

The Relationship between Internally Deposited Alpha-particle Radiation and Subsite-specific Liver Cancer and Liver Cirrhosis: an Analysis of Published Data

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Thorotrast / Plutonium / Chronic α -radiation / Liver cancer

Chronic exposure to high LET radiation has been shown to cause liver cancer in humans based on studies of patients who received Thorotrast, a colloidal suspension of thorium dioxide formerly used as a radiological contrast agent, and on studies of Russian nuclear weapons workers exposed to internally ingested plutonium. Risk estimates for these exposures and specific subtypes of liver cancer have not been previously reported. Combining published data with tumor registry data pertinent to the Thorotrast cohorts in Germany, Denmark, Portugal, and Japan and to Russian workers, we generally found significantly elevated risks of three major histologic types of liver tumors: hepatocellular carcinoma (HCC), cholangiocarcinoma (CC), and hemangiosarcoma (HS) for Thorotrast exposures. In contrast, HS was the only liver tumor significantly associated with the lower α -particle doses experienced by the Russian workers.

Excess cases per 1,000 persons exposed to Thorotrast were similar for the three liver cancer subtypes but lower for plutonium exposure. Odds ratios (OR) of HS and CC for Thorotrast were from 26 to 789 and from 1 to 31 times higher than those for HCC, respectively. ORs of liver cirrhosis for Thorotrast exposure ranged from 2.7 (95% confidence interval (CI): 2.2–3.4) to 6.7 (5.1–8.7).

INTRODUCTION

The strongest evidence of increased risk of liver cancer due to radiation exposure comes from a study of Mayak nuclear weapons workers exposed to plutonium¹ and from four follow-up studies of patients who were given Thorotrast, a colloidal suspension of thorium dioxide that was used as a radiological contrast agent from the 1930s–1950s^{2–5}. Internal deposition of these radionuclides resulted in

chronic lifetime exposure to high levels of α -particles, which was subsequently linked to significantly increased risks of liver cancer^{1–5}. The histologic types of liver tumors found in these studies were fairly evenly divided among three different subtypes: hepatocellular carcinoma (HCC), cholangiocarcinoma (CC), and hemangiosarcoma (HS). Even though the etiologies of these liver cancers differ and this subtype distribution is completely different from that found in unexposed populations, investigators have not separately calculated relative risks of each liver cancer subtype for these α -radiation exposures. The distribution of liver cancer subtypes in the Thorotrast and Mayak cohorts is also very different from that in cohorts with other radiation exposures. For example, among Atomic-bomb survivors, pathology review showed 84.4% of

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liver tumors to be HCC, 14.8% CC, 0.6% combined HCC and CC, 0.3% hepatoblastoma, and no cases of HS⁶⁾. Thorotrast studies also generally reported only *p*-values, rather than risk estimates, making it difficult to assess the strength of association between this radiation exposure and liver carcinogenesis. Information about the relationship between chronic α -radiation and subtype-specific liver cancer is important both in better understanding the relationship between α -radiation and liver cancer and in investigating the mechanisms of hepatocarcinogenesis underlying one of the world's most common and fatal cancers.

A study that examined the relationship between Thorotrast and death from liver cirrhosis in Denmark reported a standard mortality ratio (SMR) of death from cirrhosis of 11.1 (95% CI: 7.1–16.4)⁷⁾; similarly a Japanese Thorotrast study reported a 5.4-fold (95% CI: 3.0–9.7) increased risk of cirrhosis death⁸⁾. Kaick *et al.*²⁾ concluded that there was a close correlation between dose rate of liver exposure from Thorotrast and the cumulative rate of liver cirrhosis but did not report a risk estimate for this exposure. It is not clear if these studies of the Danish, Japanese, and German Thorotrast cohorts took into account deaths from liver cancer that were accompanied by cirrhosis.

The goal of the present study was to combine tumor registry data pertinent to the groups that were studied and published data for these groups to calculate odds ratios (OR) of subsite-specific liver cancer for chronic internal exposure to α -particle emitting radionuclides. Because all four Thorotrast studies reported the numbers of subjects in exposed and unexposed groups who died from cirrhosis and from liver cancer, we also wanted to reexamine these studies to calculate risk estimates for cirrhosis that took into account deaths from liver cancer accompanied by cirrhosis.

MATERIALS AND METHODS

We analyzed four studies of Thorotrast and one study of plutonium that provided information about follow-up of radiation-exposed and non-exposed sub-

jects according to subsequent diagnoses of specific histologic types of liver cancer and liver cirrhosis. We examined reports on Thorotrast-exposed cohorts in Germany²⁾, Denmark^{3,9)}, Portugal⁴⁾, and Japan⁵⁾ and two reports on workers exposed to plutonium at Russia's nuclear weapons factories at Mayak^{1,10)}. In analyzing the latter studies, we compared 2,207 monitored workers with a detectable plutonium body burden to 3,314 workers without plutonium exposure¹⁰⁾, deriving our numbers of exposed and non-exposed workers who developed HCC, CC, or HS from a report on liver cancer among Mayak workers¹⁾. The Portuguese^{11,4)} and Japanese⁵⁾ Thorotrast studies reported the numbers of deaths from liver cirrhosis among exposed and unexposed persons. The German Thorotrast study²⁾ reported these numbers as well as the number of deaths from liver cancer where cirrhosis was also present.

All four Thorotrast studies and the Mayak studies reported the total number of liver cancer cases and the number of cases with HCC, CC, and HS, the predominant histologic types. Also reported were liver tumors that were undifferentiated, of unknown or unspecified subtype, or that were found in conjunction with other liver tumors or with other cancers. We excluded from analysis all liver tumors that were not specifically recorded as HCC, CC, or HS or that were found with other tumors.

We compared the number of liver cancer and cirrhosis cases in exposed and unexposed groups in each of the five studies. We calculated the number of excess cases per 1,000 exposed subjects for HCC, CC, and HS, by subtracting the percentage of each liver cancer subtype found in the unexposed group from that in the exposed group, multiplying the result by 10. We calculated crude ORs as Mantel Haenszel cross product ratios and 95% CIs. Liver cancer cases of all three subtypes were found in exposed groups in each study, but such cases were not always found in unexposed groups. When no liver cancer cases of a specific subtype were found in an unexposed group, to avoid infinite ORs, we assumed the occurrence of one liver cancer case in this group. This case was apportioned to the specific subtype based on the relative frequency of that subtype compared to the total number of HCC,

CC, and HS cases occurring in the country or region of the study. For example, if a study reported no HCC cases in their unexposed group and if 62.5% of that country's unexposed HCC, CC, and HS cases were HCC, then we assumed that 0.625 cases of HCC were found in the non-exposed group. To assign such tumors occurring in the German²⁾ and Danish^{9,3)} comparison groups, we used national tumor registry data available for these countries¹²⁾. Because national data were not available for the Russian^{1,10)} and Portuguese⁴⁾ studies we made these assignments using combined data from the following European tumor registries: Czech Republic, 1988–1992; Denmark, 1988–1992; Finland, 1987–1992; France, 3 registries, 1988–1992; Germany, Eastern States 1988–1989; Netherlands, 1989–1992; Norway, 1988–1992; Poland, Warsaw, 1989–1992; Spain, Granada, 1988–1992; Sweden, 1988–1992; Switzerland, 2 registries, 1988–1992; and UK, England and Wales, 1988–1990¹²⁾. We calculated mean proportions of cases that were either HCC, CC, or HS; these means were weighted by the total number of liver cancer cases reported by each registry multiplied by the number of registries; the product was divided by the total number of cases.

ORs of cirrhosis for Thorotrast exposures were calculated using published data for the German²⁾, Portuguese⁴⁾, and Japanese⁵⁾ cohorts. In the Japanese study⁵⁾, numbers of subsite-specific liver cancer cases were reported for a group of 357 Thorotrast-exposed patients and for an autopsy series of 431,239 persons; deaths due to cirrhosis were reported for the same exposed group and for a selected group of 160,700 persons in the autopsy series who had similar age and sex distributions. In the Portuguese⁴⁾ and German²⁾ studies the same exposed and unexposed groups were used for comparisons of both liver cancer and cirrhosis. Because the German study listed both deaths due to cirrhosis and deaths due to liver cancer accompanied by cirrhosis, we calculated ORs of cirrhosis with or without liver cancer. The other two studies listed separately the numbers of deaths due to cirrhosis and liver cancer without specifying whether these cancers were accompanied by cirrhosis. Because liver cancer is frequently accompanied by cirrhosis, we first

excluded from analysis persons in the Japanese and Portuguese studies for whom liver cancer was listed as the cause of death. However, because excluding likely cases of cirrhosis from exposed groups causes ORs of cirrhosis to be underestimated, we also conducted an alternative analysis in which we assumed that a certain proportion of persons with liver cancer also had cirrhosis, rather than excluding them from analysis.

Mean radiation exposure for the Japanese cohort was from a paper by Ishikawa *et al.*¹³⁾ who used the methods of Kato *et al.*¹⁴⁾ and Kaul and Noffz¹⁵⁾ to convert mean Thorotrast injection amounts to mean annual radiation dose rates. We converted mean injection amounts reported by the German, Danish, and Portuguese Thorotrast studies to annual liver irradiation levels in Gy based on the methods of Kaul and Noffz¹⁵⁾. Radiation exposures for the Mayak workers study were taken from published reports^{1,5)}. All analyses were performed using the Statistical Analysis System (SAS) version 6.12 (SAS Institute Incorporated, Cary, North Carolina).

RESULTS

Radiation exposures

As shown in Table 1, mean radiation liver irradiation levels for the Thorotrast-exposed groups in each study were similar, with the exception of those for the Danish cohort, which were slightly lower. Although the total doses shown for Mayak workers would be quickly reached by Thorotrast recipients just a few years after injection, some Mayak workers were additionally exposed to gamma radiation while employed, so their mean liver irradiation levels would be higher than shown here. The percentage of exposed subjects who were male ranged from 56% in the Danish study to 90% in the Japanese study. Average follow-up time for the studies was about 50 years, with the exception of the Portuguese study, for which duration of follow-up was about half as long.

Internally deposited radionuclides and liver cancer

Table 2 shows the combined numbers of HCC,

Table 1. Epidemiologic studies of chronic α -radiation exposure and liver cancer.

First author of study, reference	Location	Percent male	Time of study	Length of follow-up (years)	Mean radiation exposure ^a
<i>Studies of patients exposed to Thorotrast</i>					
Van Kaick ²⁾	Germany	74% male	1937–1988	51	0.250 Gy/year ^b
Andersson ^{3,9)}	Denmark	56% male	1935–1992	57	0.180 Gy/year ^b
da Silva Horta ^{4,11)}	Portugal	not stated	1946–1974	28	0.260 Gy/year ^b
Mori ⁵⁾	Japan	90% male	1937–1990	53	0.220 Gy/year ^b
<i>Study of Mayak workers exposed to plutonium</i>					
Gilbert ¹⁾	Russia	69% male	1948–1996	48	0.600 Gy ^c

^a For German, Danish and Portuguese Thorotrast recipients, Thorotrast injection amount in ml was converted to annual liver dose based on results of Kaul and Noffz¹⁵⁾. Exposure of Japanese Thorotrast recipients was based on results for 206 recipients reported by Ishikawa and associates¹³⁾. Exposure estimates for the Mayak study were reported by Gilbert *et al.* and Koshurnikiva *et al.*^{1,10)}

^b Annual α -particle liver dose at injection (the dose rate increases as the liver shrinks with prolonged exposure).

^c Total α -particle liver dose from plutonium, sometimes supplemented with external gamma ray exposure

Table 2. Liver cancer cases in unexposed and exposed groups in Thorotrast and Mayak studies.^a

Country, reference number	Unexposed group			Exposed group		
	No.	No. HCC, CC, or HS cases (no. with other liver tumors) ^b	Liver cancer prevalence (%)	No.	No. HCC, CC, or HS cases (no. with other liver tumors) ^b	Liver cancer prevalence (%)
Germany ²⁾	1,890	0 (2)	0.1	2,326	292 (118)	17.6
Denmark ^{3,9)}	1,480	0 (0)	0	1,003	119 (8)	12.7
Portugal ⁴⁾	829	0 (1)	0.1	1,237	31 (44)	6.1
Japan ⁵⁾	431,239	28,416 (4,610)	7.7	357	200 (40)	67.2
Russia ^{1,10)}	3,314	9 (4)	0.4	2,207	20 (3)	1.0

^a Abbreviations: HCC: hepatocellular carcinoma, CC: cholangiocarcinoma, and HS: hemangiosarcoma.

^b “Other liver tumors” includes those that were unclassified, unspecified, of unknown histology, or undifferentiated, as well as liver tumors of multiple histologic subtypes and those found with other cancers.

CC, or HS liver cancers, the number of other liver tumors among the unexposed and exposed subjects, and liver cancer prevalence in each of the five studies. In the German study²⁾ the exposed cases classified as “other” were primarily cancers that either were histologically diagnosed without classification or that were clinically diagnosed but not histologically classified. In the Portuguese study⁴⁾, “other liver tumors” were primarily tumors for which histological diagnoses could not be obtained. In the Japanese study⁵⁾, “other

liver tumors” in both exposed and unexposed groups were primarily tumors that the authors defined as combined malignant tumors of the liver consisting of two to four types of malignant tumors occurring in the liver or in the liver and other organs. In addition, 1 exposed and 1,665 unexposed liver cancer cases were diagnosed with undifferentiated tumors⁵⁾. Two exposed cases were diagnosed with liver cancers of unknown histological types⁵⁾. Liver cancer prevalences were substantially higher in both the Japanese exposed

(67.2%) and unexposed groups (7.7%), compared to the other cohorts. The prevalence of liver cancer in the Portuguese study's exposed group at 6.1% was notably lower than those in the other Thorotrast studies.

Table 3 shows the proportions of liver tumors that were diagnosed as each of the three histologic subtypes in the unexposed and exposed groups and the numbers of excess cases per 1,000 exposed persons. Percentages for the unexposed groups, which, with the exception of Japan, were based on registry data, were used to apportion a single liver cancer case into one or more of the three subtypes when liver cancer of a specific subtype was not found in one of the unexposed comparison groups. This was necessary for all three subtypes in calculating excess cases rates for the German, Danish, and Portuguese studies because no specifically diagnosed cases of HCC, CC, or HS were found in the unexposed groups in these studies. No HS cases were found in the unexposed group in the Mayak study. A footnote in Table 3 notes the groups for which this procedure was performed. Because sex of subjects was not specified for the Portuguese cohort and because a high proportion of females was included in the Mayak study, we combined males and females in

calculating weighted mean proportions of subtype-specific liver cancers for the 15 European registries. The resulting mean proportions and standard errors for each subtype are shown in Table 3 (unexposed liver cancer cases, Portugal and Russia).

As shown in Table 3, the percentage breakdown of the three liver cancer subtypes derived from registry data and from the large Japanese comparison group were reasonably similar. The proportion of liver cancers that were HCC was slightly higher in the Japanese non-exposed group (87.3%) than in the other four studies, reflecting the high background rate of HCC in this country. Among the four Thorotrast studies, the mean number of excess cases per 1,000 exposed was 33.6 for HCC, 109.5 for CC, and 37.2 for HS. Excess case estimates were somewhat lower for the Portuguese cohort and much lower for the Mayak workers.

Table 4 presents ORs and 95% CIs of subsite-specific liver tumors for Thorotrast and plutonium exposure. As shown here, based on ORs, risks of HS were most increased by Thorotrast and plutonium exposures relative to background incidence rates of this exceptionally rare cancer. ORs of HS ranged from 1,489 in the Portuguese study to 6,063 in the German

Table 3. Relative proportions and excess cases of hepatocellular carcinoma (HCC), cholangiocarcinoma (CC), and heman-giosarcoma (HS) according to plutonium and Thorotrast exposures.

Location of study, reference number	% of unexposed liver cancer cases with each subtype ^a			% of exposed liver cancer cases with each subtype (excess cases per 1,000 exposed) ^b		
	HCC	CC	HS	HCC	CC	HS
Germany ²⁾	62.5	36.1	1.4	24.3 (31.9) ^c	43.1 (56.9) ^c	32.5 (43.0) ^c
Denmark ^{3,9)}	54.8	43.7	1.5	37.8 (43.0) ^c	34.4 (40.8) ^c	27.7 (33.1) ^c
Portugal ⁴⁾	69.1	30.0	0.9	6.4 (0.9) ^c	32.3 (8.0) ^c	61.3 (15.9) ^c
Japan ⁵⁾	87.3	12.5	0.2	18.5 (58.6)	54.0 (332.3)	27.5 (173.4)
Russia ^{1,10)}	69.1	30.0	0.9	40.0 (1.8)	15.0 (0.5)	45.0 (4.1) ^c

^a Non-exposed group proportions based on data provided by IARC 12) for the German, Eastern States Tumor Registry, 1988–1989 (Germany); Denmark Tumor Registry, 1988–1992 (Denmark); combined data for 15 European tumor registries (Portugal and Russia), and on an autopsy survey of 431,239 subjects reported by Mori *et al.* 5) Standard errors for Registry-based mean percentages for Portugal and Russia were 2.96%, 2.86%, and 0.17% for HCC, CC and HS, respectively.

^b Percentages of primary liver cancers among exposed groups found to be either HCC, CC, or HS in cited studies.

^c Possible underestimation because this liver cancer subtype was not found in the unexposed group. To calculate excess cases per 1,000 exposed persons we assumed one unexposed subject with PLC, which was apportioned to this histologic subtype according to the relative proportions of HCC, CC, and HS shown here for unexposed persons.

Table 4. Relationship of internally deposited radionuclides and hepatocellular carcinoma (HCC), cholangiocarcinoma (CC), and hemangiosarcoma (HS) by liver cancer subtype.

Location of study, reference number	Odds ratio (95% confidence interval) by liver cancer subtype ^a		
	HCC	CC	HS
Germany ²⁾	100 (31.2–322) ^b	316 (108–928) ^b	6,063 (932–39,445) ^b
Denmark ^{3,9)}	128 (39.6–411) ^b	145 (41.4–510) ^b	3,377 (352–32,422) ^b
Portugal ⁴⁾	2.0 (0.1–29.4) ^b	23.3 (1.9–278.4) ^b	1,489 (29.3–75,732) ^b
Japan ⁵⁾	2.1 (1.5–3.0)	64.4 (54.1–69.6)	1,658 (1,538–1,788)
Russia ^{1,10)}	2.0 (0.7–5.7)	1.5 (0.3–7.4)	1,507 (30.4–74,744) ^b

^a To calculate odds ratios and confidence intervals, liver tumors that were not classified as one of these subtypes were excluded from each study.

^b Possible underestimation because this liver cancer subtype was not found in the unexposed group. To make calculations we assumed one unexposed subject with liver cancer, which was apportioned to this histologic subtype according to the relative proportions of the three subtypes reported by national or regional tumor registries.

study and were similarly elevated in the Mayak study. ORs of HCC and CC were substantially lower in the Japanese and Portuguese studies than in the German and Danish studies. In the Portuguese study, the 95% CI for the OR of HCC for Thorotrast included the null value of 1.0, as did the ORs of HCC and CC in the Mayak study. In the Thorotrast studies, ORs of CC were from 1 to 31 times larger than those for HCC, and ORs of HS were from 26 to 789 times larger than those for HCC.

Internally deposited radionuclides and liver cirrhosis

Table 5 shows that in all comparisons Thorotrast exposure was significantly related to increased risks of liver cirrhosis. In the German study, Thorotrast recipients were 6.7 times more likely to die with cirrhosis, with or without liver cancer, than were persons not so exposed. In the Portuguese and Japanese studies, Thorotrast-exposed patients were, respectively, at 3.0- and 2.1-fold increased risks of death due to liver cirrhosis not accompanied by liver cancer. These latter

Table 5. Thorotrast exposure and liver cirrhosis mortality

Location of study, reference number	Unexposed group		Exposed group		Odds ratio (95% confidence interval)
	Number	Number with cirrhosis	Number	Number with cirrhosis ^a	
<i>With or without concurrent liver cancer</i>					
Germany ²⁾	1,890	50	2,326	357	6.7 (5.1–8.7)
<i>Without concurrent liver cancer (liver cancer cases excluded)</i>					
Portugal ⁴⁾	828 ^b	6	1,162 ^b	25	3.0 (1.2–6.9)
Japan ⁵⁾	147,872 ^c	15,545	117 ^c	23	2.1 (1.3–3.2)

^a In Portuguese study, outcome was “liver cirrhosis/fibrosis”.

^b Analysis excluded 1 unexposed subject and 75 exposed subjects who had liver cancer of unspecified cirrhosis status. Assuming the same proportion of liver tumors accompanied by cirrhosis as in the German Thorotrast study (31%)²⁾, the OR (95% CI) of cirrhosis/fibrosis would be 5.3 (2.5–11.2).

^c Analysis excluded 12,828 unexposed and 240 exposed subjects with liver cancer of unspecified cirrhosis status. Assuming the same proportion of liver tumors accompanied by cirrhosis as in the German Thorotrast study (31%)²⁾, the OR (95% CI) of cirrhosis would be 2.7 (2.2–3.4).

two ORs were calculated excluding from analysis persons with liver cancer, for whom cirrhosis status was unknown. Assuming that the same proportion of such cases concurrently had cirrhosis as did persons with liver cancer in the German study, ORs of death with cirrhosis, respectively, would be 5.3 (95% CI: 2.5–11.2) and 2.7 (95% CI: 2.2–3.4).

DISCUSSION

This study provides convincing evidence that three types of liver cancer, hemangiosarcoma, cholangiocarcinoma and hepatocellular carcinoma, are significantly associated with chronic exposure to high LET α -particle radiation resulting from use of Thorotrast as a radiological contrast agent. Based on our reanalysis of the Mayak study, exposures to lower levels of α -particle radiation were significantly associated only with elevated risks of HS and not HCC or CC. Although the extent to which Mayak workers were also exposed to gamma radiation is not clear from the studies published so far, our results suggest that this additional exposure did not substantially increase these worker's risks of HCC. Overall, ORs and excess case rates for the Thorotrast studies were remarkably consistent, especially considering our dependence on published data and differences in study designs and populations.

Numbers of excess cases of the three subtypes per 1,000 persons exposed to Thorotrast were reasonably similar in the four Thorotrast studies but substantially lower in the Mayak study. Excess cases of HCC were also markedly lower in the Portuguese study than in the other Thorotrast studies. ORs of HS and CC were high in all the Thorotrast studies, ranging from 1,489 to 6,063 and from 23.3 to 316, respectively. The Mayak HS OR was also in this range, even though it may be underestimated due to the lack of HS cases among unexposed Mayak workers. ORs of HCC reached 100 in the German and Danish studies but were notably lower in the Japanese and Portuguese studies. Our finding that excess case rates were similar for all three subtypes in the Thorotrast studies suggests

that chronic exposure to this high LET source of α -radiation similarly elevates absolute risks of all three liver cancer subtypes. The Japanese study's markedly lower OR of HCC may reflect the comparison of this study's exposed group with an unexposed group that had a many fold higher background level of liver cancer than in the other studies, thereby reducing the relative increase. Our finding that HCC relative risks for Thorotrast-related, α -particle radiation exposures are markedly lower where hepatitis B and C viruses are more prevalent suggests that these viruses do not synergistically interact with this radiation exposure to increase HCC risks.

The low OR and excess case rate of HCC in the Portuguese study, where the background prevalence of HCC is much lower than in Japan, may relate to that study's much shorter length of follow-up, a period about half as long as those in the other studies. Mori *et al.*⁵⁾ found that the percentage of liver cancers composed of HCC increased in the Japanese Thorotrast-exposed cohort with increasing duration of exposure, rising from 13.1% during the first 30 years of follow-up to 17.3 % during the next 14 years. Thus, more HCC cases might have been detected in the Portuguese study had the study been continued for a longer time. This idea is supported by a more recent study of this cohort reporting the results of follow-up through 1996¹⁶⁾. After 50 years of follow-up, those investigators reported 104 (10.1%) liver cancer deaths among 1,131 Thorotrast-exposed subjects, as opposed to 75 (6.1%) among 1,237 subjects in their earlier study; the larger proportion is more comparable to those listed for the other Thorotrast cohorts in Table 2. Because information about liver cancer subtypes was not included in this more recent report, it is not known what percent of the additional cases were HCC, and, thus, we could not analyze those data for the current study.

Our reanalysis of these data is limited by the small size of the unexposed groups in the Danish, Portuguese, and German Thorotrast cohorts. No subtype-specific cases of liver cancer were found in these unexposed groups, although small numbers of subtype-unknown liver cancers were detected in the latter

two studies. No liver cancer cases were detected in the unexposed group in the Danish study, which was 78% as big as the German study's unexposed group where two such cases were found. Our assumption of one liver cancer case per unexposed group in these studies and our sorting of it into subtype categories based on tumor registry data is consistent with the findings of those studies and with the expected subtype distribution of liver cancer cases in populations not exposed to Thorotrast. CIs for ORs in the German, Danish, and Portuguese studies were wide, reflecting the rarity of liver cancer in these countries and the small size of unexposed groups in these studies. These CIs are notably tighter and, thus, risks are better quantified in the Japanese study, reflecting this study's much larger unexposed group and higher background incidence of HCC. Also, although our point estimates of relative risks in the German and Danish studies were not precise, the lower bounds of the 95% CIs for these estimates all greatly exceeded the null value of 1.0, as did the OR of HS in the Russian study.

We excluded all liver cancer cases of unknown subtype from analysis. This would influence the results of this study only if there were a selection bias that caused certain liver cancer subtypes to be more likely to be classified as unknown than others. However, studies of liver cancer among Japanese atomic-bomb survivors¹⁷⁾ have found that when liver cancer subtypes cannot be determined, the usual reason is lack of liver tissue for pathology review, not increased difficulty in diagnosing a particular subtype. Similarly, among 10,898 males with liver cancer listed by the 15 European tumor registries included in this study, lack of microscopic verification prevented the 69% of the 4,959 liver tumors with unknown subtypes from being classified¹²⁾. Investigators in the Mayak and Thorotrast studies were concerned with all liver cancers, and there is no reason to suspect that they preferentially preserved tissues from patients with particular liver cancer subtypes, especially since they were unlikely to know the subtype until after tissue collection. Thus, our excluding cases of unknown subtype from analysis should not affect the results of this study.

Differences in pathology judgments about how to

classify liver tumors of multiple subtypes might have affected our results. Compared to pathologists in the other studies, pathologists in the Japanese study were much more likely to classify liver tumors as having combined multiple tumors either within the liver or in the liver and other organs. In the Japanese study, 23% of all liver tumors detected in Thorotrast recipients from 1976 to 1990 were so classified⁵⁾, compared to no such cases in the Russian¹⁾, German²⁾, and Portuguese⁴⁾ studies, and just 0.7% of exposed liver cancer cases in the Danish study³⁾. This difference in pathology diagnoses might partially account for differences in ORs and excess case rates for the Japanese Thorotrast cohort compared to those other groups.

This study's dependence on published data limited us to calculating crude estimates of ORs and CIs, that could not be adjusted for differences in age, sex, or other possible confounders. However, although differences in age and sex distributions between cohorts may partially account for some of the differences in ORs between cohorts that we documented, confounders cannot account for the large differences we found within cohorts in ORs for HCC, CC, and HS. Also, many of the lower 95% confidence bounds of crude ORs for Thorotrast are high enough for the three subtypes that they would be unlikely to drop below the null value of 1.0 if adjusted for age, sex or other possible confounders. It also seems unlikely that the ORs of HCC and CC in the Russian study would be greatly elevated if such adjustments were made.

An advantage of the current study is that average annual liver exposures to α -particle radiation were similar in three of the Thorotrast studies, ranging from 0.220 to 0.260 Gy per year. Thus, differences in the results of these studies are unlikely to be due to differences in Thorotrast exposure. Exposures were slightly lower in the Danish Thorotrast cohort at 0.180 Gy/year and substantially lower in the Mayak workers cohort at 0.600 Gy total dose. The relative biological effectiveness (RBE) of these high LET, α -particle radiation exposures has been estimated to range from 15 to 20 for the induction of liver chromosome aberrations,¹⁸⁾ so equivalent Sv doses would be high.

Results of the current study add to the evidence

that chronic radiation exposure significantly increases risks of liver cirrhosis. Mori *et al.*⁸⁾ reported a 5.4-fold (95% CI: 3.0–9.7) increase in deaths due to cirrhosis in patients exposed to Thorotrast; reanalyzing their data using a different control group and roughly adjusting for liver cancer cases who also had cirrhosis, we found an OR of death with cirrhosis of 2.7 (95% CI: 2.2–3.3) in the current study. Reanalyzing the data of Van Kaick *et al.* who reported a significant relationship between Thorotrast exposure in Germany and death from cirrhosis²⁾, we found an OR of 6.7 (95% CI: 5.1–8.7) of death with cirrhosis. The German result is also consistent with our reanalysis of the Portuguese Thorotrast data, which disclosed an OR of death with cirrhosis of 5.3 (95% CI: 2.5–11.2), again roughly adjusting for subjects with liver cancer who also had cirrhosis. In the Denmark Thorotrast study, Andersson *et al.* reported an 11-fold increased risk of death from cirrhosis (95% CI: 7.1–16.4)⁷⁾.

In summary, the results of the present study suggest that chronic exposure to internally deposited, α -emitting radiation sources significantly increases the risk of cirrhosis, both in the presence of liver cancer and when liver cancers are not found. Our results suggest that such high dose, high LET α -radiation exposures significantly increase risks of HS, CC and HCC. Among Mayak workers, increased risks of liver cancer from lower α -radiation exposures were primarily due to significantly increased risks of HS but not HCC or CC.

ACKNOWLEDGEMENTS

The author is grateful to Drs. Gen Suzuki, Harry Cullings, Kojiro Koyama, and John Cologne for helpful discussions. This study was supported by contract NCI-4893-8-001 from the U.S. National Institutes of Health. RERF is a private nonprofit foundation funded equally by the Japanese Ministry of Health and Welfare and the U.S. Department of Energy through the U.S. National Academy of Sciences. Additional funding for this project was provided by grant number 14031227 from the Japanese Ministry of Education,

Culture, Sports, Science, and Technology.

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Received on July 10, 2002

1st. Revision on September 26, 2002

Accepted on October 7, 2002