Statistical Study on Thorotrast-induced Cancer of the Liver

By

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Epidemiological study of carcinogenesis of thorotrast was made in the following three ways of survey.

1) Prospective study: Of 147 thorotrast patients surveyed, 3 cases of liver cancer (cholangiocarcinoma), 2 cases of liver cirrhosis and 1 case of leukemia were found, while, of 1,678 of non injected cases, 1 case of leukemia, 5 cases of liver cirrhosis and no liver cancer occurred more frequently in the thorotrast group than in controls.

2) Retrospective study: Of 466 liver cancer patients surveyed, 4 or 0.85% had thorotrast shadow in the roentgenogram of the upper abdomen, while, of 1,938 controls, 1 or 0.07% the thorotrast shadow. Statistically, the thorotrast maintaining rate is higher in liver cancer patients than in controls.

3) Autopsy case study: Of 38 autopsied cases of thorotrast, 21 were primary liver malignancy, which consisted of 4 hepatomas (19%), 14 cholangiocarcinomas (67%) and 3 endotheliomas (14%). As compared with the autopsy cases of Japanese, cholangiocarcinoma and endothelioma are extremely frequent in thorotrast cases with a statistically significant difference.

Radiation carcinogenesis in man has been studied by the present research group since 1961. Of the results obtained, relationship between medical external irradiation and consequent human cancer was already published elsewhere in 1963 (Takahashi et al.1). The purpose of this paper is to describe a statistical study on carcinogenesis in patients who were irradiated for a long time by the internally introduced thorotrast, colloidal thorium dioxyde (Oka),2 for the diagnostic aid.
METHODS AND RESULTS

This study consisted of three independent surveys: that is, a prospective and retrospective survey (Witts, Mainland) on thorotrast-injected patients and statistical analysis of autopsy cases in Japan.

(1) **Prospective study:** The follow-up survey was done on patients who were given thorotrast for radiography over 20 years ago, and the incidence of malignant diseases in this group was compared with that in controls.

(2) **Retrospective study:** The thorotrast cases were surveyed among the patients with liver cancer clinically diagnosed and was compared with that in controls.

(3) **Statistical analysis of autopsy cases:** The composition of death cause was analyzed in patient with primary liver malignancy developed after thorotrast administration. Cases were collected from the department of pathology in big hospitals in Japan.

1. **Prospective study**

About 20,000 clinical records on the war-wounded were examined, which had been charged of in the Sagamigahara National Hospital, Shimofusa National Sanatorium, Konodai National Hospital, and Kofu National Hospital (Mori et al.). These 4 hospitals are formerly the Japanese Army Hospitals. Many clinical records on the war-wounded still have been charged of, and frequently angiographic examinations using thorotrast seemed to have been taken during the War in these hospitals. All of these war-wounded were Japanese male, and had been injured between 1935 and 1943. Of 20,000, 147 were evidently thorotrast maintainers confirmed by the clinical records. These patients had received 3 to 75 cc of thorotrast injection when they were 20 to 36 years of age. Of 147, 138 were examined by angiography, 1 by hepatolienography, 3 by pyelography, 1 by bronchography, 2 by myelography, and 2 by neurography.

Questionnaires, asking for answer the present state of health, were sent to 147 patients of their family. Since most patients had changed their address during and after the War, the permanent address was chiefly utilized, because, in accordance with Japanese law, the permanent address was not changed through one's life time. When a patient was already died, the clinical record just before death and/or the autopsy record was referred. However, when these clinical or autopsy record could not be examined, a death certificate which was written by the doctor who examined a patient before death and was charged of in the city, town, or village offices or in the Bureau of Judicial Affairs was checked. In case these offices were destroyed by fire during the War or by other reasons, the cause of death was not checked.

Prognosis thus ascertained in 147 patients was as follows: 112 or 76.19% were alive healthy in 1964, 27 or 18.37% were died, and no confirmation of life
or death was obtained in 8 or 5.44%. Among 27 deaths, there were 3 cases of cholangiocarcinoma, 2 cases of liver cirrhosis, 1 case of leukemia, 10 cases of inflammatory disease, 5 cases of other non-malignant diseases, and 6 cases of unknown causes. All of 3 cholangiocarcinomas were proved histopathologically.

On the other hand, the same survey was planned on 1,678 control persons who also were the war-wounded admitted in each of the Army Hospitals during the same period as thorotrast patients but not examined radiologically using contrast media. They were in the same conditions as the thorotrast group except for non-injection of thorotrast. That is, all of controls were Japanese male and were war-wounded, and had been injured between 1935 and 1943. At that time they were 20 to 35 years of age and were being admitted to the Army Hospitals. They were not injected thorotrast and not radiographed. Prognosis of controls was as follows: 1,209 or 72.01% lived in 1964 without need of medical treatment, 217 or 12.92% were died before 1963, and 252 or 15.01% were unknown of life or death. Among the 217 dead, there were 1 case of leukemia, 5 cases of liver cirrhosis, 8 cases of stomach cancer, 1 case of rectal cancer, 1 case of osteosarcoma, 2 cases of brain tumor, 144 cases of other nonmalignant diseases and 55 cases of unknown cause. No liver cancer was reported in controls.

Now, according to the proper statistical execution, unknown causes in the thorotrast group should be disregarded as liver cancers, and those in controls should be regarded as liver cancer cases. If a significant difference exits even by calculation in such a way between them, it can be concluded that thorotrast injection leads to later development of carcinoma of the liver. However, in this survey, there were 100 times cases of unknown cause in the control group as that of liver cancer cases. Therefore the proper statistical inference cannot be applied to this study, so that some presumptive considerations became necessary.

(A) The incidence of liver cancer in thorotrast and control group were compared each other under the condition of disregarding unknown cause of death.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Group</th>
<th>Thorotrast group</th>
<th>Control group</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignancies, total</td>
<td>4 ( 2.72%)</td>
<td>13 ( 0.77%)</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>Liver cancer</td>
<td>3 ( 2.05%)</td>
<td>0 ( 0.00%)</td>
<td>$X^2 = 22.56$</td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>1 ( 0.68%)</td>
<td>1 ( 0.06%)</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>2 ( 1.28%)</td>
<td>5 ( 0.30%)</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>Total surveyed</td>
<td>147 (100.00%)</td>
<td>1,678 (100.00%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n.s.: Not significant statistically.

**: Statistically significant at 1% level.
In other words, it was presumably regarded that there was no death of leukemia, liver cancer or liver cirrhosis among the dead of unknown cause in both groups. Under such an assumption, as is shown in Table I, all malignant diseases including leukemia tended to occur more frequently in thorotrast patients than in controls. However, the statistical test showed that only the rate of cholangiocarcinoma of the liver was higher in the thorotrast group with a statistically significant difference at the 1% level.

(B) A comparison of the composition of causes of death in both groups was made on the same assumption as (A). In A, the death rate between both groups was shown with the cases of the concerned disease divided by the whole number of cases surveyed, while in B, with the cases of the concerned disease divided by the number of the dead. Results are tabulated in Table II. The death rate from malignant diseases tended to be larger in the thorotrast group than in control, particularly the death rate from liver cancer (cholangiocarcinoma) in the thorotrast group was evidently higher than that in controls with a statistically significant difference at the 1% level.

(C) With the assumption that no particular statistical bias was present in unknown cause of death, cases of unknown cause in both groups were proportionally allotted to a known disease distribution. However, since in controls no liver cancer cases were reported, no allotment of liver cancer cases could be given to this group. If the rate of liver cancer was regarded as zero in controls, there might have been underestimated. Therefore we assumed the rate of liver cancer to be in the same level as the general Japanese males in 1951 (near the mid-age bet-

### Table II. Prospective Survey: Comparison of Distribution of Death Causes

<table>
<thead>
<tr>
<th>Causes of death</th>
<th>Thorotrast group</th>
<th>Control group</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignancies, total</td>
<td>4 (14.82%)</td>
<td>13 (5.99%)</td>
<td>$X^2 = 1.68$ n.s.</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>3 (11.11%)</td>
<td>0 (0.00%)</td>
<td>$X^2 = 16.12$ **</td>
</tr>
<tr>
<td>Leukemia</td>
<td>1 (3.70%)</td>
<td>1 (0.46%)</td>
<td>$X^2 = 0.40$ n.s.</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>2 (7.41%)</td>
<td>5 (2.30%)</td>
<td>$X^2 = 0.79$ n.s.</td>
</tr>
<tr>
<td>Others</td>
<td>15 (55.56%)</td>
<td>170 (78.34%)</td>
<td></td>
</tr>
<tr>
<td>Total died</td>
<td>27 (100.00%)</td>
<td>217 (100.00%)</td>
<td></td>
</tr>
</tbody>
</table>

n.s.: Not significant statistically.
** : Statistically significant at 1% level.
between a period of usage of thorotrast and the present), that is 8.84 per 10^5 (Vital statistics). The final data thus proportionally allotted are shown in Table III. If the final numbers of liver cancer in controls was considered to be 0, although a really calculated value was 0.15, liver cancer was concluded to occur more frequently in the thorotrast group than in controls with a statistically significant difference at the 1% level. However, the final numbers of liver cancer in controls was regarded as 1, no statistically significant difference was revealed.

(D) We compared the rate of liver cancer in the thorotrast group with that in the general Japanese males over 30 years of age in 1951 (Vital statistics), instead of use of the control group surveyed in this survey. The population of the general Japanese males over 30 years of age in 1951, the population of the thorotrast group (man-year), the real and expected numbers of death in each cause

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**Table III. Prospective Survey: Comparison of Distribution of Causes of Death (Unknown Cases Allotted Proportionally)**

<table>
<thead>
<tr>
<th></th>
<th>Thorotrast group</th>
<th>Controls</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignancies, total</td>
<td>4</td>
<td>16</td>
<td>*</td>
</tr>
<tr>
<td>Liver cancer</td>
<td>3</td>
<td>1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Leukemia</td>
<td>1</td>
<td>1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>2</td>
<td>6</td>
<td>n.s.</td>
</tr>
<tr>
<td>Others</td>
<td>18</td>
<td>235</td>
<td></td>
</tr>
<tr>
<td>Total death</td>
<td>28</td>
<td>259</td>
<td></td>
</tr>
<tr>
<td>Total surveyed</td>
<td>147</td>
<td>1,678</td>
<td></td>
</tr>
</tbody>
</table>

n.s.: Not significant statistically.

*: Statistically significant at 5% level.

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**Table IV. Prospective Survey: Comparison of Incidence of Diseases between Thorotrast Group and General Japanese Males**

<table>
<thead>
<tr>
<th></th>
<th>Thorotrast group</th>
<th>Japanese males over 30 years of age (1951)</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignancies, total</td>
<td>4(0.1237%)</td>
<td>34,387(0.2279%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Liver cancer</td>
<td>3(0.0928%)</td>
<td>3,633(0.0241%)</td>
<td>X^2=6.05</td>
</tr>
<tr>
<td>Leukemia</td>
<td>1(0.0309%)</td>
<td>306(0.0020%)</td>
<td>X^2=8.10</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>2(0.0618%)</td>
<td>3,203(0.0214%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Population</td>
<td>3,234 (man-years)</td>
<td>15,093,000</td>
<td></td>
</tr>
</tbody>
</table>

n.s.: Not significant statistically.

*: Statistically significant at 5% level.

†: Statistically significant at 1% level.
are tabulated in Table IV. The conformity test (Masuyama) indicated that the real composition of cause of death was much different from the expectancy with a statistically significant difference at the 1% level showing the chi-square value to be 18.98 (d.f. = 3). The factors which made the chi-square value increase were liver cancer and leukemia. Therefore the statistical test was given whether the surveyed numbers are to be within \( \pm 2\sigma \) or \( \pm 3\sigma \) of the expected numbers or not. That is, 3 liver cancers were being outside of \( np \pm 2\sqrt{np} \) but within the scope of \( np \pm 3\sqrt{np} \), and 1 leukemia was outside of the scope of \( np \pm 3\sqrt{np} \), where \( n \) is the surveyed numbers (man-year), \( p \) the expected death rate of the respective diseases. Results of these calculations indicated that the incidence of leukemia and liver cancer in the thorotrast-injected patients was significantly higher than that in the general Japanese males.

2. Retrospective survey

In this study the thorotrast maintaining rate in liver cancer patients and controls was surveyed and compared (Kitabatake et al.). Questionnaires were sent to 970 departments of the internal and surgical medicine in big hospitals in Japan having over 250 beds for inpatients. They were requested for answer to (1) number of patients with total malignant diseases, and (2) name, sex, age, histological diagnosis, and X-ray findings of the abdomen in patients with primary liver cancer diagnosed clinically from 1. Aug., 1962 to 31. July 1963. Two hundred and two departments (20.8%) have responded to this survey.

During a period of survey, 19, 517 patients with malignant tumor visited to 202 departments responded. Of 19, 517, 518 or 2.65% were primary liver cancer diagnosed clinically, of which 234 or 54.2% were histologically proved.

Now, in our country, thorotrast was used in patients mainly over 10 years of age and before 1935 (Takahashi et al.), therefore it is unlikely to be thorotrast-injected patients under 39 years of age at present. Therefore patients under 39 years of age were intentionally excluded from 518 cases collected for statistical analysis, consequently 466 cases of liver cancer were adopted as is shown in Table

<table>
<thead>
<tr>
<th>Sex</th>
<th>40-49</th>
<th>50-59</th>
<th>60-69</th>
<th>70-79</th>
<th>80-</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>51</td>
<td>130(3)</td>
<td>109</td>
<td>32</td>
<td>2</td>
<td>324(3)</td>
</tr>
<tr>
<td>Female</td>
<td>17(1)</td>
<td>50</td>
<td>58</td>
<td>16</td>
<td>1</td>
<td>142(1)</td>
</tr>
<tr>
<td>Total</td>
<td>68(1)</td>
<td>180</td>
<td>167</td>
<td>48</td>
<td>3</td>
<td>466(4)</td>
</tr>
</tbody>
</table>

(Values in the parenthesis indicate number of thorotrast maintaining persons.)
V. Of 466, 140 were hepatoma, 61 were cholangiocarcinoma, 1 was sarcoma (details unknown), and 264 were not proved histologically. There were 4 cases (0.85%) with thorotrast shadows in the hepatic and splenic region on the abdominal X-ray film. Histologically all of 4 cases were cholangiocarcinoma.

On the other hand, abdominal mass survey was carried out on 8,500 employees and their families over 40 years of age working in several kinds of companies in Aichi prefecture. The size of X-ray film used was 6×6 cm. Four films were taken per person; that is, the erect PA, erect oblique, prone, and supine projections. The thorotrast patients were detected by reading of radiograms, as thorotrast was imaged in the upper abdomen with characterized milliary shadow in the liver and spleen or with calcium-like shadow in the lymph nodes (Looney, Okinaka).\textsuperscript{10,11} Radiograms were interpreted by the diagnostic radiologists. In this mass survey, persons who were receiving at the time of examination any kinds of medical treatment were made an exception of survey. Before reading of X-ray films, just 3 times numbers of each column in Table V were randomly selected from 8,500, and made these selected persons to the control group for retrospective study. The reason, why 3 times numbers of liver cancer patients were selected from 8,500 persons as controls, was that there were only 7 males and 3 females over 80 years of age among 8,500 persons. These were the maximum numbers to select control correspondingly 3 times of liver cancer patients. Of 1,398 controls thus chosen, thorotrast shadows were seen over the lienohepatic region in 1 or 0.07%.

Comparison showed that the thorotrast maintaining rate was fairly higher in the liver cancer group than in controls (Table VI). According to the chi-square test,

| Table VI. Retrospective Survey: 2×2 Table for Statistical Analysis |
|-----------------------------|-----------------------------|-----------------------------|
|                             | Thorotrast (+) | Thorotrast (-) | Total            |
| Liver cancers               | 4              | 462            | 466              |
| Controls                    | 1              | 1,397          | 1,398            |
| Total                       | 5              | 1,859          | 1,864            |

after the Yate's correction, \(X^2=5.42\) (d.f. = 1) was given, which indicated the presence of statistical significant difference at the 5% level. However, since the thorotrast maintaining rate was very small particularly in controls as was already seen before, the chi-square value may become unexpectedly larger even after the Yates' correction. Therefore, if thorotrast maintained persons were assumed to be followed by a Poisson distribution with \(\mu=np\) as a mean of the population (Masuyama),\textsuperscript{7} hence

\[
\frac{\mu_2}{\mu_1} \leq F_{\frac{r_1+1}{2}} \quad \text{where, } n_1 \text{ number of the liver cancer group, } r_1 \text{ number of}
\]
thorotrast maintained persons in the liver cancer group, \( p_1 \) the thorotrast maintaining rate of the liver cancer group, \( n_1 \) number of controls, \( r_2 \) number of thorotrast maintained persons in controls, and \( p_2 \) the thorotrast maintaining rate of controls.

Therefore,

\[
\frac{p_1}{p_2} > \frac{r_1}{n_1 + 1} \cdot \frac{n_2}{n_1} \cdot \frac{1}{F} = 1.56
\]

Here,

\[
F_{11}^{11}(0.05) = 3.84
\]

Namely, \( p_1 \) is significantly higher than \( p_2 \) at the 5% level.

By the retrospective survey described in this section, an absolute risk could not be given as pointed out by the other authors. However, no cases of unknown prognosis were produced as seen in this study, so that the fact, that there was a positive relationship between an administration of thorotrast and consequent development of liver cancer, has been confirmed.

3. Analysis of autopsy data of thorotrast cases

Pathologists belonging to the university hospitals and to the other big hospitals in Japan were requested for reporting autopsy data of thorotrast patients (Miyakawa). Of 228 questionnaires sent to pathologists, 124 or 54.4% were responded. Thorotrast cases were reported in 29 replies, in which there were 38 autopsy cases of thorotrast deposition in the liver and spleen. Primary liver malignancy was seen in 21 of 38, and metastatic liver cancer in 1 case. Comparison of a disease distribution was made between 21 thorotrast cases collected in this survey and 100 primary liver malignancy patients recorded in “Japanese Autopsy Report 1962”. As is seen in Table VII, cholangiocarcinoma and endothelioma was much frequently seen in thorotrast patients than in general autopsy cases without thorotrast injection. On the contrary, hepatoma was rather decreased in the thorotrast maintained liver malignancy patients. The statistical test was conducted for analysis whether any significant difference was present or

<p>| Table VII. Autopsy Case Study: Distribution of Primary Liver Malignancies |
|---------------------------------|-------------------|-------------------|
| Thorotrast maintaining cases    | General autopsy cases |</p>
<table>
<thead>
<tr>
<th>Number</th>
<th>Expectancy</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatoma</td>
<td>5</td>
<td>18</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td>Endothelioma</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Others</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>27</td>
</tr>
</tbody>
</table>
not between the actual distribution of histopathological classification in thorotrast maintained liver malignancy patients and expectancy expected from general autopsy primary liver malignancy cases. Namely that is $X^2 = 35.5$ (d.f. = 3), which indicated that the conformity of the two was extremely disagreed. It is concluded that more frequent cholangiocarcinoma and endothelioma and less frequent hepatoma were seen among thorotrast maintained patients with primary liver malignancy, as compared with general autopsy cases of primary liver malignancy.

Next, the latent period, a period from injection of thorotrast to an onset of disease, and the purpose of injection of thorotrast was known in 9 of 14 cases of cholangiocarcinoma. The average latent period was 20.3 years in 3 patients with cholangiocarcinoma developed after injection of thorotrast for hepatolienography for which probably 60 to 75 cc of media were used, and was 25.0 years in 6 cholangiocarcinomas developed after angiography for which under 30 cc of thorotrast might have been used. Namely, the latent period tended to be smaller with an increase of volume of thorotrast given.

**DISCUSSION**

It is considered to be most pertinent to take a statistical or epidemiological method for a study on late radiation effects in the human beings, because of impossibility of experimental exposure in man, of a long latent period of late effects, and of very small incidence of disease (Faber; Berrett and McRae; Yakazu et al. Of epidemiological methods, a prospective study is believed to be most reliable and traditional, by which an absolute risk, that is, a dose-effect relationship in radiation effect could be estimated, if random sampling and selection of pertinent controls would be possible (Witts). For such reasons, we have conducted a prospective survey at first time.

In old days in our country as well as U.S.A and Europe, thorotrast had been widely practised as contrast medium for angiography or hepatolienography (Okinaka et al.; Yakazu et al.; Takahashi et al.). However many hospitals in Japan, in which clinical records were preserved, were burnt by the Second World War. Therefore it is generally very difficult to secure at present a certain size of samples of thorotrast injected patients. In 4 hospitals surveyed in this study, fortunately, all old clinical records have been preserved. We may not be able to get thorotrast population in the present Japan except for a group chosen in this paper.

Now, we could not give precise statistical conclusions in this prospective survey, because of too many cases of unknown death cause. This was produced not by a lack of or insufficient effort for a survey, but by change of address and missing of patients, annihilation of family, and a loss of clinical chart in hospitals due to war fire.
We could not treat, in this paper, a dose-effect relationship. This was due
to so small numbers as only 3 liver cancer cases in the thorotrast group in a
prospective study, and to the fact that the radiation dose contributed from depo-
sited thorotrast in the liver was theoretically much different ranging from 60
rad/year to $3 \times 10^4$ rad/year (Okajima).\(^1\)

Secondly, we have adopted a retrospective study, because a prospective
survey did not give us satisfactory results based on many unknown death cause
cases. According to this method, we could not get an absolute risk, but no
unknown cases were produced. Therefore statistical analysis can be conducted
without any assumptions.

We gave epidemiological considerations using insufficient number of
objects in both prospective and retrospective surveys. However, a further
larger samples of thorotrast patients will be unpromisingly obtained in Japan.

Recently Kaneda reported an experimental development of liver cirrhosis in
rabbits after intravenous injection of thorotrast (Kaneda and Kobayashi).\(^2\) Also
Mori reported thorotrast-induced spindle cells sarcoma in the subcutaneous tissue
of the face of hamster (Mori).\(^3\) These may support our conclusions of epide-
miological survey in this paper.

**CONCLUSIONS**

Three statistical studies were carried out in Japan on development of liver
cancer following injection of thorotrast.

1. **Prospective study:** Prognosis was surveyed for war-wounded patients
   injected thorotrast over 25 years ago for X-ray examination. Of 147 thorotrast
   injected patients, there were 3 cases of liver cancer (cholangiocarcinoma), 2 cases of
   liver cirrhosis, and 1 case of leukemia. On the other hand, there were 1 case of
   leukemia, 5 cases of liver cirrhosis, and no cases of liver cancer among 1,678
   controls. Statistical analysis showed that liver cancer occurred more frequently
   in the thorotrast group than in controls, and leukemia and liver cirrhosis also
tended to increase in the former group.

2. **Retrospective study:** The thorotrast maintaining rate was surveyed in
   liver cancer patients and in controls. Among 466 liver cancer patients over 40 years
   of age collected from big hospitals in Japan, 4 or 0.85% had thorotrast shadows in
   the hepatic region, while 1 or 0.07% showed the same shadows in 1,398 controls.
   Statistical test indicated that the thorotrast maintaining rate was evidently
   higher in liver cancer patients than in controls.

3. **Autopsy case study:** Thirty-eight autopsies of thorotrast maintained
   patients were reported by pathologists belonging to big hospitals in Japan. Of
   38, 21 were primary liver malignancy, in which 4 hepatomas (19%), 14 cholangio-
carcinomas (67%), and 3 endotheliomas (14%) were included. As compared with
   the distribution of cause of death of autopsied patients in general Japanese
population, cholangiocarcinoma and endothelioma was extremely frequent in autopsied thorotrast-injected patients with a statistically significant difference.

From these surveys the authors concluded that primary liver malignancy particularly cholangiocarcinoma tended to occur frequently in thorotrast injected persons.

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References

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20) Mori, T. ibid., in press.