Does radiation cause liver cancer? Comparison of radiation effects in atomic bomb survivors and other populations

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Abstract

Recent studies of atomic bomb survivors have shown that risks of liver cancer are significantly increased by radiation exposure. This contrasts with mortality studies of other radiation-exposed populations, which generally have not shown a significant radiation effect for this cancer. Because the liver is a frequent site to which other tumors metastasize, liver cancer is one of the most difficult cancers to correctly diagnose. Studies of liver cancer in A-bomb survivors and other populations have documented high percentages of tumors metastasized to the liver being incorrectly diagnosed as liver tumors. In addition, many deaths due to liver cancer have been incorrectly attributed to cirrhosis or chronic hepatitis. Studies of incident or pathology-confirmed liver cancer cases in A-bomb survivors have found higher radiation risk estimates for liver cancer than mortality studies in this cohort. Most studies of radiation and liver cancer in other radiation-exposed cohorts have been mortality studies, and thus, would include many misclassified liver cancers. Liver cancer was consistently associated with radiation exposure in studies of four cohorts exposed to Thorotrast, a previously used radiology contrast agent. However, the histologic subtypes of liver cancer and type of radiation exposure (external rather than internal) differ from those experienced by the A-bomb survivors. Liver cancer in atomic bomb survivors is primarily hepatocellular carcinoma (HCC), rather than the cholangiocarcinoma and hemangiosarcoma subtypes more associated with Thorotrast exposure. A recent case control study of the joint effects of radiation and viral hepatitis in the etiology of HCC, showed that A-bomb radiation had a significantly stronger effect among subjects who were infected with the hepatitis C virus (HCV). No significant interaction between hepatitis B viral infections and radiation in the etiology of this disease was found. We compared incidence and mortality studies of liver cancer conducted in a wide variety of radiation-exposed populations, in terms of their radiation risk estimates for liver cancer, the background level of liver

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cancer in the cohort, HCV prevalence in the population from which the cohort was drawn, and other factors. The differences between the radiation risk estimates for atomic bomb survivors and other cohorts may reflect liver cancer diagnosis errors. Varying risk estimates may also reflect differences in the prevalence of HCV in radiation-exposed cohorts. © 2002 Elsevier Science B.V. All rights reserved.

**Keywords:** Hepatocellular carcinoma; Radiation; Hepatitis C virus; Liver cancer

### 1. Introduction

Previous studies of cancer risks in atomic bomb survivors have shown that exposure to low-LET ionizing radiation significantly increases mortality rates [1] and incident rates of liver cancer [2,3], which in this cohort is primarily HCC [4]. Although, most other mortality studies of liver cancer conducted in populations where HCV infections are less prevalent have not found radiation to be a significant risk factor for liver cancer [5–12], radiation risk estimates were significantly elevated in the combined study of underground, radon-exposed miners in Europe and North America [13].

A significant radiation effect was also found in the study of Mayak nuclear workers exposed to both external gamma radiation and internally deposited plutonium [14]. Like Thorotrast-related liver cancers, liver cancers in the Mayak workers were more likely to be hemangiosarcomas (24% of liver cancers with known histologic types) [14] than were liver cancers among A-bomb survivors (84% HCC, 15% cholangiocarcinoma, and 0% hemangiosarcoma) [4]. Radioactive thorium dioxide from injected Thorotrast migrates to the connective tissue and results in greater radiation exposures of the nearby liver bile duct and vascular cells than of the hepatic cells. In contrast, subjects in the atomic bomb survivor and the other non-Thorotrast cohorts received mostly penetrating gamma rays, resulting in whole-body exposures involving not only bile duct and vascular cells in the liver and hepatic cells, but also bone marrow and hematopoietic cells. Liver cancers in the German, Danish, and Japanese cohorts exposed to Thorotrast were fairly equally divided between HCC, cholangiocarcinoma, and hemangiosarcoma (reviewed in Ref. [4]). Of the liver cancers in the Portuguese Thorotrast cohort, 61% were hemangiosarcoma, 32% cholangiocarcinoma, and just 6% HCC (reviewed in Ref. [4]).

A large number of consistently positive studies have established HBV and HCV as strong risk factors for hepatocellular carcinoma [15]. In a nested case control study of HCC among atomic bomb survivors, we found super-multiplicative interaction between radiation and HCV in the etiology of HCC not accompanied by cirrhosis ($p = 0.039$). However, no interaction between radiation and HBV ($p = 0.91$) was noted in the etiology of HCC regardless of cirrhosis status (data not shown).

The goal of the present study was to compare studies of liver cancer and radiation in order to determine if discrepancies in the results of these studies might be related to differing exposures of these cohorts to risk factors for liver cancer. Because of our recent finding of interaction between radiation and HCV in the etiology of HCC, we particularly wanted to determine how liver cancer risks varied with prevalences of HCV in these cohorts.
2. Materials and methods

Analysis was limited to mortality studies of radiation and liver cancer. When several reports for the same cohort study were published, we surveyed the latest report available. Study characteristics recorded include (1) time span of subject follow-up, (2) country of residence of the subjects used in the radiation risk calculations, (3) nature of the radiation exposure of the cohort, (4) mean radiation exposure for exposed subjects, (5) total number of subjects, (6) number of subjects with any exposure to radiation, (7) total liver cancer deaths during the follow-up period, (8) radiation risk estimate, and (9) confidence interval (CI) for the risk estimate. These factors for each study were compared to the prevalence of HCV in the area from which study subjects were drawn. The HCV prevalences were based on a review by Wasley and Alter [16], which surveyed studies calculating HCV prevalences based on enzyme immunoassays confirmed by supplemental testing. China’s estimate was based on two studies of blood donors [17,18]; we did not find a study, which reported HCV prevalence for the region of Russia containing the Mayak facility. The HCV prevalences for A-bomb survivors were based on a clinical study of 6121 subjects [19] and an autopsy study of 897 A-bomb survivors who died before 1988 from diseases other than primary liver cancer (data not shown). We also included a study of Osaka blood donors aged 55–64 years [20].

2.1. Assessment of background level of liver cancer in cohorts

Ideally, the background level would be calculated as liver cancer deaths per 100,000 person-years of follow-up, but person-year totals were not available in most of the reports. We roughly calculated person-years as the total number of persons included in each study multiplied by the maximum duration of each study, assuming that each study had no other deaths or loss to the follow-up. The number of liver cancer deaths was divided by this number and the product multiplied by 100,000. Our method overestimated person-years and, correspondingly, underestimated liver cancer deaths per 100,000 person-years.

3. Results

The table lists the studies of radiation and liver cancer analyzed for this study. HCV prevalences were substantially higher in the A-bomb survivor cohort (7.8–8.9%) than in most other areas where cohort studies were conducted. HCV prevalences in the UK, where many of the mortality studies were conducted, were particularly low, ranging from 0.01% to 0.1%, with HCV prevalences ranging from 0.2% to 0.5% in North America and Western Europe [16].

Background liver cancer levels were low in most of the cohorts studied, ranging from 0.2 in the Canadian worker study [7] to 1.6 in the combined analysis of underground miners in North America, France, Sweden, UK, and the Czech Republic [13]. Background levels were substantially higher than this in the Chinese iron ore miner cohort, where hepatitis B was highly prevalent, in the peptic ulcer patient cohort [8] and in the uterine bleeding cohort [12]; these studies were conducted in areas of low HCV prevalence and
<table>
<thead>
<tr>
<th>Reference (first author)</th>
<th>Population</th>
<th>Location</th>
<th>Time of study</th>
<th>Total subjects (number radiation exposed)</th>
<th>Total liver cancer deaths (background level)</th>
<th>Mean radiation exposure level</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Studies of chronic radiation exposure in areas of low hepatitis C virus prevalence</strong></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Cardis [5]</td>
<td>nuclear workers</td>
<td>US, UK, and Canada</td>
<td>1944–1988</td>
<td>95,673 (all)</td>
<td>33 (0.8)</td>
<td>0.040 Sv (2% &gt; 0.400 Sv)</td>
<td>trend test p: 0.495</td>
</tr>
<tr>
<td>Chen [6]</td>
<td>underground iron ore miners</td>
<td>China</td>
<td>1970–1982</td>
<td>6444 (all)</td>
<td>17 (19.7)</td>
<td>0.021–0.030 Sv annually</td>
<td>SMR: 0.8; 95% CI: 0.4–1.2</td>
</tr>
<tr>
<td>Darby [13]</td>
<td>underground miners, mainly of uranium</td>
<td>US, Canada, UK, Sweden, Czech Republic, and Western Europe</td>
<td>1941–1990</td>
<td>64,209 (all)</td>
<td>50 (1.6)</td>
<td>155 working level months (WLM)</td>
<td>O/E: 1.73; 95% CI: 1.29–2.28; p for trend: 0.81</td>
</tr>
</tbody>
</table>

| **Studies of chronic radiation exposure in areas of unknown hepatitis C virus prevalence** |
| Gilbert [14]             | Mayak nuclear workers exposed to plutonium | Russia | 1948–1994 | 11,000 (2207) | 60 (11.8) | 0.31–1.74 Gy | SMR: 1.8 (1.4–2.3) |

<p>| <strong>Studies of acute radiation exposure in areas of low hepatitis C virus prevalence</strong> |
| Ashmore [7]              | workers with radiation exposures | Canada | 1951–1987 | 206,620 (28,917) | 16 (0.2) | 0.006 Sv | ERR/Sv: males: –0.9; 90% CI: –22.3–20.5 |
| Griem [8]                | peptic ulcer patients receiving radiotherapy | US | 1937–1985 | 3609 (1831) | 20 (11.5) | 4.61 Gy (mean liver dose) | adjusted RR: 0.79; 95% CI: 0.3–2.1 |
| Boice [9]                | cervical cancer patients receiving radiotherapy | US, Canada, UK, and Northern Europe | 1960–1983 | 182,040 (82,616) | 21 (0.5) | 1.5 Gy (mean liver dose) | O/E: 1.0; p&gt;0.05 |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Country</th>
<th>Year Range</th>
<th>Total Subjects</th>
<th>Liver Cancer Deaths</th>
<th>Mean Liver Dose</th>
<th>RR</th>
<th>90% CI</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darby [10]</td>
<td>participants in UK nuclear tests</td>
<td>UK</td>
<td>1952–1991</td>
<td>43,691 (21,358)</td>
<td>17 (1.0)</td>
<td>0.008 Sv</td>
<td>RR: 2.46; 90% CI: 0.92–6.92</td>
<td></td>
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</tr>
<tr>
<td>Weiss [11]</td>
<td>ankylosing spondylitis patients receiving radiotherapy</td>
<td>UK</td>
<td>1935–1992</td>
<td>15,577 (14,556)</td>
<td>11 (1.2)</td>
<td>2.13 Gy (mean liver dose)</td>
<td>RR: 0.81; 95% CI: 0.40–1.44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inskip [12]</td>
<td>women receiving radiotherapy for uterine bleeding</td>
<td>US</td>
<td>1925–1984</td>
<td>4153 (all)</td>
<td>15 (6.4)</td>
<td>0.21 Gy</td>
<td>SMR: 0.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Studies of acute radiation exposure in areas of high hepatitis C virus prevalence

Pierce [1] atomic bomb survivors Hiroshima and Nagasaki, Japan 1950–1990 86,572 (50,113 0.005 Sv) 753e (21.7) 0.20 Sv ERR/Sv males: 0.52; 90% CI: 0.22–0.91; females: 0.11; 90% CI: 0.08–0.59

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a Liver cancer deaths divided by [total subjects multiplied by maximum duration of study] multiplied by 100,000, our rough approximation of the mortality rate of liver cancer in each cohort, assuming no other deaths or loss to follow-up.
b Prevalence of hepatitis C virus based on review by Wasley and Alter [16]: UK and Scandinavia: 0.01–0.1%; North America and Western Europe: 0.2–0.5%; and China: 0.3–1.2% [17,18].
c 504 of the 4153 women were followed until 1966.
d HCV prevalence was 7.8% among hepatocellular carcinoma cases in a recent case control study and 8.9% in a clinical study of A-bomb survivors [19]; prevalence was 8.5% in Osaka blood donors age 55–64 years [20].
e Includes deaths with underlying cause coded as liver cancer, primary or liver cancer not specified as primary or secondary.
showed no significant radiation risks for liver cancer. Background liver cancer rates were also elevated in two studies reporting significantly increased liver cancer risks for radiation: the Mayak workers, for whom HCV prevalences were unknown, and A-bomb survivors, the group with the highest HCV prevalence rates [1]. The study of the underground miners, with both a low background rate of liver cancer and a low HCV prevalence, also reported a significantly increased risk of liver cancer (O/E ratio: 1.73; 95% CI: 1.29–2.28).

4. Discussion

There are several possible explanations for the wide variation in radiation risk estimates for liver cancer that we describe. These findings are primarily based on mortality studies. Liver cancer is one of the most difficult tumors to correctly diagnose, because the liver is a frequent site to which other tumors metastasize and because death from liver cancer is often incorrectly attributed to cirrhosis or chronic hepatitis. We found that from 1958 to 1987, about half of the A-bomb survivors whose death certificates recorded liver cancer as the cause of death, died from other causes, and that about two-thirds of the persons recorded as dying from cirrhosis or chronic hepatitis were found on pathology review to have died from primary liver cancer [21]. The A-bomb survivor studies of incident cases of primary liver cancer [2,3], which corrected for some of these diagnosis errors, reported slightly higher ERR per Sv risk estimates than the A-bomb survivor mortality study included in the table.

Because HCV prevalence estimates for the UK, Europe, and China are primarily based on blood donor studies, they are likely to be underestimated in comparison to the A-bomb survivors and US prevalence estimates. However, the high HCV prevalence in the A-bomb survivor cohort is consistent with a 1994 Osaka, Japan blood donor study that reported a HCV prevalence of 8.5% for donors aged 55–64 years [20].

Our background liver cancer index underestimates liver cancer death rates but is useful for comparing background liver cancer mortality rates in the cohorts. For example, we estimated the background level for the Mayak study at 11.8 liver cancer deaths per 100,000 per year (Table 1), which compares to an estimate of 14.0 liver cancers per 100,000 person-years that can be calculated from person-year information provided in this report [14]. It is not clear if the differences in background liver cancer rates can explain the differences in radiation risk estimates between studies. In the A-bomb survivor [1] and the Mayak worker [14] studies, which reported significant risks of liver cancer for radiation, background levels were high. In contrast, however, the Chinese iron ore miner [6], peptic ulcer patient [8], and uterine bleeding [12] studies also had high background levels of liver cancer, but found no increased risk of liver cancer for radiation. Two studies by Darby et al. [10,13], conducted in areas with low background rates, disclosed point estimates consistent with a radiation effect, but in both studies the authors concluded that the increase was unconnected with radiation exposure. Those investigators attributed their finding of a statistically significant, but not dose-dependent, radiation effect in the study of underground miners to high alcohol consumption and the possible confusion of primary with secondary liver cancers [13], a criticism that could also be leveled against all mortality studies of liver cancer deaths occurring before the mid-1980s.
The finding of interaction between HCV and radiation in the etiology of HCC, suggests that studies of radiation and liver cancer that do not adjust for HCV infections overestimate radiation risks when HCV levels are high. Thus, radiation risk estimates for the A-bomb survivors might be inflated by the high prevalence of HCV in this cohort. Because HCV prevalences appear to be low in the Chinese miner [6], peptic ulcer [8], and uterine bleeding [12] cohorts, where background liver cancer rates were high, their lower HCV prevalences may explain why these studies did not find elevated radiation risks. Radiation risk estimates were significantly elevated in the Mayak worker study [14], where background liver cancer levels were high and the HCV prevalence in the cohort could not be determined. Furthermore, the nature of the radiation exposure (internal deposition and external, rather than just external) differed from the other cohorts.

Acknowledgements

This study was supported by contract NCI-4893-8-001 from the US National Institutes of Health. RERF is a private nonprofit foundation funded equally by the Japanese Ministry of Health and Welfare and the US Department of Energy through the US National Academy of Sciences.

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