

Site-Specific Cancer Incidence and Mortality after Cerebral Angiography with Radioactive Thorotrast

Lois B. Travis,^{a,1} Michael Hauptmann,^a Linda Knudson Gaul,^b Hans H. Storm,^c Marlene B. Goldman,^d Ullakarin Nyberg,^e Eric Berger,^f Murray L. Janower,^g Per Hall,^h Richard R. Monson,ⁱ Lars-Erik Holm,^j Charles E. Land,^a David Schottenfeld,^k John D. Boice, Jr.^l and Michael Andersson^m

^a Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, DHHS, Bethesda, Maryland 20892; ^b Austin, Texas; ^c Danish Cancer Society, 49 Strandboulevarden, DK 2100, Copenhagen, Denmark; ^d Harvard Medical School and Beth Israel Deaconess Medical Center, Boston, Massachusetts; ^e Radiumhemmet, Karolinska University Hospital, Stockholm, Sweden; ^f Information Management Services, Rockville, Maryland; ^g Worcester Medical Center, Worcester, Massachusetts; ^h Department of Medical Epidemiology, Karolinska Institute, Stockholm, Sweden; ⁱ Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts 02115; ^j Swedish Radiation Protection Authority, Stockholm, Sweden; ^k Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, Michigan; ^l International Epidemiology Institute, Rockville, Maryland and Vanderbilt University Medical Center, Nashville, Tennessee; and ^m Department of Oncology 5073, Rigshospitalet, DK 2100 Copenhagen, Denmark

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Few opportunities exist to evaluate the carcinogenic effects of long-term internal exposure to α -particle-emitting radionuclides. Patients injected with Thorotrast (thorium-232) during radiographic procedures, beginning in the 1930s, provide one such valuable opportunity. We evaluated site-specific cancer incidence and mortality among an international cohort of 3,042 patients injected during cerebral angiography with either Thorotrast ($n = 1,650$) or a nonradioactive agent ($n = 1,392$) and who survived 2 or more years. Standardized incidence ratios (SIR) for Thorotrast and comparison patients (Denmark and Sweden) were estimated and relative risks (RR), adjusted for population, age and sex, were generated with multivariate statistical modeling. For U.S. patients, comparable procedures were used to estimate standardized mortality ratios (SMR) and RR, representing the first evaluation of long-term, site-specific cancer mortality in this group. Compared with nonexposed patients, significantly increased risks in Thorotrast patients were observed for all incident cancers combined (RR = 3.4, 95% CI 2.9–4.1, $n = 480$, Denmark and Sweden) and for cancer mortality (RR = 4.0, 95% CI 2.5–6.7, $n = 114$, U.S.). Approximately 335 incident cancers were above expectation, with large excesses seen for cancers of the liver, bile ducts and gallbladder (55% or 185 excess cancers) and leukemias other than CLL (8% or 26 excess cancers). The RR of all incident cancers increased with time since angiography ($P < 0.001$) and was threefold at 40 or more years; significant excesses (SIR = 4.0) persisted for 50 years. Increasing cumulative dose of radiation was associated with an increasing risk of all incident cancers taken together and with cancers of the liver, gallbladder, and peritoneum and other digestive sites; simi-

lar findings were observed for U.S. cancer mortality. A marginally significant dose response was observed for the incidence of pancreas cancer ($P = 0.05$) but not for lung cancer. Our study confirms the relationship between Thorotrast and increased cancer incidence at sites of Thorotrast deposition and suggests a possible association with pancreas cancer. After injection with >20 ml Thorotrast, the cumulative excess risk of cancer incidence remained elevated for up to 50 years and approached 97%. Caution is needed in interpreting the excess risks observed for site-specific cancers, however, because of the potential bias associated with the selection of cohort participants, noncomparability with respect to the internal or external comparison groups, and confounding by indication. Nonetheless, the substantial risks associated with liver cancer and leukemia indicate that unique and prolonged exposure to α -particle-emitting Thorotrast increased carcinogenic risks. © 2003 by Radiation Research Society

INTRODUCTION

Between 2.5 and 10 million people worldwide have been exposed diagnostically to Thorotrast, a radiographic contrast agent used widely between 1928 and 1954 (1). Thorotrast is a colloidal solution of thorium oxide. Thorium-232 has a physical half-life of more than 10 billion years (2) and a decay chain including α -particle emitters. After intravascular injection, Thorotrast was not excreted to any meaningful extent from the body (3) but was sequestered in the reticuloendothelial system. About 60% of the Thorotrast load was deposited in the liver, 20% in the spleen, 12% in the red bone marrow, and 3% in the non-marrow bone, according to Kaul (4). The remaining 5% was deposited, in descending order of concentration, in the testes,

¹ Address for correspondence: National Cancer Institute, Executive Plaza South, Suite 7086, Bethesda, MD 20892; e-mail: travisl@mail.nih.gov.

TABLE 1
Demographic Characteristics of 3,042 Patients who Underwent Cerebral Angiography with or without Radioactive Thorotrast and Survived 2 or More Years

| | Denmark | | Sweden | | U.S. | | Total | |
|---|--------------|-----------------|-------------|------|-------------|------|--------------|-------|
| | No. (%) | PY ^a | No. (%) | PY | No. (%) | PY | No. (%) | PY |
| Number of patients | | | | | | | | |
| Thorotrast-exposed ^b | 773 (100.0) | 18249 | 431 (100.0) | 7231 | 446 (100.0) | 8740 | 1650 (100.0) | 34221 |
| Males | 428 (55.4) | 9584 | 242 (56.2) | 3649 | 230 (51.6) | 4127 | 900 (54.5) | 17360 |
| Females | 345 (44.6) | 8665 | 189 (43.9) | 3582 | 216 (48.4) | 4613 | 750 (45.5) | 16861 |
| Comparison group ^c | 1180 (100.0) | 29254 | 0 (0.0) | 0 | 212 (100.0) | 4951 | 1392 (100.0) | 34205 |
| Males | 559 (47.4) | 12966 | 0 (0.0) | 0 | 110 (51.9) | 2412 | 669 (48.1) | 15378 |
| Females | 621 (52.6) | 16288 | 0 (0.0) | 0 | 102 (48.1) | 2539 | 723 (51.9) | 18827 |
| Age at angiography (years) ^d | | | | | | | | |
| Thorotrast-exposed | | | | | | | | |
| <20 | 130 (16.8) | 4256 | 57 (13.2) | 1320 | 34 (7.6) | 1025 | 221 (13.4) | 6601 |
| 20–39 | 366 (47.4) | 9468 | 230 (53.4) | 4357 | 164 (36.8) | 4050 | 760 (46.1) | 17875 |
| 40–59 | 243 (31.4) | 4160 | 137 (31.8) | 1514 | 198 (44.4) | 3156 | 578 (35.0) | 8830 |
| ≥60 | 34 (4.4) | 365 | 7 (1.6) | 40 | 50 (11.2) | 510 | 91 (5.5) | 915 |
| Comparison group | | | | | | | | |
| <20 | 198 (16.8) | 6429 | 0 (0.0) | 0 | 22 (10.4) | 769 | 220 (15.8) | 7198 |
| 20–39 | 417 (35.3) | 12079 | 0 (0.0) | 0 | 75 (35.4) | 2263 | 492 (35.3) | 14342 |
| 40–59 | 467 (39.6) | 9709 | 0 (0.0) | 0 | 96 (45.3) | 1739 | 653 (40.4) | 11447 |
| ≥60 | 98 (8.3) | 1038 | 0 (0.0) | 0 | 19 (9.0) | 181 | 117 (8.4) | 1218 |
| Calendar years of injection | | | | | | | | |
| Thorotrast-exposed | | | | | | | | |
| 1932–1940 | 116 (15.0) | 2606 | 173 (40.1) | 2709 | 3 (0.7) | 43 | 292 (17.7) | 5358 |
| 1941–1950 | 657 (85.0) | 15643 | 258 (59.9) | 4523 | 365 (81.8) | 7593 | 1280 (77.6) | 27759 |
| 1951–1960 | 0 (0.0) | 0 | 0 (0.0) | 0 | 78 (17.5) | 1104 | 78 (4.7) | 1104 |
| Comparison group | | | | | | | | |
| 1932–1940 | 0 (0.0) | 0 | 0 (0.0) | 0 | 0 (0.0) | 0 | 0 (0.0) | 0 |
| 1941–1950 | 335 (28.4) | 8796 | 0 (0.0) | 0 | 144 (67.9) | 3149 | 478 (34.3) | 11944 |
| 1951–1960 | 845 (71.6) | 20459 | 0 (0.0) | 0 | 68 (32.1) | 1802 | 913 (65.6) | 22261 |
| Volume (ml) of Thorotrast injected ^e | | | | | | | | |
| 3–10 | 320 (41.4) | 8331 | 92 (21.4) | 1623 | 44 (9.9) | 1050 | 456 (27.6) | 11004 |
| 11–20 | 292 (37.8) | 6498 | 106 (24.6) | 1629 | 89 (20.0) | 1926 | 487 (29.5) | 10053 |
| 21–30 | 92 (11.9) | 1985 | 28 (6.5) | 333 | 145 (32.5) | 2789 | 265 (16.1) | 5107 |
| 31–40 | 38 (4.9) | 803 | 7 (1.6) | 102 | 79 (17.7) | 1407 | 124 (7.5) | 2313 |
| ≥40 | 27 (3.5) | 516 | 4 (0.9) | 23 | 22 (4.9) | 275 | 53 (3.2) | 814 |
| Unknown | 4 (0.5) | 118 | 194 (45.0) | 3521 | 67 (15.0) | 1292 | 265 (16.1) | 4931 |
| Known, without extravasation | 717 (92.8) | 16847 | 232 (53.8) | 3635 | 379 (85.0) | 7448 | 1328 (80.5) | 27930 |
| Survival after angiography (years) ^f | | | | | | | | |
| Thorotrast-exposed | | | | | | | | |
| 2–9 | 773 (100.0) | 5376 | 431 (100.0) | 0 | 446 (100.0) | 3076 | 1650 (100.0) | 8452 |
| 10–19 | 652 (84.3) | 5776 | 431 (100.0) | 1184 | 341 (76.5) | 2892 | 1424 (86.3) | 9852 |
| 20–29 | 506 (65.5) | 4177 | 391 (90.7) | 3083 | 232 (52.0) | 1726 | 1129 (68.4) | 7034 |
| 30–39 | 317 (41.0) | 2233 | 264 (61.3) | 1992 | 125 (28.0) | 865 | 706 (42.8) | 3386 |
| 40–49 | 148 (19.2) | 686 | 159 (36.9) | 972 | 46 (10.3) | 181 | 353 (21.4) | 1838 |
| 50+ | 12 (1.5) | 19 | 31 (7.2) | 124 | 1 (0.2) | 0.2 | 44 (2.6) | 143 |
| Comparison group ^g | | | | | | | | |
| 2–9 | 1180 (100.0) | 8606 | 0 (0.0) | 0 | 212 (100.0) | 1522 | 1392 (100.0) | 10129 |
| 10–19 | 991 (84.0) | 8975 | 0 (0.0) | 0 | 171 (80.7) | 1522 | 1162 (83.5) | 10497 |
| 20–29 | 806 (68.3) | 7036 | 0 (0.0) | 0 | 134 (63.2) | 1060 | 940 (67.5) | 8096 |
| 30–39 | 606 (51.4) | 4207 | 0 (0.0) | 0 | 89 (42.0) | 687 | 695 (49.9) | 4895 |
| 40+ | 181 (15.3) | 409 | 0 (0.0) | 0 | 55 (25.9) | 159 | 236 (17.0) | 568 |

Note. PY, person-years.

^a Refers to number of person-years of observation for the designated category.

^b Patients underwent cerebral angiography with Thorotrast and survived 2 or more years.

^c Patients underwent cerebral angiography with a non-radioactive contrast agent and survived 2 or more years.

^d Maximum age at time of cerebral angiography was 79.2 and 79.1 years, respectively, for the Thorotrast-exposed and nonexposed patients.

^e The smallest volume injected was 3 ml. The median (range) volume of administered Thorotrast for patients in age categories <20, 20–39, 40–59

TABLE 2
Site-Specific Cancer Incidence among Thorotrast-Exposed and Nonexposed Patients in Denmark and Sweden

| Site | Thorotrast-exposed ^d | | Comparison group ^b | | RR ^c | 95% CI |
|--|---------------------------------|--------------------|-------------------------------|----------------------|-------------------|------------|
| | Observed | SIR | Observed | SIR | | |
| All cancer | 480 | 3.3 ^d | 196 | 1.0 | 3.4 ^d | 2.9–4.1 |
| Males | 239 | 3.2 ^d | 78 | 1.0 | 3.6 ^d | 2.8–4.8 |
| Females | 241 | 3.4 ^d | 118 | 1.1 | 3.3 ^d | 2.6–4.2 |
| All cancer except brain and nervous system | 455 | 3.2 ^d | 188 | 1.0 | 3.5 ^d | 2.9–4.2 |
| Oral cavity | 3 | 0.9 | 7 | 1.8 | 0.4 | 0.1–2.1 |
| Pharynx | 2 | 2.9 | 1 | 1.4 | 2.2 | 0.1–123.2 |
| Stomach | 13 | 1.2 | 6 | 0.5 | 2.7 ^d | 1.1–7.9 |
| Small intestine | 5 | 10.1 ^d | 1 | 1.9 | 8.1 | 0.6–250.7 |
| Colon | 16 | 1.5 | 16 | 1.0 | 1.5 | 0.7–3.0 |
| Rectum | 8 | 1.0 | 7 | 0.7 | 1.8 | 0.6–5.3 |
| Liver, primary | 136 | 108.9 ^d | 0 | 0 (1.5) ^g | Inf. ^d | 44.2–Inf. |
| Liver, not specified as primary | 22 | 33.0 ^d | 0 | 0 (1.0) ^g | Inf. ^d | 8.2–Inf. |
| Bile ducts | 17 | 17.1 ^d | 1 | 0.6 | 26.4 ^d | 4.3–1133.9 |
| Gallbladder | 10 | 9.9 ^d | 1 | 1.1 | 11.0 ^d | 1.3–391.0 |
| Pancreas | 11 | 2.4 ^d | 5 | 0.8 | 3.8 ^d | 1.3–12.3 |
| Peritoneum, other digestive | 5 | 14.6 ^d | 0 | 0 (0.6) ^g | Inf. ^d | 1.7–Inf. |
| Lung, primary; trachea | 28 | 2.1 ^d | 26 | 1.3 | 1.3 | 0.7–2.2 |
| Female breast | 27 | 1.7 ^d | 26 | 1.2 | 1.6 | 0.9–2.8 |
| All female genital | 22 | 1.4 | 24 | 1.1 | 1.1 | 0.6–2.1 |
| Uterine cervix | 6 | 1.0 | 9 | 1.1 | 0.6 | 0.2–1.8 |
| Uterine corpus | 5 | 1.1 | 10 | 1.6 | 0.6 | 0.2–1.8 |
| Ovary, tube, broad ligament | 9 | 2.0 | 3 | 0.5 | 4.3 ^d | 1.1–24.3 |
| All male genital | 17 | 1.5 | 5 | 0.5 | 4.7 ^d | 1.8–15.0 |
| Prostate | 14 | 1.4 | 4 | 0.5 | 4.5 ^d | 1.6–16.3 |
| Testis | 2 | 3.2 | 1 | 1.1 | 5.2 | 0.2–164.8 |
| Kidney | 12 | 2.7 ^d | 4 | 0.8 | 5.7 ^d | 1.9–21.0 |
| Urinary bladder | 8 | 1.2 | 14 | 1.5 | 0.8 | 0.3–1.9 |
| Melanoma, skin | 2 | 1.0 | 7 | 2.4 | 0.4 | 0.1–2.1 |
| Other skin cancer | 14 | 1.5 | 17 | 0.9 | 1.3 | 0.6–2.8 |
| Metastases ^e | 11 | 8.3 ^d | 1 | 0.4 | 12.2 ^d | 3.3–989.7 |
| Non-Hodgkin's lymphoma | 4 | 1.5 | 3 | 0.9 | 1.6 | 0.3–11.4 |
| Hodgkin's disease | 1 | 1.0 | 1 | 1.0 | 1.5 | 0.1–81.8 |
| Multiple myeloma | 5 | 2.9 | 2 | 1.0 | 3.7 | 0.5–30.9 |
| CLL | 6 | 3.7 ^d | 1 | 0.5 | 9.3 | 0.9–356.6 |
| Leukemia, all non-CLL | 28 | 15.2 ^d | 2 | 0.9 | 15.2 ^d | 4.4–149.6 |
| Other and unspecified | 10 | 3.9 ^d | 2 | 1.0 | 6.1 | 0.8–35.6 |
| Thorotrast-related cancers ^f | 191 | 37.5 ^d | 4 | 0.6 | 76.2 ^d | 32.2–247.8 |

Notes. CI, confidence interval; CLL, chronic lymphocytic leukemia; RR, relative risk; SIR, standardized incidence ratio; Inf., infinite.

^a Includes 1204 patients who underwent cerebral angiography with Thorotrast and survived 2 or more years. This group includes patients from Denmark and Sweden.

^b Includes 1180 patients who underwent cerebral angiography with a nonradioactive contrast agent and survived 2 or more years. This group includes patients from Denmark.

^c Relative risk of Thorotrast-exposed compared to nonexposed patients, adjusted for age, calendar time, and sex.

^d $P < 0.05$.

^e These data were available only for Danish patients.

^f Thorotrast-related cancers: non-CLL and primary cancers of the liver, gallbladder and bile ducts.

^g Expected number of cases in parentheses.

←

and 60+ years was similar: 12 ml (12–12 ml), 15 ml (8–80 ml), 20 ml (7–60 ml), and 16 ml (3–70 ml), respectively, in Sweden and Denmark combined, and 15 ml (10–20 ml), 30 ml (6–48 ml), 30 ml (8–66 ml), and 28 ml (4–92 ml) in the U.S.

^f Number indicates patients who were alive at the beginning of the indicated interval. Survival is measured in terms of time since cerebral angiography.

^g Patients in the comparison group could not have survived 50 or more years from the date of arteriography, given that the earliest date of arteriography was 1944, and study follow-up ended in 1992 (Denmark, U.S.) or 1993 (Sweden).

TABLE 3
Site-Specific Cancer Mortality among Thorotrast-Exposed and Nonexposed Patients in the U.S.

| Site | Thorotrast-exposed ^a | | Comparison group ^b | | RR ^c | 95% CI |
|--|---------------------------------|-------------------|-------------------------------|----------------------|-------------------|-----------|
| | Observed | SMR | Observed | SMR | | |
| All cancer | 114 | 3.8 ^d | 24 | 1.4 | 4.0 ^d | 2.5–6.7 |
| Males | 56 | 3.6 ^d | 13 | 1.4 | 3.9 ^d | 2.0–8.2 |
| Females | 58 | 4.0 ^d | 11 | 1.3 | 4.1 ^d | 2.1–8.7 |
| All cancer except brain and nervous system | 93 | 3.1 ^d | 18 | 1.0 | 5.3 ^d | 3.1–9.7 |
| Buccal cavity and pharynx | 4 | 5.9 ^d | 0 | 0 (0.4) ^g | Inf. | 0.4–Inf. |
| All digestive organs and peritoneum | 32 | 3.4 ^d | 4 | 0.8 | 8.9 ^d | 3.0–38.1 |
| Large intestine | 5 | 1.5 | 0 | 0 (2.0) ^g | Inf. | 0.5–Inf. |
| Liver | 22 | 25.1 ^d | 1 | 2.2 | 22.5 ^d | 1.8–464.3 |
| Pancreas | 3 | 1.9 | 3 | 3.2 | 0.9 | 0.1–4.4 |
| Respiratory system, all | 12 | 2.0 ^d | 4 | 1.0 | 2.7 | 0.8–11.0 |
| Lung | 11 | 2.0 | 3 | 0.8 | 3.3 | 0.7–13.7 |
| Bone | 2 | 13.9 ^d | 0 | 0 (0.1) ^g | Inf. | 0.1–Inf. |
| Female breast | 6 | 2.1 | 3 | 1.8 | 0.9 | 0.3–7.2 |
| Prostate | 1 | 0.7 | 2 | 2.6 | 0.2 | 0.0–5.1 |
| Bladder | 3 | 3.7 | 0 | 0 (0.5) ^g | Inf. | 0.2–Inf. |
| Kidney | 1 | 1.7 | 0 | 0 (0.4) ^g | Inf. | 0.1–Inf. |
| Brain and other central nervous system | 21 | 33.6 ^d | 6 | 15.6 ^d | 1.3 | 0.6–3.7 |
| Multiple myeloma | 1 | 2.6 | 1 | 4.1 | 1.8 | 0.1–51.6 |
| All lymphopoietic cancer ^e | 13 | 5.0 ^d | 2 | 1.2 | 9.8 | 0.9–37.0 |
| Lymphosarcoma and reticulosarcoma | 2 | 3.6 | 0 | 0 (0.3) ^g | Inf. | 0.1–Inf. |
| Hodgkin's disease | 1 | 4.2 | 0 | 0 (0.1) ^g | Inf. | 0.0–Inf. |
| Leukemia | 8 | 7.3 ^d | 1 | 1.5 | 16.8 | 0.6–211.7 |
| Thorotrast-related cancers ^f | 30 | 15.3 ^d | 2 | 1.8 | 20.1 ^d | 2.2–73.4 |

Notes. CI, confidence interval; RR, relative risk; SMR, standardized mortality ratio; Inf., infinite.

^a Includes 439 patients who underwent cerebral angiography with Thorotrast and survived 2 or more years and had a known cause of death.

^b Includes 207 patients who underwent cerebral angiography with a nonradioactive contrast agent and survived 2 or more years and had a known cause of death.

^c Relative risk of Thorotrast-exposed compared with nonexposed patients, adjusted for age, calendar time, and sex.

^d $P < 0.05$.

^e Includes lymphosarcoma and reticulosarcoma, Hodgkin's disease, leukemia and cancer of other lymphatic tissue.

^f Thorotrast-related cancers: liver cancer and leukemia.

^g Expected number of cases in parentheses.

adrenal glands, gallbladder, lung, pancreas, small intestine, kidney, thyroid and stomach (5). Given the long biological half-life (400 years) (6) of Thorotrast, patients received life-long irradiation with α particles from thorium decay products, concentrated at the sites of localization. In addition, the decay product radon-220 is translocated via the blood stream from tissue deposits to the lungs, where further decay and irradiation occur before exhalation. Other decay products of thorium-232 include radium-224 and radium-228, which preferentially translocate into the skeletal system (7).

Interest in the carcinogenic effects of Thorotrast extends beyond concern for the millions of injected patients, since it provides a valuable opportunity to examine the effects of prolonged exposure to internally deposited α -particle emitters. Occupational and environmental sources of internally deposited radionuclides include naturally occurring radon gas, dietary sources, fallout from nuclear weapons testing in years past, and contamination from nuclear reactor accidents (8). In addition, there is ongoing concern about the possible effects of radiation on persons who live in geographic areas proximal to nuclear facilities or milling and

mining activities. There are a considerably larger number of epidemiological studies of populations exposed to external sources of ionizing radiation than of those exposed to internally deposited radionuclides. Although the tissue distribution of α -particle-emitting radionuclides may vary depending on chemical properties and solubility, comparable risks can be estimated based on the radiation doses received by specific organs. Moreover, comparisons with other human surveys can provide data on the relative biological effectiveness of α particles contrasted with γ or X rays in causing specific cancers (9). Thorotrast-exposed patients also have been effectively studied in several other countries, including Germany (10), Portugal (11) and Japan (12, 13).

To provide new information on long-term trends in site-specific cancer incidence and mortality related to chronic radiation exposure, we conducted an international study of over 3,000 patients who survived 2 or more years after injection with either Thorotrast or a nonradioactive contrast agent during cerebral angiography. We chose only cerebral angiography patients to minimize the confounding effect of indication(s) for Thorotrast administration, which frequent-

TABLE 4
Site-Specific Cancer Incidence in Relation to Time since Injection among Thorotrast-Exposed and Nonexposed Patients in Denmark and Sweden (with Relative Risks for the Thorotrast Group) by Follow-up Period^a

| | Follow-up period (years) | | | | | <i>P</i> value for trend ^b |
|---|-----------------------------|-------------------------------|-------------------------------|----------------------------------|------------------------------|---------------------------------------|
| | 2–9 | 10–19 | 20–29 | 30–39 | 40+ | |
| Number of patients | | | | | | |
| Thorotrast | 1204 | 1083 | 897 | 581 | 264 | |
| Comparison group | 1180 | 991 | 806 | 606 | 181 | |
| Person-years | | | | | | |
| Thorotrast | 5375 | 6959 | 7259 | 4225 | 1657 | |
| Comparison group | 8606 | 8975 | 7036 | 4207 | 409 | |
| Site | Observed | Observed | Observed | Observed | Observed | |
| All cancer | | | | | | |
| Thorotrast | 23 | 49 | 120 | 184 | 104 | |
| Comparison group | 11 | 45 | 83 | 50 | 7 | |
| Relative risk (95% CI) | 4.9 ^d (1.8–12.9) | 2.2 ^d (1.3–3.6) | 2.1 ^d (1.4–2.9) | 5.0 ^d (3.4–7.4) | 3.1 ^d (1.4–6.8) | <0.001 |
| All cancer except brain and nervous system | | | | | | |
| Thorotrast | 14 | 42 | 114 | 181 | 104 | |
| Comparison group | 8 | 45 | 78 | 50 | 7 | |
| Relative risk (95% CI) | 7.1 ^d (2.3–22.1) | 2.0 ^d (1.2–3.4) | 2.2 ^d (1.5–3.2) | 4.9 ^d (3.3–7.3) | 3.1 ^d (1.4–6.8) | <0.001 |
| Stomach | | | | | | |
| Thorotrast | 1 | 2 | 1 | 7 | 2 | |
| Comparison group | 1 | 2 | 2 | 1 | 0 | |
| Relative risk (95% CI) | 35.4 (0.0–126.7) | 1.5 (0.1–16.5) | 1.7 (0.0–7.9) | 6.3 (0.8–270.9) | Inf. (0.0–Inf.) | 0.07 |
| Liver, primary | | | | | | |
| Thorotrast | 0 | 2 | 24 | 69 | 41 | |
| Comparison group | 0 | 0 | 0 | 0 | 0 | |
| Relative risk (95% CI) | — (—) | Inf. (0.5–Inf.) | Inf. ^d (9.4–Inf.) | Inf. ^d (22.2–Inf.) | Inf. ^d (2.4–Inf.) | <0.001 |
| Bile ducts | | | | | | |
| Thorotrast | 0 | 0 | 2 | 11 | 4 | |
| Comparison group | 0 | 0 | 0 | 1 | 0 | |
| Relative risk (95% CI) | — (—) | — (—) | Inf. (0.3–Inf.) | 36.2 ^d (1.8–539.0) | Inf. (0.2–Inf.) | 0.002 |
| Gallbladder | | | | | | |
| Thorotrast | 0 | 0 | 5 | 3 | 2 | |
| Comparison group | 0 | 1 | 0 | 0 | 0 | |
| Relative risk (95% CI) | — (—) | 0.0 (0.0–94.8) | Inf. ^d (1.5–Inf.) | Inf. (0.5–Inf.) | Inf. (0.1–Inf.) | 0.27 |
| Pancreas | | | | | | |
| Thorotrast | 0 | 0 | 1 | 7 | 3 | |
| Comparison group | 0 | 1 | 4 | 0 | 0 | |
| Relative risk (95% CI) | — (—) | 0.0 (0.0–76.0) | 0.2 (0.0–3.3) | Inf. ^d (1.6–Inf.) | Inf. (0.1–Inf.) | 0.07 |
| Kidney | | | | | | |
| Thorotrast | 0 | 1 | 2 | 5 | 4 | |
| Comparison group | 0 | 1 | 2 | 1 | 0 | |
| Relative risk (95% CI) | — (—) | 11.4 (0.0–147.8) | 9.7 (0.1–16.9) | 24.2 (0.6–253.0) | Inf. (0.2–Inf.) | <0.001 |
| Thorotrast-related cancers | | | | | | |
| Thorotrast | 2 | 7 | 40 | 93 | 49 | |
| Comparison group | 0 | 1 | 2 | 1 | 0 | |
| Relative risk (95% CI) | Inf. (0.5–Inf.) | 21.3 ^d (1.8–617.7) | 33.5 ^d (7.5–246.2) | 135.2 ^d (19.8–4507.9) | Inf. ^d (3.0–Inf.) | <0.001 |

Note. Inf., infinite.

^a The table is limited to specific sites for which 10 or more cancers occurred in the Thorotrast-exposed group and for which significantly increased relative risks were observed in Table 2. Fewer subjects in the comparison group have long follow-up because their angiographies were performed later, when Thorotrast was gradually replaced by non-radioactive agents.

^b *P* value for temporal trend in relative risk based on continuous follow-up time among exposed patients.

^c Relative risk of indicated outcome for Thorotrast-exposed patients compared with nonexposed patients, adjusted for age, sex and calendar year.

^d *P* < 0.05.

^e Thorotrast-related cancers: non-CLL and primary cancers of the liver, gallbladder and bile ducts.

TABLE 5
Site-Specific Cancer Incidence and Relative Risk (RR) in Relation to a Surrogate Measure of Cumulative Radiation Dose among Thorotrast-Exposed and Nonexposed Patients in Denmark and Sweden^a

| Site | Estimated cumulative radiation dose in ml-years (ml of injected Thorotrast × max [0, years since injection-5] × 10 ²) | | | | | |
|--|--|-------------------|-------------|----------|-------------------|-------------|
| | 0-29 | | | 30-49 | | |
| | Observed | RR | (95% CI) | Observed | RR | (95% CI) |
| All cancer | 122 | 2.5 ^c | (1.9-3.2) | 105 | 3.1 ^c | (2.4-3.9) |
| All cancer except brain and nervous system | 110 | 2.5 ^c | (2.0-3.3) | 102 | 3.1 ^c | (2.4-3.9) |
| Stomach | 6 | 4.1 ^c | (1.1-15.2) | 3 | 2.3 | (0.5-13.2) |
| Liver, primary | 10 | Inf. ^c | (9.2-Inf.) | 30 | Inf. ^c | (40.8-Inf.) |
| Bile ducts | 2 | 15.8 | (0.4-398.7) | 3 | 18.5 ^c | (1.5-988.0) |
| Gallbladder | 0 | 0.0 | (0.0-176.6) | 2 | 10.3 | (0.7-756.1) |
| Pancreas | 1 | 1.4 | (0.0-6.3) | 0 | 0.0 | (0.0-6.1) |
| Peritoneum, other digestive | 0 | (—) | (—) | 1 | Inf. | (0.2-Inf.) |
| Lung, primary; trachea | 10 | 1.6 | (0.7-3.4) | 8 | 1.3 | (0.5-2.7) |
| Kidney | 1 | 2.7 | (0.0-8.5) | 6 | 10.9 ^c | (3.0-44.2) |
| Multiple myeloma | 2 | 5.9 | (0.3-48.7) | 2 | 5.5 | (0.4-77.0) |
| Leukemia, all non-CLL | 11 | 16.1 ^c | (3.9-165.5) | 9 | 28.1 ^c | (5.7-263.8) |
| Thorotrast-related cancers ^d | 23 | 30.7 ^c | (11.4-107) | 44 | 68.9 ^c | (27.7-230) |

Notes. CI, confidence interval; CLL, chronic lymphocytic leukemia; Inf., infinite.

^a Results in table are limited to 1180 non-exposed patients and 949 Thorotrast-exposed patients for whom the administered amount of Thorotrast was known and who did not have Thorotrastomas recorded.

^b *P* value for trend in relative risk based on continuous cumulative radiation dose among exposed patients; parentheses indicate negative trend.

^c *P* < 0.05.

^d Thorotrast-related cancers: non-CLL and primary cancers of the liver, gallbladder and bile ducts.

ly included hepatosplenic disorders. The considerable number of study patients, including 589 40-year survivors, facilitates characterization of lifetime temporal and site-specific cancer risks. We also report for the first time the long-term results of site-specific cancer mortality among U.S. patients.

PATIENTS AND METHODS

Study Subjects and Follow-up

Patient cohorts who underwent cerebral arteriography with either Thorotrast or a nonradioactive contrast agent between January 1, 1935 and December 31, 1963 were identified in Denmark, Sweden and the United States. Methods used for patient selection and follow-up have been described elsewhere (14-19) and were summarized recently by Travis *et al.* (20). The study was exempted from institutional review board review since it used only existing anonymized data. The underlying cohort consisted of patients who underwent cerebral arteriography with Thorotrast because of symptoms and signs suggestive of cerebral disorders at two medical centers in Denmark during 1935-1947, one hospital in Sweden (1932-1950), and three centers in the United States (1936-1955). In addition, comparison groups of patients who underwent cerebral arteriography with nonradioactive contrast agents were identified in Denmark and the United States. At the Swedish study hospital (the Serafimer Institute, which contained the only operational neurosurgical department in the country at that time), all neurosurgical patients who underwent cerebral arteriography were imaged with Thorotrast; thus a nonexposed comparison group was not available.

Eligibility criteria for the present study cohort included survival for 24 or more months after angiography. The 2-year survival criterion was selected to minimize any effect of mortality related to the underlying disorder for which angiography was performed and to permit a sufficient latent period for the manifestation of radiation-related effects. Registry-based patient follow-up began 2 years after arteriography, or at the time

of establishment of the cancer registry in Denmark (January 1, 1943) and Sweden (January 1, 1958) if that occurred later, and ended at the earliest of the following dates: emigration (Denmark and Sweden), death (all sites) or end of study (all sites). Study end date was January 20, 1992 in Denmark, December 31, 1992 in the U.S., and December 31, 1993 in Sweden. Patients in Denmark and Sweden were followed with regard to vital status and cancer by linkage to the national cancer registry. Both countries have compulsory cancer registration procedures that require physicians to report all newly detected cancers, including any occurring in patients with a prior cancer and those diagnosed at autopsy. It is estimated that case ascertainment in the Danish and Swedish Cancer Registries is more than 95% complete (21). Multiple primary cancers in a Danish or Swedish patient were counted as separate events. Incident cancers in Danish and Swedish patients were initially classified and coded according to each country's version of the International Classification of Diseases (ICD), 6th-9th revisions (ICD-6-9). Coding classifications in Denmark and Sweden were adapted to the local version of ICD-7.

In the U.S., patients were followed by linkage with the National Death Index and a search of the records of the Department of Vital Statistics in Massachusetts or the office of the State Registrar and Center for Health Statistics at the Michigan Department of Public Health. Information with regard to cause of death was abstracted from death certificates obtained from states. Cause-of-death coding was performed as outlined previously (20). Only the cancer site coded as the cause of death was counted for the U.S. patients. Application of the date of cancer registry establishment, 2-year survival, residence and other exclusion criteria resulted in a decrease in the Thorotrast-exposed cohorts from 1,095 to 773 in Denmark, 1,117 to 431 in Sweden, and 723 to 446 in the U.S.; the comparison groups were reduced from 1,480 to 1,180 in Denmark and 315 to 212 in the U.S.

Data Collection

Abstracted data included date of birth, sex, date of angiography, injection site, contrast agent, presence of tissue extravasation, and injected volume. Injected volume was used as a surrogate for radiation activity,

TABLE 5
Extended

| Estimated cumulative radiation dose in ml-years (ml of injected Thorotrast \times max [0, years since injection-5] $\times 10^2$) | | | | | | | <i>P</i> value for trend |
|---|--------------------|--------------|----------|--------------------|--------------|---------|-----------------------------|
| 50-69 | | | 70+ | | | | |
| Observed | RR | (95% CI) | Observed | RR | (95% CI) | | |
| 78 | 5.5 ^c | (4.2-7.2) | 70 | 7.6 ^c | (5.7-10.0) | <0.001 | |
| 76 | 5.5 ^c | (4.2-7.3) | 69 | 7.6 ^c | (5.7-10.1) | <0.001 | |
| 0 | 0.0 | (0.0-13.5) | 2 | 7.2 | (0.9-50.6) | 0.997 | |
| 36 | Inf. ^c | (123.9-Inf.) | 34 | Inf. ^c | (169.8-Inf.) | <0.001 | |
| 4 | 50.5 ^c | (6.1-3039.8) | 1 | 14.5 | (0.3-1865.2) | 0.58 | |
| 3 | 38.0 ^c | (3.7-2438.0) | 2 | 33.8 ^c | (2.4-2696.2) | 0.03 | |
| 3 | 9.6 ^c | (1.3-43.7) | 2 | 8.5 | (0.8-52.2) | 0.05 | |
| 0 | (—) | (—) | 3 | Inf. ^c | (11.7-Inf.) | 0.01 | |
| 3 | 1.5 | (0.3-4.6) | 2 | 1.3 | (0.2-5.5) | 0.44 | |
| 1 | 4.4 | (0.1-34.9) | 0 | 0.0 | (0.0-32.1) | (0.23) | |
| 0 | 0.0 | (0.0-76.0) | 1 | 11.1 | (0.2-202.7) | (0.998) | |
| 2 | 11.5 ^c | (1.2-219.1) | 2 | 25.1 ^c | (1.7-331.7) | 0.31 | |
| 45 | 154.4 ^c | (61.6-518) | 39 | 217.9 ^c | (86.6-732) | <0.001 | |

in accordance with methods implemented in prior reports (10-12, 17-20, 22). The actual volume of administered Thorotrast was known for 79% ($n = 949$) of patients in the combined Danish and Swedish cohort and 85% ($n = 379$) of U.S. patients. For 32% ($n = 247$) of the Danish patients, the total Thorotrast volume was estimated using the injected number of unit doses (10 ml) and clinical data, including the number of radiographic views obtained (22); the total volume of injected Thorotrast was considered to have been administered on the date of first arteriography if a patient had the procedure done more than once, since multiple injections were usually administered within a few days of each other and at a maximum within a few weeks. The development of Thorotrastomas (granulomas resulting from extravasation at the injection site) was documented in 57 (4.7%) of the patients in the combined Danish and Swedish cohort and 1 (<0.1%) U.S. patient. These subjects were excluded from dose-response analyses.

Statistical Methods

Person-years of observation were calculated according to sex, country, age (5-year intervals) and calendar year (5-year intervals). The standardized incidence ratio (SIR) for Danish and Swedish patients, or standardized mortality ratio (SMR) for U.S. patients, for each cancer site category was calculated as the ratio of observed to expected cases in the general population. The SIR was estimated for Danish and Swedish patients, since national cancer incidence statistics were available, and the SMR for U.S. patients, since cancer mortality was evaluated. The observed numbers were assumed to follow a Poisson distribution; two-sided 95% confidence intervals were calculated for each SIR and SMR (23, 24). To investigate the variation in risk between Thorotrast and comparison patients, relative risks were also calculated using Poisson regression (25); models were loglinear and were stratified by sex, country, age and calendar year. Thorotrast effects were evaluated as exposed compared to nonexposed and as categories of the following exposure variables: Thorotrast volume injected, time since injection, and a surrogate for radiation dose (injected volume of Thorotrast multiplied by the time since injection, lagged 5 years [ml injected \times max [0, years since injection - 5] $\times 10^2$) (20). Likelihood-based 95% confidence intervals were used; however, when the number of cases in a group or in the corresponding reference category was less than 4, exact confidence intervals were calculated (25). Tests of trend were based on the estimated slope for each continuous exposure variable in a loglinear model restricted to Thorotrast subjects. Cumulative incidence and mortality (1 - cumulative survival to diagnosis or death, respectively) were calculated by the Kaplan-Meier method (26). EPI-

CURE software was used for Poisson regression and Kaplan-Meier calculations (27).

RESULTS

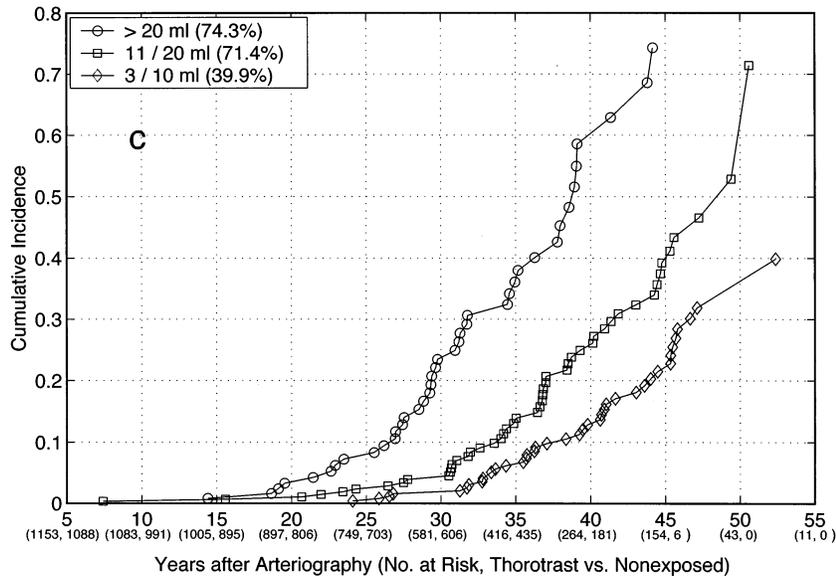
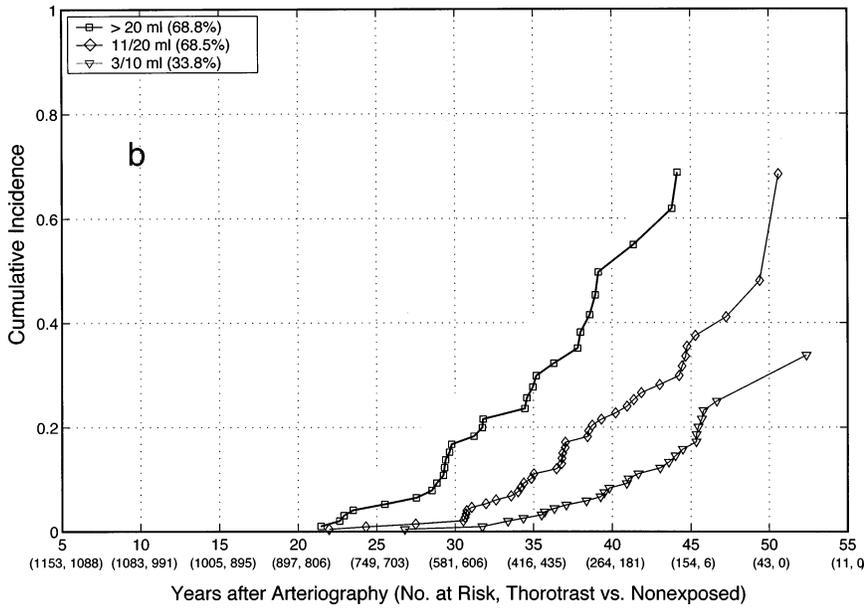
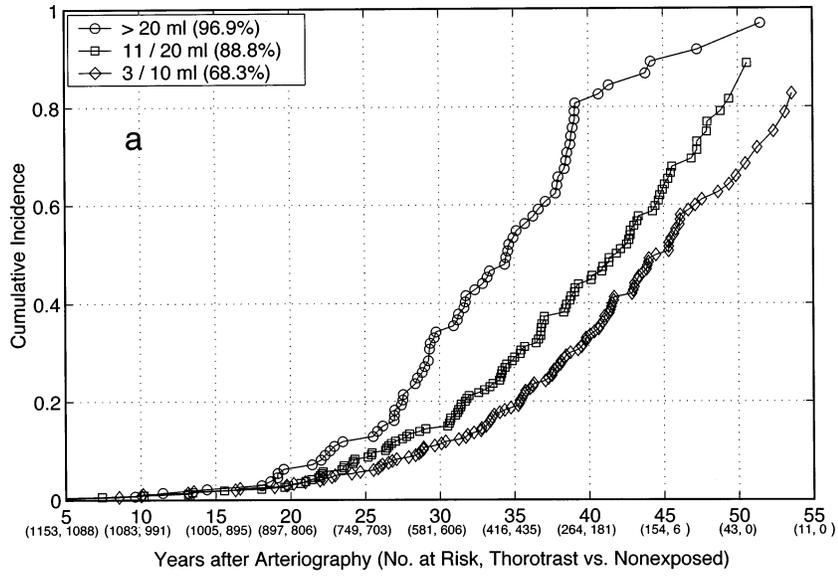
Patient Characteristics and Survival after Arteriography

The final cohort for the present study included 1650 Thorotrast patients and 1392 comparison subjects who survived 2 or more years after angiography (Table 1). Overall, approximately 46% and 52%, respectively, of the Thorotrast and comparison cohorts were female. Patient age at the time of arteriography was similar for Thorotrast (mean = 36.4 years, range 0.5-79.1 years) and comparison (mean = 38.1 years, range 0.4-79.2 years) subjects. Of all patients, 2069, 1401, 589 and 44 were followed for at least 20, 30, 40 and 50 years, respectively. At the end of follow-up, 51 (3.1%) of the Thorotrast patients and 47 (3.4%) of the comparison group patients remained alive and had not emigrated.

Site-Specific Cancer Incidence among Danish and Swedish Patients

Overall 480 cancers were reported among 440 Thorotrast patients and 196 cancers among 180 comparison group subjects (Table 2). For all cancers taken together, the SIRs for the Thorotrast and comparison cohorts were 3.3 and 1.0, respectively, with a stratified relative risk of 3.4 (95% CI = 2.9-4.1); risks were similar for males and females. Thirty-five Thorotrast patients developed two cancers, one patient three cancers, and one patient four cancers; 16 patients in the comparison group developed two cancers each.

Thorotrast patients experienced significantly elevated relative risks for cancers of stomach (RR = 2.7), bile ducts (RR = 26.4), gallbladder (RR = 11.0), pancreas (RR = 3.8), ovary, tube, and broad ligament (RR = 4.3), prostate



(RR = 4.5), kidney (RR = 5.7), brain and other nervous system (RR = 2.5), metastases (RR = 12.2), and all leukemia except chronic lymphocytic leukemia (CLL) (RR = 15.2). Significantly elevated risks were also observed for primary liver cancer (SIR = 108.9), liver cancer not specified as primary (SIR = 33.0), and cancer of the peritoneum and other digestive sites (SIR = 14.6). Among males, non-significant excesses of non-Hodgkin's lymphoma (RR = 2.5) and rectal cancer (RR = 3.2) were seen, while excesses of nonmelanoma skin cancer (RR = 2.8), multiple myeloma (RR = 3.7), and cancers of the colon (RR = 1.9), lung (RR = 1.6) and thyroid (RR = 1.8) were observed only among women (data not shown); none of the differences between men and women were statistically significant.

Site-Specific Cancer Mortality among U.S. Patients

The relative risk for cancer mortality at all sites after Thorotrast exposure was 4.0 (95% CI: 2.5–6.7) among U.S. Thorotrast patients, with similar excesses in males and females (Table 3). Significantly elevated relative risks were observed for death due to cancers of the liver (RR = 22.5), digestive organs and peritoneum (RR = 8.9), and lymphopoietic sites (RR = 9.8), while nonsignificant 17-fold risks occurred for leukemia mortality. Significant excesses were also observed for mortality due to cancers of buccal cavity and pharynx (SMR = 5.9) and bone (SMR = 13.9).

Cancer Incidence among Danish and Swedish Patients in Relation to Time since Arteriography and a Surrogate Measure of Cumulative Radiation Dose

The relative risks for all cancers taken together for the Thorotrast patients were 4.9, 2.2, 2.1, 5.0 and 3.1 in the 2–9-year, 10–19-year, 20–29-year, 30–39-year, and 40+ year intervals after injection, respectively, compared to nonexposed patients ($P < 0.001$, Table 4). Similar temporal patterns were observed for males and females. Five decades after initial exposure, Thorotrast patients remained at significantly increased risk of cancer compared with the general population (SIR = 4.0; $n = 10$), with significantly increased site-specific risks for tumors of the liver (SIR = 160; $n = 5$) and small intestine (SIR = 88.9; $n = 1$) (data not shown). Relative risks increased significantly with time since Thorotrast injection for primary cancers of the liver ($P < 0.001$), bile ducts ($P = 0.002$) and kidney ($P < 0.001$) and non-CLL ($P = 0.007$, data not shown for latter).

For cancers of the stomach ($P = 0.07$) and pancreas ($P = 0.07$), risk increased with time since injection, but the trends were only marginally significant.

Site-specific relative risks increased significantly with increasing cumulative radiation dose (Table 5) for all cancers taken together ($P < 0.001$), primary cancers of the liver ($P < 0.001$) and gallbladder ($P = 0.03$), and all cancers previously related to Thorotrast (i.e. non-CLL and primary cancers of the liver, gallbladder, and bile ducts) ($P < 0.001$). Risks also increased with increasing cumulative radiation dose for cancers of the peritoneum and other digestive sites ($P = 0.01$) but not for lung cancer. A marginally significant trend of increasing risk with increasing dose was evident for pancreas cancer ($P = 0.05$).

The cumulative risk of all cancer excluding the brain and nervous system in relation to injected dose of Thorotrast and time since arteriography is shown in Fig. 1a. Fifty years after injection, the cumulative risk of cancer was 68.3, 88.8 and 96.9% for patients injected with 3–10, 11–20 and >20 ml of Thorotrast, respectively (P for nonhomogeneity in dose category < 0.0001); risk did not vary by gender. The cumulative risk of primary liver cancer, which was also similar for males and females, increased with increasing volume of Thorotrast to reach 68.8% 50 years after arteriography for those given over 20 ml (P for nonhomogeneity in dose category < 0.0001 ; Fig. 1b). For all cancers previously related to Thorotrast, the cumulative risk 50 years after arteriography was 39.9, 71.4 and 74.3% for patients injected with 3–10, 11–20 and >20 ml of Thorotrast, respectively (P for nonhomogeneity in dose category < 0.0001 ; Fig. 1c.)

Cancer Mortality among U.S. Patients in Relation to Time after Arteriography and a Surrogate Measure of Cumulative Radiation Dose

The relative risk of death due to any cancer increased steadily from 1.4 at 2 to 9 years after arteriography to 15.6 after 40 years (P trend < 0.001) (Table 6). Similar temporal patterns were apparent for males and females. Relative risk of mortality increased significantly with time since Thorotrast exposure for cancers of the digestive organs and peritoneum (P trend < 0.001), liver (P trend < 0.001), and lung (P trend = 0.039) and for all lymphopoietic cancer (P trend = 0.02); much of the latter category was accounted for by leukemia (P trend = 0.02) (data not shown). Mortality in-

←

FIG. 1. Panel a: Cumulative risk of all incident cancers excluding brain and CNS among Thorotrast-exposed patients in Denmark and Sweden in relation to the injected dose of Thorotrast and years since arteriography (P for nonhomogeneity in dose category < 0.0001). Each panel of this figure includes only those patients ($n = 2,129$) for whom the injected volume of Thorotrast was known and for whom extravasation did not occur. The percentages in parentheses indicate the actuarial risk for all cancer incidence 50 years after injection. Panel b: Cumulative risk of primary liver cancer among Thorotrast-exposed patients in Denmark and Sweden in relation to the injected dose of Thorotrast and years since arteriography (P for nonhomogeneity in dose category < 0.0001). The percentages in parentheses indicate the actuarial risk for all liver cancer incidence 50 years after injection. Panel c: Cumulative risk of all Thorotrast-related cancers among patients in Denmark and Sweden in relation to injected dose and years since arteriography (P for nonhomogeneity in dose category < 0.0001). The percentages in parentheses indicate the actuarial risk for all Thorotrast-related cancers 50 years after injection.

TABLE 6
Site-Specific Cancer Mortality in Relation to Time since Injection among Thorotrast-Exposed and Nonexposed Patients in the U.S. (with Relative Risks for the Thorotrast Group) by Follow-up Period^a

| | Follow-up period (years) | | | | | <i>P</i> value for trend ^b |
|---|--------------------------|-----------------|-------------------------------|-------------------------------|------------------------------|---------------------------------------|
| | 2–9 | 10–19 | 20–29 | 30–39 | 40+ | |
| Number of patients | | | | | | |
| Thorotrast | 446 | 341 | 232 | 125 | 45 | |
| Comparison group | 212 | 171 | 134 | 89 | 55 | |
| Person-years | | | | | | |
| Thorotrast | 3075 | 2892 | 1726 | 864 | 180 | |
| Comparison group | 1522 | 1521 | 1060 | 687 | 159 | |
| Site | Observed | Observed | Observed | Observed | Observed | |
| All cancer | | | | | | |
| Thorotrast | 21 | 19 | 27 | 34 | 13 | |
| Comparison group | 6 | 4 | 5 | 7 | 2 | |
| Relative risk (95% CI) | 1.4 (0.5–3.6) | 2.6 (0.9–7.8) | 4.2 ^d (1.52–11.3) | 6.8 ^d (2.8–16.6) | 15.6 ^d (1.2–49.9) | <0.001 |
| All cancer except brain and nervous system | | | | | | |
| Thorotrast | 8 | 13 | 26 | 33 | 13 | |
| Comparison group | 2 | 3 | 5 | 6 | 2 | |
| Relative risk (95% CI) | 1.6 (0.4–17.0) | 2.7 (0.6–12.0) | 4.2 ^d (1.5–11.6) | 8.2 ^d (3.2–21.3) | 15.8 ^d (1.2–49.9) | <0.001 |
| All digestive organs, peritoneum | | | | | | |
| Thorotrast | 2 | 4 | 7 | 15 | 4 | |
| Comparison group | 0 | 1 | 2 | 0 | 1 | |
| Relative risk (95% CI) | Inf. (0.1–Inf.) | 2.8 (0.2–96.7) | 2.2 (0.4–21.7) | Inf. ^d (2.7–Inf.) | 3.2 (0.3–155.4) | <0.001 |
| Liver | | | | | | |
| Thorotrast | 0 | 0 | 5 | 13 | 4 | |
| Comparison group | 0 | 0 | 1 | 0 | 0 | |
| Relative risk (95% CI) | — (—) | — (—) | 3.5 (0.3–141.7) | Inf. ^d (2.3–Inf.) | Inf. (0.5–Inf.) | <0.001 |
| Lung | | | | | | |
| Thorotrast | 0 | 2 | 5 | 2 | 2 | |
| Comparison group | 0 | 1 | 1 | 1 | 0 | |
| Relative risk (95% CI) | — (—) | 1.5 (0.1–69.9) | 3.4 (0.4–163.1) | 0.8 (0.1–90.7) | Inf. (0.2–Inf.) | 0.039 |
| All lymphopoietic cancer | | | | | | |
| Thorotrast | 1 | 2 | 7 | 1 | 2 | |
| Comparison group | 0 | 0 | 0 | 2 | 0 | |
| Relative risk (95% CI) | Inf. (0.0–Inf.) | Inf. (0.1–Inf.) | Inf. (1.0–Inf.) | 0.7 (0.0–7.5) | Inf. (0.2–Inf.) | 0.02 |
| Thorotrast-related cancers^e | | | | | | |
| Thorotrast | 0 | 1 | 11 | 14 | 4 | |
| Comparison group | 0 | 0 | 1 | 1 | 0 | |
| Relative risk (95% CI) | — (—) | Inf. (0.0–Inf.) | 13.0 ^d (1.1–300.0) | 37.7 ^d (1.6–455.3) | Inf. (0.5–Inf.) | <0.001 |

Notes. CI, confidence interval; Inf., infinite.

^a The table is limited to those sites for which 10 or more cancer deaths were reported in the Thorotrast-exposed group and for which significantly increased relative risks were observed in Table 3.

^b *P* value for temporal trend in relative risk based on continuous follow-up time among exposed patients.

^c Relative risk of indicated outcome for Thorotrast-exposed compared with nonexposed patients, adjusted for age, sex, and calendar year.

^d *P* < 0.05.

^e Thorotrast-related cancers: liver cancer and leukemia.

creased significantly with increasing cumulative radiation dose for death due to all cancers taken together (*P* = 0.009) and marginally for liver cancer (*P* = 0.06) (Table 7).

DISCUSSION

This paper presents the first report of long-term site-specific cancer mortality among U.S. Thorotrast patients and

the final results of a five-decade follow-up survey of cancer incidence in the combined cohort of Danish and Swedish patients. The large number of patients in the study and the long follow-up period provide a high level of statistical power for evaluating the effects of chronic, low-dose-rate exposure to internal α -particle irradiation. The significantly increased risk of cancer incidence and cancer mortality persisted for life and increased in relation to cumulative radi-

ation dose. In interpreting our findings, the effect of possible biases should be kept in mind, as reviewed previously (20). Although the comparison groups of patients in Denmark and the U.S. consisted only of patients who underwent cerebral angiography with a nonradioactive contrast agent, subjects were not matched on indication for the procedure (20). Thus any residual discrepancies in underlying disease between the exposed and comparison groups could confound the comparison. Further, given that Thorotrast was virtually the sole contrast medium used in Denmark prior to 1945, a comparison group of patients who underwent cerebral angiography during the same calendar years could not be constructed (17). As a result, the spectrum of baseline illnesses in the Thorotrast group may not be equivalent to that in the comparison group of patients, especially as radiologists gained more familiarity with angiographic procedures over time. The possible impact on the results of the non-overlapping years of cerebral angiography among the Danish patients has been considered in detail by Andersson *et al.* (17).

Our findings are summarized below in relation to those observed in other Thorotrast series, including those in Germany (10), Portugal (11) and Japan (12, 13). The Portuguese study consisted of 1,931 Thorotrast-exposed patients who were matched by sex, age and underlying disease to 2,258 subjects given a nonradioactive contrast agent (11). The radiological procedures used for Thorotrast administration included cerebral arteriography (81%), limb arteriography or phlebography (14%), and aortography (1%); the alternative contrast agent was administered by these routes in 41, 29 and 26% of patients, respectively. Only 59% of the Thorotrast patients and 46% of the comparison group were successfully followed. In Germany, Thorotrast-exposed patients ($n = 2,326$) underwent either cerebral (70%) or other (30%) types of angiography (10). A comparison series ($n = 1,890$) was comprised of hospital patients matched on age and sex but not on index disease or hospital department; most of the comparison group did not undergo angiography (10) ($n = 1,890$). In the combined Japanese study (13), 412 of 416 Thorotrast-exposed male patients were followed through 1998; all patients were injected with Thorotrast intravascularly for the diagnosis of war-related trauma. A comparison series consisted of 1,649 war-wounded males matched to the Thorotrast-exposed patients by age and time of hospitalization but not by angiography status. Liver cirrhosis, overall mortality, and selected cancer mortality were evaluated for the combined Thorotrast exposure cohort, with selected causes of mortality analyzed for a subset of subjects ($n = 255$) (12).

Hepatobiliary Cancer

Liver cancer. Significantly elevated risks for liver cancer incidence and/or mortality have been reported in all major epidemiological surveys of Thorotrast patients (10, 11, 28, 29). The strong correlation between increasing cumulative

radiation dose and liver cancer which we observed has been noted previously (10), and dose to the liver is estimated to be about 400 mGy per year after a standard injection of Thorotrast (4). The hepatic dose is nonuniformly distributed, however, with areas of the liver containing bile ducts, from which cholangiocarcinomas arise, receiving a daily dose of α -particle radiation about 15 times higher than that of hepatic cord tissue (30). This distribution is consistent with the development of specific histological types of liver tumors (i.e. cholangiocarcinomas and hemangioendotheliomas) in Thorotrast patients, as initially observed by da Motta and colleagues (31). Subsequent histopathological studies have confirmed that the spectrum of liver cancer in Thorotrast patients differs from that of nonexposed comparison cohorts, in which about 90% of tumors consist of hepatocellular carcinomas (12, 13, 32–34). About equal proportions of hepatocellular carcinomas, cholangiocarcinomas and hemangiosarcomas (or at least a predominance of non-hepatocellular carcinomas) are observed in Thorotrast patients (12, 13, 33–35). Although Thorotrast, vinyl chloride, and arsenic are traditionally the only agents known to cause hemangiosarcomas (36), a high incidence of hepatic hemangiosarcomas was recently reported in Mayak nuclear workers internally exposed to α particles from plutonium (37). Significant excesses of liver cancer have also been observed in subjects exposed to the α -particle emitter radium-224, with a histological distribution of approximately 50% hepatocellular carcinomas and 50% cholangiocarcinomas, with no hemangiosarcomas reported (38). Significantly increased risks of liver cancer have been found for atomic bomb survivors acutely exposed to γ radiation and neutrons, with risk directly related to dose (39, 40), although the role of hepatitis virus could not be completely discounted. Hepatocellular carcinomas comprised approximately 90% of the cancers (409). No increased incidence in liver cancer, however, has been observed in large series of cervical cancer patients treated mainly with X rays or γ rays (41).

Virtually all incident liver cancers in our series occurred 20 or more years after Thorotrast injection, and increased risks compared with the general population persisted for more than 50 years. Other series have shown that the usual latent period of Thorotrast-related liver cancers is several decades, with a minimum of 11 years (10, 29, 34, 35), and is not altered by age at injection (35). The latency likely reflects the time necessary for the prolonged exposure to result in a carcinogenic dose and for an initiated cell to progress to a clinically evident cancer.

Extrahepatic bile ducts and gallbladder. Increased mortality due to cancers of the extrahepatic bile ducts has been reported for Thorotrast patients in Japan (29), Germany (10) and Portugal (11). Because of their integral relationship to the liver, in which most of the injected Thorotrast is deposited, the extrahepatic bile ducts likely receive substantial α -particle exposure. Although the gallbladder is a minor site of Thorotrast storage (5), the elevated risk of

TABLE 7
Site-Specific Cancer Mortality and Relative Risk (RR) in Relation to a Surrogate Measure of Cumulative Radiation Dose among Thorotrast-Exposed and Nonexposed Patients in the U.S.^a

| Site | Estimated cumulative radiation dose in ml-years (ml of injected Thorotrast × max [0, years since injection-5] × 10 ²) | | | | | |
|--|--|------------------|-------------|----------|------------------|-------------|
| | 0-29 | | | 30-49 | | |
| | Observed | RR | (95% CI) | Observed | RR | (95% CI) |
| All cancer | 29 | 1.9 ^c | (1.1-3.2) | 15 | 2.9 ^c | (1.4-5.6) |
| All cancer except brain and nervous system | 19 | 2.7 ^c | (1.4-5.5) | 14 | 3.6 ^c | (1.7-7.4) |
| All digestive organs and peritoneum | 7 | 6.1 ^c | (1.5-30.8) | 3 | 4.3 | (0.4-17.3) |
| Liver | 1 | 7.0 | (0.0-115.6) | 2 | 11.3 | (0.4-495.9) |
| Lung | 1 | 1.3 | (0.0-10.4) | 4 | 5.0 | (0.9-35.2) |
| All lymphopietic cancer | 4 | 6.8 | (0.4-16.8) | 2 | 5.0 | (0.2-22.2) |
| Thorotrast-related cancers ^d | 4 | 13.3 | (0.5-35.2) | 3 | 9.8 | (0.7-72.9) |

Notes. CI, confidence interval; RR, relative risk.

^a Results in table are limited to 212 nonexposed patients and 379 Thorotrast-exposed patients for whom the administered amount of Thorotrast was known and who did not have Thorotrastomas recorded.

^b *P* value for trend in relative risk based on continuous cumulative radiation dose among exposed patients; parentheses indicate negative trend.

^c *P* < 0.05.

^d Thorotrast-related cancers: liver cancer and leukemia.

cancer at this site which we observed is consistent with its location on the visceral surface of the liver and thus its proximity to continual α -particle exposure, although misclassification may play a role (35). Significantly elevated risks for gallbladder cancer were also observed in the German cohort of Thorotrast patients (10). The long latent periods which we observed for excess cancers of extrahepatic bile ducts and gallbladder paralleled findings for liver cancer.

Other Gastrointestinal Cancers

Pancreas. The pancreas is a minor site of Thorotrast deposition and has been estimated to receive a dose of only 3 mGy per year (5). Nonetheless, the temporal trend of pancreas cancer incidence and its relationship to cumulative radiation dose in this survey are suggestive of a possible radiogenic etiology. The anatomic juxtaposition of a portion of the pancreas to the spleen, in which large deposits of Thorotrast are associated with eventual organ atrophy, may partially explain this finding. Death due to pancreas cancer was significantly elevated in the German study of Thorotrast-exposed patients (10) but not in the Japanese survey (13). The pancreas is not considered especially susceptible to the carcinogenic effects of ionizing radiation except after large doses (42, 43). Significant four- to five-fold excesses of pancreas cancer have been reported among long-term survivors of Hodgkin's disease (44) and cancers of the testis (45) and ovary (46) after therapeutic doses of radiation; during typical abdominal radiotherapy for Hodgkin's disease or testicular cancer, estimated doses to the pancreas range from 4.2 to 34.0 Gy (45, 47).

Small intestine. The increased eightfold relative risk for small intestine cancer observed in the combined Danish and Swedish cohort is noteworthy, given the rarity of these tumors. The German (10), Portuguese (11) and Japanese (28)

studies did not address risks for cancer at this site. Our finding was based on small numbers (five cases), which did not permit further evaluation of risks by cumulative radiation dose. Significantly elevated threefold risks of small intestine cancer have been observed after therapeutic doses of radiation for testicular seminomas (45), during which the small intestine may receive 12.5 Gy, but considerably lower doses (2.8 mGy per year) have been estimated for Thorotrast patients (5).

Peritoneum and other digestive sites. The relationship between cumulative radiation dose surrogate and significant excesses of cancers of peritoneum and other digestive tract sites among Thorotrast patients in Denmark and Sweden is consistent with a radiogenic etiology. Cancer mortality at this site was significantly elevated in the Japanese study (13), with nonsignificant excesses of peritoneal mesothelioma observed in the German series (10). The consistency of this finding between studies and the intimate proximity of portions of the peritoneum to the major areas of Thorotrast deposition further support the radiogenic etiology of cancers at this site. Malignant mesothelioma has also been reported as a second primary tumor after high doses of radiation given to treat cancer (48).

Hematopoietic Cancer

Significantly elevated mortality rates due to all types of leukemia except CLL have been noted consistently in most major Thorotrast epidemiological studies (10, 11, 28, 29). About 12% of an injected dose of Thorotrast is deposited in the bone marrow (4), where it is concentrated in groups of macrophages commonly located near blood vessels and bone surfaces (49); the nonuniform distribution reflects Thorotrast's colloidal nature and its uptake by phagocytic cells. A typical 25-ml injection of Thorotrast results in an annual dose to bone marrow of about 10 cGy (4). Cyto-

TABLE 7
Extended

| Estimated cumulative radiation dose in ml-years (ml of injected Thorotrast \times max [0, years since injection-5] $\times 10^3$) | | | | | | | P value for trend |
|---|-------------------|--------------|----------|-------------------|-------------|--------|----------------------|
| 50-69 | | | 70+ | | | | |
| Observed | RR | (95% CI) | Observed | RR | (95% CI) | | |
| 12 | 3.4 ^c | (1.6-7.0) | 36 | 7.0 ^c | (3.9-12.9) | 0.009 | |
| 12 | 4.1 ^c | (1.9-8.6) | 35 | 7.6 ^c | (4.1-14.5) | 0.007 | |
| 4 | 8.8 ^c | (1.8-48.5) | 15 | 16.7 ^c | (5.0-77.8) | 0.11 | |
| 4 | 30.5 ^c | (3.1-1526.7) | 14 | 40.6 ^c | (13.3-3700) | 0.06 | |
| 2 | 3.0 | (0.3-28.4) | 3 | 5.6 | (0.4-23.2) | 0.16 | |
| 2 | 5.0 | (0.3-35.6) | 3 | 5.4 | (0.6-33.2) | (0.90) | |
| 5 | 19.7 ^c | (2.9-185.1) | 16 | 32.1 ^c | (10.2-390) | 0.12 | |

genetic studies of Thorotrast patients demonstrate aberrations of at least one chromosome in about 30% of peripheral blood lymphocytes, with most representing stable aberrations such as translocations (50). Increased frequencies of unstable chromosome aberrations, which include dicentric and rings, have also been reported in Thorotrast patients (51). Thus it is likely that throughout life Thorotrast patients continue to accumulate cytogenetically abnormal lymphoid stem cells as a result of exposure to α particles; a sizable percentage of the aberrations are not unstable and thus do not result in eventual cell death. Incident leukemias were diagnosed in all intervals after Thorotrast administration, consistent with the wide spectrum for the average latent period (8 to 40 years) previously noted for the development of leukemia in these patients (52). The large range likely reflects the continual radiation exposure. In contrast, after acute exposure to external radiation, the risk for leukemia typically peaks within 10 years (53).

Other Cancer Sites

Lung. One of the products of the thorium decay chain is radon-220. This gas is transported in the blood from sites of Thorotrast deposition to the lungs, where it is exhaled in measurable amounts (2, 54). Recent re-evaluations of α -particle doses to sensitive target cells in the bronchial and pulmonary epithelia indicate that doses to these sites are considerably lower than previously estimated (55, 56). Ishikawa *et al.* (5) estimated that the lung receives an overall radiation dose of only 5.3 mGy per year. Exhalation of radon gas apparently does not result in as high an exposure to target cells as does inhalation of this gas. Even with various corrections, the dose of α -particle radiation to pulmonary tissue of Thorotrast patients may be in the same range as doses received by underground miners exposed to radon (54), who experience significantly elevated risks of lung cancer (8). However, we found no overall increase in the risk of incident lung cancers in this study, nor did we find any relationship to cumulative radiation dose. Although a nonsignificant threefold risk for lung cancer mortality was apparent in U.S. Thorotrast-exposed patients, this

finding may represent misclassification of metastatic cancers as primary tumors. The risk of lung cancer was nonsignificantly increased in the Portuguese (11) and the Japanese (29) Thorotrast studies, but it was not elevated in the German study (10).

Kidney. Because small amounts of Thorotrast are excreted (6, 7), the kidney could be continuously exposed to low doses of thorium daughter products. Ishikawa *et al.* (5) estimate that the kidneys may receive a dose of 1.5 mGy per year. It is unlikely, however, that these low levels are sufficient to induce notable excesses of renal cancer, especially since the kidney is not considered especially susceptible to the carcinogenic effects of radiation (57). Although the risk of kidney cancer increased with time since Thorotrast injection among Danish and Swedish patients in our study, no relationship to cumulative radiation dose was observed. The risk of kidney cancer was nonsignificantly elevated in the German study (10) and was not increased in the Japanese study (13).

Oral cavity and pharynx. Thorotrastomas in the neck could provide a radiation source in proximity to the oral cavity and pharynx, which might possibly account for the significantly increased risk for cancer at this site among U.S. Thorotrast patients. This finding, however, was based on small numbers, and no increased risk was observed for the combined Danish and Swedish cohort. Nonsignificant excesses in deaths due to laryngeal cancer were found in the German Thorotrast study (10) and in one of the Japanese reports (13).

Bone cancer. Bone cancer was significantly elevated among the U.S. patients, but this was based on only two deaths, and no incident cases were noted in the Danish and Swedish cohort. Bone cancer increases are not generally found in studies of Thorotrast patients. Nonsignificant increases have been observed in the Portuguese patients (11). The thorium decay series includes the bone-seeking radionuclide ^{224}Ra , which has been associated with high risks of osteosarcomas, and the total skeletal dose from all radionuclides in the decay scheme could range between 3 to 9 Gy (58). Thus a small excess of bone cancers among Tho-

rotrast patients would not be unexpected. However, evidence from radium dial painters (59) suggests that osteosarcomas rarely if ever develop at skeletal doses under 10 Gy, so the inconsistency among studies might be related to the very high dose necessary to cause radiation-induced bone cancer.

Comments

A major impetus for the conduct of the present and similar radiation epidemiological studies is the desire to obtain reliable estimates of the risk of untoward effects, notably cancer, with the aim of applying these estimates to exposure situations in which data for humans are not available. Of particular interest, current recommendations by the International Council on Radiation Protection (60) rely primarily on Thorotrast data to specify risks of radiation-induced liver cancer, including risks from external exposures. Recently, Harrison and Muirhead (9) reviewed the literature and compared quantitative estimates of lifetime cancer risk in humans after exposure to internally deposited radionuclides with external radiation. For liver cancer, these investigators (9) found the estimates of risk derived from Thorotrast patients in Germany, Denmark and Japan to be similar to estimates derived from the A-bomb survivor data, assuming a relative biological efficacy (RBE) of 20 and a reduction factor of two to convert from high dose/high dose rate to low dose/low dose rate. In contrast, for hematopoietic malignancies, they found that the RBE appears to be 2 to 3, rather than the current assumption of 20, indicating that this conclusion is supported by animal data. Thus, according to Harrison and Muirhead (9), current assumptions may overestimate risks from internally deposited α -particle-emitting radionuclides in terms of leukemogenesis. Still, it should be kept in mind that the risk estimates derived from Thorotrast-exposed patients also have inherent uncertainties, especially with regard to dosimetry (4, 61).

A number of Thorotrast studies were summarized recently (62), and it is unlikely that additional cohorts of patients will be assembled. Nonetheless, complications of Thorotrast exposure continue to be documented in the medical literature (63–67), with cancer the most serious sequela. This multi-center study in the U.S., Sweden and Denmark was conducted to learn whether any further insights into carcinogenesis after exposure to high-LET radiation could be gleaned. The large number of patients in our survey allowed for a more powerful statistical evaluation of long-term site-specific carcinogenesis, including leukemia and cancers of liver, extrahepatic bile ducts, gallbladder, pancreas, kidney and lung. Our analyses were based primarily on the volume of injected Thorotrast, an approach which facilitated comparisons with other investigations. Quantification of Thorotrast organ dose is complicated by the continual nature of the exposure, the dose received after the initiating events had passed or that may have contributed to killing of transformed cells, and the

effect of tissue damage and regeneration (especially hepatic) on subsequent risk from the protracted exposure. Nonetheless, our results show that Thorotrast-exposed patients experience increased risks of cancer throughout life, with a cumulative risk of 97% at 50 years of follow-up for those who received more than 20 ml. The Thorotrast experience indicates that any tissue that came in continuous contact with this substance could be seriously damaged. It is reasonable to suggest that other α -particle emitters with prolonged residence times in the body might elicit untoward effects, and in particular that a number of tissues having extended contact with carcinogenic substances at sufficiently high doses might be susceptible to the development of neoplasia.

It is important to be careful in generalizing the Thorotrast experience to other circumstances. Thorotrast was unique and essentially remained in the body for life because of its colloidal nature, continuously exposing tissue. The International Agency for Research on Cancer judged that sufficient evidence existed to classify Thorotrast as a human carcinogen (62). On the other hand, thorium, which is readily excreted from the body after intake (58), was not judged to be carcinogenic. The high rate of leukemia is also unique to Thorotrast and is related to the directed exposure of bone marrow from the macrophage-transported Thorotrast (68). Other studies of patients exposed to α -particle emitters, such as the radium dial painters, did not find excess leukemias (9), in part because the α particles from bone were unlikely to hit the stem cells in the bone marrow, which are thought to be more centrally located. Alpha particles from osteophilic radionuclides have little penetrating power, and the stem cells within the bone marrow would not be reached effectively (69, 70). Finally, it is of note that studies of uranium workers involved in processing, manufacturing and milling have failed to identify a cancer risk despite large numbers and many years of follow-up (71). Again, this is due to the generally short residence time of most uranium compounds in the body. The uniqueness of the Thorotrast studies is the clear demonstration in humans of the potential for α particles to result in cancer when exposure occurs over a period of 10 to 50 years.

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