For females there was a noticeable decline in risk for exposures after age 20 years, the high risks before this age being due mainly to the contributions of breast and thyroid cancer. The estimated risk of radiation-induced cancer from a lung CT at age 2 years was 24 per 100,000 for females compared with 1.0 per 100,000 at age 50 years and for males the risks were 6 and 0.3 per 100,000, respectively. We considered several other exposure scenarios to examine their effect on the estimated cancer risks. These are illustrated using the example assuming median survival to about age 50 years.

1. If annual monitoring were conducted only for adults and started therefore at age 18 years rather than at age 2 years, then the estimated cumulative risk of radiation-induced cancer would be approximately halved to 0.03% in males and 0.23% in females.

Table 1. Estimated Cumulative Risk of Radiation-Induced Cancer After Annual Lung Computed Tomography Starting at Age 2 Years

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Median Survival Age, 36 yr</th>
<th>Median Survival Age, 50 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>Esophagus</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Stomach</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Liver</td>
<td>0.3</td>
<td>0.1</td>
</tr>
<tr>
<td>Pancreas</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Lung</td>
<td>1.1</td>
<td>2.3</td>
</tr>
<tr>
<td>Breast</td>
<td>—</td>
<td>26.3</td>
</tr>
<tr>
<td>Thyroid</td>
<td>3.5</td>
<td>34.9</td>
</tr>
<tr>
<td>Thymus</td>
<td>1.4</td>
<td>1.7</td>
</tr>
<tr>
<td>Total: solid cancers</td>
<td>7.2</td>
<td>66.2</td>
</tr>
<tr>
<td>Leukemia</td>
<td>8.1</td>
<td>6.5</td>
</tr>
<tr>
<td>Total: all cancers</td>
<td>15.3</td>
<td>72.7</td>
</tr>
</tbody>
</table>

* Cumulative risk to age 40 years.
† Cumulative risk to age 65 years.

Figure 1. Estimated cumulative risk of radiation-induced cancer* (per 100,000) from a single lung CT according to age at exposure. *Cumulative risk to age 65 years, assuming median survival to age 50 years.
2. If monitoring started at age 6 years rather than age 2 years, then the estimated risks for all cancers would be reduced to 0.06% in males and 0.37% in females.

3. If biennial monitoring rather than annual monitoring were used, this would halve the risks.

4. If the CT tube current settings used for children were halved from 120 to 60 mA, then this would reduce the total radiation-induced cancer risk by approximately 25% (because childhood exposures accounted for approximately 50% of the total risk and radiation dose is proportional to tube current).

5. If a gantry rotation time of 0.4 second rather than 1 second were used, this would proportionally reduce estimated doses and hence risks, by approximately 60%.

**DISCUSSION**

We estimate that using annual lung CT to monitor people with cystic fibrosis may result in a risk of radiation-induced cancer of about 0.02% for males and 0.07% for females (assuming current median survival to the mid-30s). The risks are greater for females than for males because of the risk of radiation-induced breast cancer and the higher risk of radiation-induced thyroid cancer. If median survival improves in future, as has been suggested, to about age 50 years then these patients will start living into the age at which cancer rates start to increase considerably and will also undergo more annual CT scans; hence they will have a higher risk of radiation-induced cancer. However, even assuming this considerable improvement in median survival the estimated risk of radiation-induced cancer from annual CT scans was still relatively low: 0.08% for males and 0.46% for females.

Our estimates are much lower than those previously published by de Jong and coworkers (3), who estimated that the cancer risks were about 13% for both males and females assuming median survival to age 50 years. Our findings are discrepant even though, wherever appropriate, we used the same methods and scenarios as they did. The only clear difference in our methods that may have resulted in lower risks is our use of organ-specific radiation doses and risk models. We used this approach because a lung CT scan does not expose all parts of the body to the same level of radiation exposure. Our estimated risk for “all solid cancers” is the sum of the risks from these exposed organs only. de Jong and coworkers (3) assumed that a lung CT scan delivers a uniform dose to all organs in the body, and applied this dose estimate to a risk model for “all solid cancers” directly. This approach will probably have resulted in somewhat higher risk estimates but does not fully explain the magnitude of the differences. Also, we estimated that the doses to adults were 30–40% lower than the radiation doses to children, whereas de Jong and coworkers used the same radiation dose for all age groups (1 mSv). In our calculations the adulthood exposures accounted for approximately one-half of the cumulative risk and hence, if our adulthood doses had been 40% higher, then our total cumulative risk would be increased by approximately 20%.

As none of these methodologic differences could fully account for the large difference in estimates we compared the estimates calculated by de Jong and coworkers with the examples given in the BEIR VII report (5). For a uniform dose to all organs of 1 mGy/year throughout life the estimated cumulative risk of radiation-induced leukemia mortality is 0.047% for males and 0.038% for females in the BEIR VII report, compared with estimates by de Jong and coworkers of 1.21% (males) and 0.63% (females). We would have expected the BEIR VII risks to be somewhat higher than those of de Jong and coworkers because they are cumulated to age 100 years and assume survival probabilities for the general population that are higher than for people with cystic fibrosis.

One difference in our methods that should have resulted in our estimates being higher rather than lower than those of de Jong and coworkers is that we estimated radiation-induced cancer incidence rather than mortality. We estimated risks for incident cancers because several organs that receive measurable radiation doses from lung CT scans develop cancers with low case-fatality rates, in particular the thyroid gland and thymus. The estimation of cancer incidence ensures that these cancers are included as detrimental effects from lung CT scans. For example, the risk of radiation-induced thyroid cancer is particularly high after childhood radiation exposure (7). Cancer mortality estimates will be somewhat lower, but the magnitude of the difference will depend on the cure rates for each cancer site.

There are a number of sources of uncertainty in radiation risk estimation exercises including the lack of precision in the parameter estimates and uncertainty due to assumptions, such as the form of the dose–response relationship. In the current article the risk estimation was performed under the linear no-threshold assumption (13). It has been suggested that the dose–response relationship may be sublinear for low doses or low dose rates, and the BEIR VII committee suggested that for doses lower than 0.1 Gy the risk estimates should be reduced by the application of a dose and dose reduction effectiveness factor (DDREF) (5). On the basis of a combination of animal radiobiological data and data from the Japanese atomic bomb survivors they suggested a DDREF of 1.5. Application of this DDREF would reduce all risk estimates presented in the current article by a factor of 1.5. However, there is also epidemiologic and radiobiological evidence that supports a downwardly curving slope at low doses and if this were the correct form of the dose–response then the linear extrapolation used here would underestimate the radiation risks (13).

Another uncertainty involved in radiation risk assessment is the transfer of risk models estimated from the Japanese to other populations with different background cancer rates. The approach of the BEIR VII committee to this uncertainty was to use a weighted average of two risk models with different underlying assumptions: the excess relative risk model, which is based on the assumption that the risk from radiation exposure multiplies the background cancer risk in the population, and the absolute excess risk model, which is based on the assumption that the risk from radiation exposure adds to the background cancer risk in the population. There had been concerns that previous risk models that were based solely on the multiplicative risk assumption may have overestimated radiation risks in non-Japanese populations if this assumption was incorrect.

Because there are no data available directly on cancer incidence rates for people with cystic fibrosis our calculations were based on the assumption that they will have the same cancer incidence rates as the general population of the United States. This means that we are assuming that they are exposed to the same levels of other cancer risk factors as the general population. For some exposures this assumption may not be correct. For example, there is evidence that patients with cystic fibrosis have lower smoking rates than the general U.S. population (14) and hence their lung cancer rates will be lower. However, differences in levels of risk factors for other cancers might mean that some cancer incidence rates are higher. For example, women with cystic fibrosis are likely to have fewer children than women in the general population (15) and hence their breast cancer rates could be higher.

Another factor in the calculations that was based on the general population, but which may be different for patients with cystic fibrosis, was the dose estimates. The software used to estimate the doses assumes the person is of the typical size and...
weight for their age or sex (6). As patients with cystic fibrosis may weigh less and be shorter than the general population this may have resulted in underestimation of the radiation doses. However, the degree of underestimation is likely to be relatively small as the dose estimates of de Jong and coworkers, which were based on height and weight measurements for children with cystic fibrosis, were only slightly higher than our estimates (effective dose, 0.82 mSv [males] and 0.98 mSv [females] compared with the estimate of 1 mSv by de Jong and coworkers).

We used the CT protocol that was specified by de Jong and coworkers (3), which was based on a GE CT Prospeed SX scanner and assumes that lower settings for children are used (see the online supplement for further details). Dose estimates and hence radiation risks from CT scans will vary with the equipment and the settings (6). In particular, if adult settings are used when scanning children then the radiation exposure and hence the cancer risks will be higher than the estimates presented here. Similarly, as we showed in RESULTS, if lower parameter settings were used this would reduce the cancer risks. Lower current settings are already commonly used for CT screening for lung cancer, and research into whether radiation doses can be reduced while maintaining image quality for monitoring cystic fibrosis is also required. An alternative approach to reduce the female breast cancer risk is through the use of breast shielding. One study suggested that the radiation exposure could be halved without significantly harming the quality of the image if such shielding were used (16).

Unlike de Jong and coworkers (3), our estimates suggest that the risk of radiation-induced cancer from annual lung CT scans for people with cystic fibrosis is quite small (less than 0.5%). However, routine monitoring should not be recommended until it is demonstrated that it results in a benefit that will outweigh these risks.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

References