

Mortality after Cerebral Angiography with or without Radioactive Thorotrast: An International Cohort of 3,143 Two-Year Survivors

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

^a Radiation Epidemiology Branch, National Cancer Institute, Bethesda, Maryland 20892; ^b Department of Oncology 5073, Rigshospitalet, DK 2100 Copenhagen, Denmark; ^c Danish Cancer Society, 49 Strandboulevarden, DK 2100, Copenhagen, Denmark; ^d Radiumhemmet, Karolinska University Hospital, Stockholm, Sweden; ^e New England Research Institutes, Watertown, Massachusetts; ^f School of Public Health, University of Texas at Houston, Health Science Center, Houston, Texas; ^g Information Management Services, Rockville, Maryland; ^h Department of Medical Epidemiology, Karolinska Institute, Stockholm, Sweden; ⁱ Radiation and Nuclear Safety Authority, Helsinki, Finland; ^j Worcester Medical Center, Worcester, Massachusetts; ^k Swedish Radiation Protection Institute, Stockholm, Sweden; ^l Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts 02115; ^m Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, Michigan; ⁿ International Epidemiology Institute, Rockville, Maryland 20852; and ^o Vanderbilt University, Department of Medicine and Vanderbilt-Ingram Cancer Center, Nashville, Tennessee

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There are few studies on the long-term sequelae of radionuclides ingested or injected into the human body. Patients exposed to radioactive Thorotrast in the 1930s through the early 1950s provide a singular opportunity, since the administration of this radiographic contrast agent resulted in continuous exposure to α particles throughout life at a low dose rate. We evaluated cause-specific mortality among an international cohort of 3,143 patients injected during cerebral angiography with either Thorotrast ($n = 1,736$) or a similar but nonradioactive agent ($n = 1,407$) and who survived 2 or more years. Standardized mortality ratios (SMRs) for Thorotrast and comparison patients were calculated, and relative risks (RR), adjusted for population, age and sex, were obtained by multivariate statistical modeling. Most patients were followed until death, with only 94 (5.4%) of the Thorotrast patients known to be alive at the closure of the study. All-cause mortality ($n = 1,599$ deaths) was significantly elevated among Thorotrast subjects [RR 1.7; 95% confidence interval (CI) 1.5–1.8]. Significantly increased relative risks were found for several categories, including cancer (RR 2.8), benign and unspecified tumors (RR 1.5), benign blood diseases (RR 7.1), and benign liver disorders (RR 6.5). Nonsignificant increases were seen for respiratory disease (RR 1.4) and other types of digestive disease (RR 1.6). The relative risk due to all causes increased steadily after angiography to reach a threefold RR at 40 or more years ($P < 0.001$). Excess cancer deaths were observed for each decade after Thorotrast injection, even after 50 years (SMR 8.6; $P < 0.05$). Increasing cumulative dose of radiation was directly associated with death due to all causes

combined, cancer, respiratory disease, benign liver disease, and other types of digestive disease. Our study confirms the relationship between Thorotrast and increased mortality due to cancer, benign liver disease, and benign hematological disease, and suggests a possible relationship with respiratory disorders and other types of digestive disease. The cumulative excess risk of cancer death remained high up to 50 years after injection with >20 ml Thorotrast and approached 50%.

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INTRODUCTION

The possible untoward biological effects of internally deposited radionuclides remain an important focus of scientific investigation and public health concern, especially in view of the need to predict the risks associated with occupational, environmental and medical exposures. Valuable information on the effects of long-term exposure to α -particle emitters can be gained through the study of patients injected with Thorotrast (thorium dioxide), a radioactive radiographic contrast agent used between 1928 and 1954 (1, 2). Most of these patients have now died, and it is important that the health effects from this historical exposure be studied comprehensively, in a final attempt to learn as much as possible from this medical experience.

There are many more epidemiological investigations of populations exposed to external sources of ionizing radiation than to internally deposited radionuclides. The relevance of studying the biological effects of the internal deposition of Thorotrast relates to quantifying organ-specific risks from α -particle-emitting radionuclides as might be ex-

¹ Author to whom correspondence should be addressed at National Cancer Institute, Executive Plaza South, Suite 7086, Bethesda, MD 20892; e-mail: travisl@epndce.nci.nih.gov.

perienced from reactor accidents, fallout from nuclear weapons testing, nuclear medicine, or natural background such as radon. Although α -particle-emitting radionuclides deposit differently throughout the body because of chemical properties and solubility, comparable risks can be computed based on the radiation dose received by specific organs. Further, comparisons with other human studies can provide information on the relative biological effectiveness of α particles contrasted with γ or X rays in causing specific cancers.

Thorotrast, a 25% colloidal suspension of the heavy metal thorium-232, provided outstanding radiographic visualization, and was especially popular for cerebral and limb angiography. Because Thorotrast was actively sequestered by the reticuloendothelial system, it also provided excellent imaging of the liver and spleen. Thorotrast, however, was not subsequently excreted to any meaningful degree by the body; thus, given its biological half-life of 400 years, administration of this agent resulted in continuous radiation exposure throughout life at a low dose rate. Medical complications due to Thorotrast exposure continue to be documented (3–7). To provide information on long-term trends in cause-specific mortality associated with chronic radiation exposure, we conducted an international study of over 3,100 patients injected with either Thorotrast or a nonradioactive contrast agent in the course of cerebral angiography and who survived 2 or more years. We chose only cerebral angiography patients to minimize the influence of indication(s) for Thorotrast administration, which commonly included hepatosplenic diseases. The substantial number of patients, including 550 40-year survivors, permits description of the lifetime temporal and site-specific patterns of mortality.

PATIENTS AND METHODS

Study Subjects

Patients who underwent cerebral angiography with either Thorotrast or a nonradioactive contrast agent between January 1, 1935 and December 31, 1960 were identified in Denmark, Sweden and the United States. Detailed descriptions of methods for identification of the underlying study cohorts have been published previously (8–10), and updated summaries were recently provided for Denmark (11) and Sweden (12). In brief, patients were identified from hospital records at the Rigshospitalet and Aarhus Municipal Hospital in Denmark and the Serafimer Hospital in Sweden. The initial cohorts consisted of 1,095 Danish and 1,117 Swedish patients exposed to Thorotrast and 1,480 Danish subjects who underwent cerebral arteriography with a nonradioactive contrast medium. Because Thorotrast served almost exclusively as the radiographic contrast agent of choice in Denmark between 1935 and 1947, it was not possible to construct a comparison group of patients injected during identical calendar years. Thus, for Denmark, the underlying comparison group consisted of patients who underwent cerebral angiography between 1946 and 1960 (11). A group of Swedish patients who underwent cerebral angiography with a nonradioactive contrast agent was not available.

The U.S. study population was derived from a previously identified group of 724 patients exposed to Thorotrast during cerebral angiography at the Massachusetts General Hospital (MGH) ($n = 201$, 1947–1955) in Boston, MA; the Lahey Clinic (LC) ($n = 174$, 1936–1948) in Burlington,

MA; and the University of Michigan Hospital (UMH) ($n = 349$, 1940–1955) in Ann Arbor, MI (9). A comparison cohort consisted of a group of 314 patients who underwent cerebral angiography with the nonradioactive contrast material Diodrast at MGH ($n = 133$, 1947–1955) or LC ($n = 181$, 1947–1948); no comparison group was available at UMH. Thorotrast was almost exclusively used at the LC from 1936 to 1948. A near-exclusive use of Diodrast was started after that time; thus the comparison group represented the period coinciding with the closure of Thorotrast use (1947–1948) (9). All cohorts in the United States were initially assembled in 1965 and followed through 1970 (9).

Eligibility criteria for the present study cohort included survival for 2 or more years (i.e. 24 or more months) after angiography and the absence of neoplastic disease at the time of the procedure. The 2-year criterion was applied to minimize the influence of mortality associated with the disease for which angiography was performed, and to allow an adequate latent period for the manifestation of radiation-related effects. When these study criteria were applied to the previously established Thorotrast-exposed (8, 9, 11) and comparison populations (9, 11), the cohort was reduced to 776 exposed and 1,179 comparison patients in Denmark, 508 exposed patients in Sweden, and 452 exposed and 228 comparison patients in the United States.

Indications for cerebral arteriography among Thorotrast-exposed patients in Denmark included symptoms consistent with intracranial tumors or cerebrovascular malformations (e.g. visual changes, headache, palsy or seizures) (11). Patients in Sweden underwent cerebral angiography for similar symptoms, typically including seizure disorder, paralysis and headache (12), while indications in U.S. Thorotrast patients included suspected brain tumor (33.7%), aneurysm (21.0%), subarachnoid hemorrhage (4.3%), and other or unknown conditions (39.5%) (9). Final diagnoses in the Danish Thorotrast-exposed patients included benign or malignant intracranial tumors, epilepsy, arachnoiditis and ill-defined atrophic cerebral disorders, with no diagnosis specified for many subjects. Conditions among Swedish Thorotrast-exposed patients included malignant or benign intracranial tumors, cerebrovascular malformations, and other disorders (12). In the United States, indication for angiography among patients in the comparison group included brain tumor (34.1%), aneurysm (17.2%), subarachnoid hemorrhage (12.1%), epilepsy or convulsions (8.0%), and other or unknown reasons (28.6%). Indications for injection for the Danish comparison group included symptoms or signs of intravascular malformations and intracranial tumors (11).

Data Collection

Collected data included date of birth, race (U.S. sites only), sex, date of angiography, site of injection, type of contrast agent used, occurrence of extravasation into soft tissues, and injected volume. For patients who had multiple angiographies, the above data were collected for each procedure. For the Danish and Swedish patients, only the date of the first angiography had been recorded; however, multiple injections were usually administered within a few days of each other, and at most within a few weeks. Data sources in each center included the original study files that were generated during the early identification and establishment of the underlying cohorts (8–10). Information on injected volume was available for approximately 80% of all Thorotrast-exposed patients. The existence of subsequent Thorotrastomas (Thorotrast-containing granulomas resulting from infiltration of soft tissues due to extravasation at the injection site) was evaluated for 1286 patients, of whom 69 (5.4%) had documented lesions; these patients were excluded from dose-response analyses.

Patient Follow-up

Patients were followed from 2 years after angiography until date of death, date of emigration (Sweden and Denmark), loss to follow-up, or study end date, whichever occurred first. The study end date varied slightly by country: January 20, 1992 in Denmark; December 31, 1992 in the United States; and December 31, 1993 in Sweden. Detailed follow-up procedures were published earlier for patients in Sweden and Denmark

TABLE 1
Demographic Characteristics of 3,143 Patients who Underwent Cerebral Angiography with or without Radioactive Thorotrast and Survived Two or more Years

	Thorotrast-exposed ^a			Comparison group ^b		
	No.	Percentage	PY ^c	No.	Percentage	PY
Total no. of patients	1,736	100.0	37,542	1,407	100.0	34,569
Females	781	45.0	18,308	733	52.1	19,094
Males	955	55.0	19,234	674	47.9	15,475
Age at angiography (years)						
<20	230	13.2	7,104	222	15.8	7,269
20-39	790	45.5	19,571	493	35.0	14,400
40-59	625	36.0	9,957	576	40.9	11,740
≥60 ^d	91	5.2	910	116	8.2	1,160
Calendar years of angiography						
1932-1940	445	25.6	9,194	—	—	—
1941-1950	1,233	71.0	27,450	626	44.5	15,700
1951-1960	58	3.3	898	781	55.5	18,869
Injected volume of Thorotrast (ml) ^e						
3-10	477	27.5	11,800	N/A		
11-20	509	29.3	10,914			
21-30	269	15.5	5,311			
31-40	129	7.4	2,498			
>40	53	3.0	848			
Unknown	299	17.2	6,171			
Survival after angiography (years) ^f						
2-9	1,736	100.0	9,204	1,407	100.0	10,242
10-19	1,493	86.0	12,180	1,176	83.6	10,618
20-29	1,139	65.6	9,251	949	67.4	8,174
30-39	710	40.9	5,090	701	49.8	4,945
40-49	310	17.9	1,674	240	17.1	590
>50	44	2.5	143	N/A ^g	—	—
Age at last follow-up (years)						
<20	4	0.2	17	5	0.4	25
20-39	112	6.5	1,009	78	5.5	972
40-59	538	31.0	9,479	399	28.4	8,873
60-69	508	29.3	11,709	357	25.4	8,761
70-79	416	24.0	10,627	363	25.8	9,577
≥80	158	9.1	4,701	205	14.6	6,360

Note. N/A, not applicable; PY, person years.

^a Patients underwent cerebral angiography with Thorotrast, were assumed free of neoplasms at that time, and survived 2 or more years.

^b Patients underwent cerebral angiography with a nonradioactive contrast agent, were assumed free of neoplasms at that time, and survived 2 or more years.

^c Refers to number of PY of observation for the designated category.

^d Maximum age at time of cerebral angiography was 78 and 79 years, respectively, for the Thorotrast-exposed and nonexposed patients.

^e The smallest volume injected was 3 ml. The median (range) volume of Thorotrast administered for patients in age categories <20 years, 20-39 years, 40-59 years, and 60+ years was similar: 15 ml (6-80 ml), 20 ml (3-66 ml), 20 ml (5-92 ml), and 20 ml (5-52 ml), respectively.

^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, United States) or 1993 (Sweden).

(11, 12). In brief, methods included computerized linkage with the national death registers by means of a unique personal identification number assigned to all subjects to obtain the date and underlying cause of death. For patients who died prior to the inception of the national death registry in Denmark [1943 ($n = 59$)], follow-up procedures included searches of death certificates or hospital records (11). In the United States, patient

follow-up was extended from 1970, the time of last assessment (9), through 1992 by means of linkage with the National Death Index and by 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. Death certificates were requested from states to obtain detailed information with regard to cause

TABLE 2
Characteristics of Thorotrast-Exposed and Comparison Patients According to Country

	Denmark	Sweden	United States	All patients
No. of patients				
Thorotrast-exposed ^a	776	508	452	1,736
Comparison group ^b	1,179	—	228	1,407
Age at angiography (years, mean)				
Thorotrast-exposed	33.9	35.3	41.2	36.2
Comparison group	37.2	—	40.2	37.7
Calendar year of angiography				
Thorotrast-exposed	1935–1947	1932–1947	1937–1956	1932–1956
Comparison group	1946–1960	—	1944–1957	1944–1960
Volume (ml) of Thorotrast injected ^c				
Mean	18.6	15.4	26.4	20.1
Median	20	16	30	20
Range	8–80	3–52	4–92	3–92
Person-years of follow-up				
Thorotrast-exposed	18,572	10,069	8,901	37,542
Comparison group	29,220	—	5,349	34,569
Length of follow-up (years, mean)				
Thorotrast-exposed	23.9	19.8	19.7	26.6
Comparison group	24.8	—	23.5	24.6
Deceased (%)				
Thorotrast-exposed	92	93	90	92.1
Comparison group	63	—	71	64.5

^a Includes 1,736 patients who underwent cerebral angiography with Thorotrast, were assumed free of neoplasms at that time, and survived 2 or more years.

^b Includes 1,407 patients who underwent cerebral angiography with a nonradioactive contrast agent, were assumed free of neoplasms at that time, and survived 2 or more years. No comparison group was available in Sweden.

^c Refers to cumulative volume of injected Thorotrast.

of death. Cause-of-death coding was done as described previously (9, 11, 12); deaths identified between 1970 and 1992 in the United States were coded according to ICD-9 (13).

Statistical Analysis

Person-years (PY) of observation were compiled according to age, sex and calendar year periods from 2 years after cerebral angiography to the date of death, date of emigration, or study end date, whichever occurred first. Mortality rates specific for each country, age (5-year groups), sex and 5-year calendar year intervals were multiplied by the accumulated PY at risk to estimate the number of deaths expected. Causes of death for all countries were grouped into 13 major categories to be consistent with the Danish cohort, for which more specific causes of death could not be evaluated (11). Standardized mortality ratios were computed for various subsets of the data, and confidence intervals were calculated assuming Poisson variation for the observed numbers. To investigate the variation in risk between Thorotrast and comparison patients, Poisson regression analysis (14, 15) was used; in these models, explicit terms were added for the following modifying variables: cohort (the U.S. and the combined Danish-Swedish subjects), sex, age at exposure, calendar period of exposure, follow-up period, and/or a surrogate for cumulative radiation dose. In the regression models, the observed number of deaths was the response variable, with the mean assumed to be equal to the expected number of deaths times an unknown parameter or a parametric function of one or more of the above modifying variables which could be numerical or categorical, i.e., indicator functions representing one level of a single modifying variable. Statistical significance was assessed in terms of improvement in fit based on a likelihood ratio test. Dose-re-

sponse analyses were conducted for the Thorotrast-exposed cohort (without nonexposed subjects) by quartiles of the following surrogate for radiation dose: injected volume of Thorotrast multiplied by the time since injection, lagged by 5 years [ml injected \times max(0, years since injection - 5) $\times 10^{-2}$]. Dose-response analyses were limited to 1,377 patients for whom the injected volume of Thorotrast was recorded and for whom extravasation did not occur; patients with missing values were excluded. Trend test statistics, by follow-up period and by dose surrogate, were calculated by log-linear regression. Cumulative mortality (1 - cumulative survival) was calculated by the Kaplan-Meier method (16).

RESULTS

Characteristics of all Thorotrast-Exposed and Comparison Group Patients

The final study cohort consisted of 1,736 Thorotrast-exposed patients and 1,407 comparison subjects who survived 2 or more years after cerebral angiography (Table 1). Approximately half of the subjects in each group were female (45% and 52%, respectively). The age distributions for Thorotrast-exposed and comparison group patients were similar. The injected Thorotrast volume was comparable for males (median 20 ml; range 5–92 ml) and females (median 19 ml; range 3–80 ml). All together, 2,088 patients were followed for at least 20 years, 1,411 for 30 years, 550 for

TABLE 3
Cause-Specific Mortality among Thorotrast-Exposed
and Comparison Patients by Gender

Cause of death	Thorotrast-exposed ^a		Comparison group ^b		RR ^c	95% CI
	Observed	SMR	Observed	SMR		
All causes combined	1,599	3.0^d	908	1.7^d	1.7^d	1.5–1.8
Females	706	3.1 ^d	442	1.6 ^d	1.8 ^d	1.6–2.1
Males	893	2.9 ^d	466	1.9 ^d	1.5 ^d	1.4–1.7
Infections	17	2.2	12	3.1^d	0.9	0.4–1.9
Females	9	3.2 ^d	8	4.3 ^d	0.8	0.3–2.2
Males	8	1.6	4	2.0	1.0	0.3–3.6
Cancer (including leukemia)	526	4.2^d	201	1.5^d	2.8^d	2.4–3.3
Females	246	4.2 ^d	107	1.4 ^d	2.9 ^d	2.3–3.7
Males	280	4.1 ^d	94	1.5 ^d	2.7 ^d	2.2–3.5
Benign and unspecified tumors^e	88	27.7^d	41	14.6^d	1.5^d	1.03–2.2
Females	37	24.1 ^d	18	11.0 ^d	1.8	1.0–3.3
Males	51	31.2 ^d	23	20.0 ^d	1.3	0.8–2.2
Endocrine and metabolic	16	1.5	21	2.2^d	0.7	0.3–1.3
Females	3	0.5	12	2.0 ^d	0.3	0.1–0.9
Males	13	2.8 ^d	9	2.5 ^d	1.1	0.5–2.6
Benign hematological disease	19	12.4^d	2	1.7	7.1^d	2.1–46.0
Females	10	13.2 ^d	1	1.4	8.9 ^d	1.7–169.2
Males	9	11.6 ^d	1	2.1	5.7	1.0–101.6
Nervous system and psychiatric disease	60	7.3^d	38	4.8^d	1.3	0.8–1.9
Females	20	5.4 ^d	15	3.4 ^d	1.3	0.7–2.6
Males	40	8.9 ^d	23	6.6 ^d	1.3	0.8–2.2
Cerebrovascular disease	195	3.5^d	103	2.0^d	1.6^d	1.2–2.0
Females	92	3.3 ^d	53	1.6 ^d	1.8 ^d	1.3–2.5
Males	103	3.7 ^d	50	2.5 ^d	1.4	1.0–2.0
Cardiac disease	320	1.4^d	264	1.3^d	1.1	0.9–1.3
Females	131	1.4 ^d	118	1.1	1.2	1.0–1.6
Males	189	1.4 ^d	146	1.4 ^d	1.0	0.8–1.2
Respiratory disease	69	2.4^d	53	1.7^d	1.4	0.96–2.0
Females	29	2.6 ^d	26	1.7 ^d	1.4	0.8–2.4
Males	40	2.2 ^d	27	1.6 ^d	1.4	0.9–2.3
Benign liver disorders	72	9.0^d	13	1.4	6.5^d	3.7–12.4
Females	39	11.7 ^d	5	1.1	11.3 ^d	4.9–33.4
Males	33	6.7 ^d	8	1.8	3.8 ^d	1.8–8.7
Digestive disease (other types)	42	3.0^d	19	1.9^d	1.6	0.9–2.8
Females	15	2.6 ^d	12	2.1 ^d	1.1	0.5–2.4
Males	27	3.3 ^d	7	1.5	2.2	1.0–5.6
Genitourinary disease	27	2.1^d	26	2.4^d	0.9	0.5–1.6
Females	15	2.9 ^d	17	2.8 ^d	1.0	0.5–1.9
Males	12	1.6 ^d	9	2.0	0.8	0.3–2.0
Ill-defined symptoms	14	2.1^d	4	0.3^d	1.7^d	1.5–1.8
Females	6	2.2	1	0.1 ^d	1.8 ^d	1.6–2.1
Males	8	2.0	3	0.5	1.5 ^d	1.4–1.7
Violent/external causes	88	2.7^d	67	2.2^d	1.2	0.9–1.7
Females	31	3.1 ^d	29	2.2 ^d	1.3	0.8–2.3
Males	57	2.6 ^d	38	2.2 ^d	1.2	0.8–1.8
All causes previously related to Thorotrast^f	617	4.6^d	216	1.5^d	3.1^d	2.6–3.6
Females	295	4.8 ^d	113	1.4 ^d	3.3 ^d	2.7–4.2
Males	322	4.4 ^d	103	1.5 ^d	2.9 ^d	2.3–3.6
All other causes of mortality	973	2.4^d	687	1.8^d	1.3^d	1.1–1.4
Females	405	2.5 ^d	327	1.7 ^d	1.3 ^d	1.2–1.6
Males	568	2.4 ^d	360	2.0 ^d	1.2 ^d	1.1–1.4

^a Includes 1,733 patients who underwent cerebral angiography with Thorotrast, were free of neoplasms at that time, and survived 2 or more years. This group includes patients from the United States, Denmark and Sweden.

^b Includes 1,407 patients who underwent cerebral angiography with a nonradioactive contrast agent, were free of neoplasms at that time, and survived 2 or more years. This group includes patients from the United States and Denmark.

^c Relative risk of Thorotrast exposed compared with nonexposed patients, adjusted for geographic region (United States; Denmark and Sweden), age and sex.

40 years, and 44 for 50 years after injection. At last follow-up, 9.1% and 14.6% of the Thorotrast-exposed and comparison patients, respectively, had lived to be 80 or more years old.

Characteristics of Patients Stratified by Country

Denmark, Sweden and the United States contributed 44.7%, 29.3% and 26.0% of Thorotrast-exposed patients, respectively, to the final study population (Table 2). The mean age at Thorotrast injection was 36.2 years, with a range of 33.9 to 41.2 years among the three countries. The average age at injection for the comparison group was 37.7 years. Overall, the mean total volume of injected Thorotrast was 20.1 ml, with larger cumulative amounts received by patients who had multiple procedures. The largest mean cumulative volume (26.4 ml) of Thorotrast was that for United States patients, 7% of whom had two or more angiographic procedures.

The mean length of follow-up since injection was 26.6 years in the Thorotrast group (median 26.4; range 2–64 years) and 24.6 years in the comparison cohort (median 24.7; range 2–45 years). Completeness of follow-up was high for all countries (98% in Denmark, 100% in Sweden, and 94% in the United States). Only 2.5% and 2.0% of patients in the Thorotrast and comparison groups, respectively, were lost to follow-up. There were 1,599 deaths (92.1%) in the Thorotrast cohort and 908 (64.5%) in the comparison group. The cause of death was available for nearly all deceased patients (100%, Denmark; 99.7%, Sweden; 98.0%, United States).

Cause-Specific Mortality: Overall and by Gender

Compared with the general population, significantly increased SMRs were observed for most causes of death in both the Thorotrast and comparison groups (Table 3). For all causes of death taken together, the SMRs for the Thorotrast and comparison cohorts were 3.0 and 1.7, respectively, with a stratified relative risk of 1.7 (95% CI: 1.5–1.8) for the Thorotrast patients. Thorotrast-exposed patients experienced a significantly elevated risk of death due to several causes, including cancer (RR 2.8), benign and unspecified tumors (RR 1.5), benign hematological disease (RR 7.1), cerebrovascular disease (RR 1.6), and benign liver disease (RR 6.5). Nonsignificant 40% and 60% excess relative risks of mortality due to respiratory disease or other types of digestive disease, respectively, were also noted.

Significantly increased mortality (RR 3.1) was observed for all causes of death previously attributed to Thorotrast [i.e., cancer, benign hematological disease, and benign liver disease combined (11)]. Mortality due to all other causes was also significantly increased (RR 1.3) for the Thorotrast group. For most causes of death, relative risks varied little between males and females. For benign liver disorders, the standardized mortality ratio for female Thorotrast patients was about two times higher than that for males; the relative risk was about three times higher in females compared with males.

Cause-Specific Mortality in Relation to Time since Angiography

The relative risks for all causes of death taken together for the Thorotrast-exposed patients were 1.1, 1.4, 1.7, 2.2 and 2.8 in the 2–9-year, 10–19-year, 20–29-year, 30–39-year, and 40+-year intervals, respectively ($P < 0.001$, Table 4). Risk due to cancer also increased steadily for five decades after Thorotrast injection, to reach sevenfold in the 40+-year interval ($P < 0.001$). Similar temporal patterns were apparent for males and females. Fifty years after Thorotrast exposure, a significantly increased risk (SMR 8.6, $n = 14$; data not shown) of cancer mortality compared with the general population remained evident; insufficient follow-up time of the comparison group precluded estimation of relative risks.

Relative risks increased significantly with time since Thorotrast exposure for benign and unspecified tumors ($P = 0.001$), respiratory disease ($P = 0.013$), benign hematological disease ($P = 0.001$), benign liver disease ($P < 0.001$), and other digestive disorders ($P = 0.046$). The largest risks (RR 3.8) for death due to respiratory disease were observed 40 or more years after injection. The relative risk increased with time after arteriography, not only for all causes previously related to Thorotrast ($P < 0.001$), but also for all other causes of mortality considered together ($P < 0.001$).

Cause-Specific Mortality in Relation to Cumulative Radiation Dose Surrogate

Relative risks of mortality increased significantly with increasing cumulative radiation dose surrogate (Table 5) due to all causes of death taken together ($P < 0.001$), and for cancer ($P < 0.001$), respiratory disease ($P = 0.014$), benign liver disorders ($P < 0.001$), and genitourinary disease ($P = 0.017$), and marginally for other types of digestive disease ($P = 0.067$) and infection ($P = 0.09$). Detailed cause-of-death codes available for 25 of the 42 Thorotrast patients (Sweden and the United States) who died of other digestive disease showed that six died due to intestinal obstruction or fistula (compared with one patient in the comparison group). For all causes of mortality previously related to Thorotrast, risk increased with cumulative radiation

^d $P < 0.05$.

^e Prior to 1951, deaths due to brain tumors (malignant or benign) in Denmark were usually classified as tumors of unspecified nature for both Thorotrast-exposed and comparison patients.

^f Includes cancer including leukemia, benign blood disorders, and benign liver disease.

TABLE 4
Observed Numbers of Deaths and Standardized Mortality Ratios among Thorotrast-Exposed and Nonexposed Patients (with Relative Risks for the Thorotrast Group) by Follow-up Period and Selected Cause of Death

	Follow-up period (years)					
	2-9		10-19		20-29	
Number of patients						
Thorotrast	1,736		1,493		1,139	
Comparison group	1,407		1,176		949	
Person-years						
Thorotrast	9,204		12,181		9,251	
Comparison group	10,242		10,618		8,174	
Cause of death	Observed	SMR	Observed	SMR	Observed	SMR
All causes combined						
Thorotrast	236	3.4 ^a	343	2.5 ^a	408	2.7 ^a
Comparison group	223	3.0 ^a	222	1.7 ^a	233	1.5 ^a
Relative risk ^b (95% CI)	1.1 (0.9-1.3)		1.4 ^a (1.2-1.7)		1.7 ^a (1.4-2.0)	
Infections						
Thorotrast	5	1.5	2	0.9	5	4.2
Comparison group	4	2.9	0	0.0	3	4.0
Relative risk (95% CI)	0.6 (0.2-2.6)		—		1.2 (0.3-5.8)	
Cancer (including leukemia)						
Thorotrast	42	2.8 ^a	70	2.2 ^a	121	3.4 ^a
Comparison group	48	2.3 ^a	42	1.2	59	1.5 ^a
Relative risk (95% CI)	1.1 (0.7-1.7)		1.7 ^a (1.1-2.4)		2.1 ^a (1.6-2.9)	
Benign and unspecified tumors						
Thorotrast	42	57.1 ^a	19	19.8 ^a	10	13.2 ^a
Comparison group	25	36.5 ^a	7	10.5 ^a	5	8.2 ^a
Relative risk (95% CI)	1.3 (0.8-2.1)		1.6 (0.7-4.0)		1.4 (0.5-4.4)	
Benign hematological disease						
Thorotrast	2	6.2	7	15.3 ^a	5	12.3 ^a
Comparison group	1	3.9	0	0.00	1	3.3
Relative risk (95% CI)	1.6 (0.2-34.6)		—		3.2 (0.5-60.0)	
Cardiac disease						
Thorotrast	46	1.7 ^a	82	1.4 ^a	87	1.3 ^a
Comparison group	44	1.6 ^a	65	1.2	78	1.2
Relative risk (95% CI)	1.1 (0.8-1.6)		1.1 (0.8-1.6)		1.1 (0.8-1.4)	
Respiratory disease						
Thorotrast	2	0.7	18	3.1 ^a	20	2.4 ^a
Comparison group	6	2.3	15	2.4 ^a	17	1.7
Relative risk (95% CI)	0.3 (0.04-1.2)		1.3 (0.7-2.7)		1.4 (0.7-2.7)	
Benign liver disorders						
Thorotrast	1	0.7	7	3.1 ^a	21	9.6 ^a
Comparison group	3	1.7	3	1.2	2	0.8
Relative risk (95% CI)	0.5 (0.02-3.5)		2.9 (0.8-13.2)		11.9 ^a (3.5-72.9)	
Digestive disease (other)						
Thorotrast	2	0.8	12	3.1 ^a	11	3.0 ^a
Comparison group	6	3.2 ^a	4	1.6	3	1.2 ^a
Relative risk (95% CI)	0.2 (0.03-1.0)		1.8 (0.6-6.5)		2.3 (0.7-0.2)	
Genitourinary disease						
Thorotrast	1	0.4	7	1.8	12	3.3 ^a
Comparison group	5	2.0	10	3.0 ^a	6	2.3
Relative risk (95% CI)	0.2 (0.01-1.2)		0.6 (0.2-1.6)		1.4 (0.6-4.1)	
All causes previously related to Thorotrast ^d						
Thorotrast	45	2.7 ^a	84	2.4 ^a	147	3.9 ^a
Comparison group	52	2.3 ^a	45	1.2	62	1.4 ^a
Relative risk (95% CI)	1.1 (0.7-1.6)		1.9 ^a (1.3-2.7)		2.5 ^a (1.9-3.4)	
All other causes of mortality						
Thorotrast	188	3.6 ^a	259	2.5 ^a	259	2.3 ^a
Comparison group	168	3.2 ^a	176	1.9 ^a	170	1.5 ^a
Relative risk (95% CI)	1.1 (0.9-1.3)		1.3 ^a (1.1-1.6)		1.4 ^a (1.2-1.7)	

TABLE 4
Extended

Follow-up period (years)				<i>P</i> value for trend ^c
30–39	40+			
710		310		
701		240		
5,090		1,816		
4,945		590		
Observed	SMR	Observed	SMR	
395	3.4 ^a	217	3.5 ^a	
202	1.4 ^a	28	1.2	
2.2 ^a (1.9–2.6)		2.8 ^a (1.9–4.3)		<i>P</i> < 0.001
3	4.1 ^a	2	5.2	
5	7.4 ^a	0	0.00	
0.5 (0.1–2.1)		—	—	<i>P</i> > 0.50
177	6.1 ^a	116	7.8 ^a	
46	1.3	6	1.0	
4.5 ^a (3.3–6.3)		7.3 ^a (3.5–18.7)		<i>P</i> < 0.001
12	28.6 ^a	5	16.4 ^a	
4	5.6 ^a	0	0.00	
4.8 ^a (1.6–17.3)		—	—	<i>P</i> = 0.001
2	8.8 ^a	3	23.3 ^a	
0	0.00	0	0.00	
—	—	—	—	<i>P</i> = 0.001
66	1.3 ^a	39	1.5 ^a	
67	1.2	10	1.1	
1.1 (0.8–1.5)		1.3 (0.7–2.7)		<i>P</i> = 0.33
19	2.6 ^a	10	2.1 ^a	
14	1.3	1	0.5	
1.8 (0.9–3.7)		3.8 ^a (0.7–67.8)		<i>P</i> = 0.013
33	21.0 ^a	10	16.6 ^a	
4	2.0	1	3.8	
9.8 ^a (3.9–32.6)		5.0 (1.0–89.7)		<i>P</i> = < 0.001
10	3.9 ^a	7	5.2 ^a	
4	1.5	2	3.8	
2.3 (0.8–8.4)		1.3 (0.3–8.8)		<i>P</i> = 0.046
5	2.5 ^a	2	2.3 ^a	
4	2.1	1	3.2	
1.0 (0.3–4.1)		0.8 (0.1–16.3)		<i>P</i> > 0.50
212	6.9 ^a	129	8.2 ^a	
50	1.3	7	1.1	
5.0 ^a (3.7–6.9)		7.2 ^a (3.6–16.9)		<i>P</i> < 0.001
181	2.1 ^a	86	1.8 ^a	
152	1.5 ^a	21	1.2	
1.3 ^a (1.1–1.7)		1.5 (0.9–2.4)		<i>P</i> < 0.001

dose, but a similar trend was not observed for all other causes of mortality taken together.

Cause-Specific Cumulative Risk of Mortality

The cumulative risk of death due to all cancer in relation to injected dose of Thorotrast and time since arteriography is shown in Fig. 1a. Fifty years after arteriography, the cumulative risk of death from cancer was 58.8%, 74.5% or 87.4% for patients injected with 3–10 ml, 11–20 ml, or >20 ml of Thorotrast, respectively (*P* for nonhomogeneity in dose category = 0.0001). The cumulative risk in the comparison group was 39.0% at 45 years after arteriography; by the end of the study, none of the comparison group patients had been followed for 50 years. The cumulative risk of death due to cancer did not vary by gender within the various Thorotrast dose groups or in the comparison patients.

The cumulative risk of death due to benign liver disease, which was similar for males and females, also increased with increasing volume of Thorotrast to reach 27.4% at 50 years after arteriography for those given over 20 ml (*P* for nonhomogeneity in dose category = 0.0001; Fig. 1b). The cumulative risk of mortality due to benign liver disease for the comparison group reached 4.1% after 45 years. Patients who received the largest volumes of Thorotrast (>20 ml) had a consistently higher cumulative risk of mortality due to respiratory disease relative to the comparison group and the other groups as well, but the differences were not significant (Fig. 1c).

For causes of mortality previously related to Thorotrast, the cumulative risk of death increased with the volume of Thorotrast injected and the time since arteriography (Fig. 1d; *P* for nonhomogeneity in dose category = 0.0001). For all other causes of mortality, the cumulative risks 50 years after arteriography were 76.4%, 80.3% and 85.2% for patients injected with 3–10 ml, 11–20 ml, and >20 ml of Thorotrast, respectively (*P* for nonhomogeneity in dose category = 0.0012; data not shown). The cumulative risk for the comparison patients was 65.8% at 45 years after cerebral arteriography.

DISCUSSION

Major findings in our investigation include the persistent increases in excess mortality rates that lasted for over five decades after administration of Thorotrast. Excesses in can-

←

^a *P* < 0.05.

^b Relative risk of indicated outcome for Thorotrast-exposed compared with nonexposed patients, adjusted for geographic region (United States; Denmark and Sweden), age, sex and calendar year.

^c *P* value for temporal trend in relative risk.

^d Includes cancer including leukemia, benign hematological disease, and benign liver conditions.

TABLE 5
Observed Number of Deaths, Standardized Mortality Ratios, and Relative Risks in Relation to Cumulative Radiation Dose Surrogate^a

Cause of death	Estimated cumulative radiation dose surrogate [ml of injected Thorotrast × max (0, years since injection - 5) × 10 ⁻²]					
	0-70			71-179		
	Observed	SMR RR	(95% CI) (95% CI)	Observed	SMR RR	(95% CI) (95% CI)
All causes combined	196	3.7 ^b 0.6 ^b	(3.2-4.2) (0.5-0.7)	192	2.2 ^b 0.5 ^b	(1.9-2.6) (0.4-0.6)
Infections	4	1.5 0.5	(0.5-3.4) (0.1-2.1)	3	2.2 0.6	(0.5-5.7) (0.1-2.6)
Cancer (including leukemia)	32	2.8 0.3 ^b	(1.9-3.8) (0.2-0.4)	44	2.2 ^b 0.3 ^b	(1.6-2.9) (0.2-0.4)
Benign and unspecified tumors	37	59.8 ^b 2.6	(42.6-81.2) (1.2-6.1)	12	19.3 ^b 1.1	(10.4-32.4) (0.4-2.7)
Benign hematological disease	1	3.9 0.1	(0.2-17.0) (0.004-0.9)	3	10.6 ^b 0.5	(6.6-27.4) (0.1-2.1)
Cardiac disease	39	2.0 ^b 1.0 ^b	(1.4-2.6) (0.7-1.5)	44	1.2 0.7	(0.9-1.6) (0.5-1.0)
Respiratory disease	1	0.5 0.1 ^b	(0.02-2.1) (0.03-0.4)	8	2.2 0.6	(1.0-4.1) (0.3-1.3)
Benign liver disorders	1	0.9 0.1 ^b	(0.05-4.1) (0.003-0.2)	3	2.2 0.1 ^b	(0.5-5.6) (0.03-0.3)
Digestive disease (other types)	2	1.0 0.2 ^b	(0.2-3.2) (0.02-0.6)	7	2.9 0.6	(1.2-5.6) (0.2-1.4)
Genitourinary disease	0	0 0	(0-1.0) 0	8	3.1 0.8	(1.4-5.8) (0.3-2.3)
All causes previously related to Thorotrast ^d	34	2.6 0.3 ^b	(1.8-3.6) (0.2-0.4)	50	2.3 ^b 0.3 ^b	(1.7-3.0) (0.2-0.4)
All other causes of mortality	160	4.0 ^b 1.0	(3.4-4.7) (0.8-1.2)	142	2.2 ^b 0.7 ^b	(1.9-2.6) (0.6-0.9)

Note. CI, confidence interval.

^a Results in table are limited to 1,377 patients for whom the administered amount of Thorotrast was known and who did not have Thorotrastomas recorded.

^b $P < 0.05$.

^c P value for trend in relative risk with cumulative radiation dose surrogate.

^d Includes cancer including leukemia, benign blood disorders, and benign liver disease.

cer deaths dominated the overall lifetime patterns. However, a strong baseline burden of illness exists in the study population, as indicated by the elevated SMRs for practically all causes of death. Higher mortality than the general population for most causes of death is likely related to the underlying conditions that prompted angiographic examination. A study design using a comparison group of patients who underwent cerebral angiography with a nonradioactive contrast agent helped to distinguish the effects of Thorotrast exposure from those related to indications for angiography. However, because subjects were not matched on indication for angiography, differences between the exposed and comparison groups in the underlying conditions could still confound the comparison. In particular, it is likely that, throughout our study population, Thorotrast may have been preferred for the diagnosis of suspected vascular disorders because its exceptional radio-opacity permitted optimal visualization (17); the excess in deaths due to cerebrovascular disease among Thorotrast-exposed patients is consistent

with this possibility. The effect of the non-overlapping years of cerebral angiography in Denmark, which adds to the noncomparability of the unexposed group, has been reviewed extensively by Andersson *et al.* (11). Because Thorotrast was virtually the only contrast agent in use in Denmark before 1945, a comparison group injected during the same calendar years could not be assembled. It is likely that indications for angiography became less strict in the later period, as radiologists became more familiar with the procedure. Thus the profile of underlying diseases in the comparison group may not be identical to those in the Thorotrast-exposed patients, who were possibly more severely ill. As a result, since the force of mortality may vary because of differences in presenting diseases, even when SMRs are adjusted by means of a comparison group, confounding by indication may still be present.

Quantification of the Thorotrast organ dose is difficult because of the continuous nature of the exposure, the dose received after the initiating events were past or which may

TABLE 5
Extended

Estimated cumulative radiation dose surrogate [ml of injected Thorotrast × max (0, years since injection - 5) × 10 ⁻²]						
180-336			337-2309			<i>P</i> value for trend ^c
Observed	SMR RR	(95% CI) (95% CI)	Observed	SMR RR	(95% CI) (95% CI)	
304	2.4 ^b	(2.2-2.7)	591	3.8 ^b	(3.5-4.1)	<0.001
	0.6 ^b	(0.5-0.7)		1.0		
2	1.9	(0.3-5.7)	6	5.5 ^b	(2.2-11.2)	0.09
	0.4	(0.1-1.8)		1.0		
96	3.3 ^b	(2.6-3.9)	257	6.6 ^b	(5.9-7.5)	<0.001
	0.4 ^b	(0.4-0.6)		1.0		
13	21.5 ^b	(11.8-35.4)	10	15.3 ^b	(7.7-26.9)	0.046
	1.4	(0.6-3.3)		1.0		
5	16.0 ^b	(5.7-34.3)	6	17.5 ^b	(6.9-35.4)	0.344
	0.9	(0.2-2.9)		1.0 ^b		
71	1.3 ^b	(1.0-1.6)	104	1.6 ^b	(1.3-1.9)	>0.50
	0.8	(0.6-1.1)		1.0		
16	2.3 ^b	(1.3-3.6)	27	2.7 ^b	(1.8-3.9)	0.014
	0.9	(0.5-1.7)		1.0 ^b		
10	5.4 ^b	(2.7-9.5)	44	18.4 ^b	(13.5-24.4)	<.001
	0.3 ^b	(0.1-0.6)		1.0		
9	3.1 ^b	(1.5-5.5)	14	4.2 ^b	(2.4-6.8)	0.067
	0.7 ^b	(0.3-1.6)		1.0 ^b		
3	1.0	(0.3-2.7)	9	3.2 ^b	(1.6-5.8)	0.17
	0.3 ^b	(0.1-0.9)		1.0		
111	3.5 ^b	(2.9-4.2)	307	7.4 ^b	(6.6-8.3)	<0.001
	0.4 ^b	(0.4-0.5)		1.0 ^b		
192	2.0 ^b	(1.8-2.3)	280	2.4 ^b	(2.2-2.7)	0.237
	0.8	(0.7-1.0)		1.0		

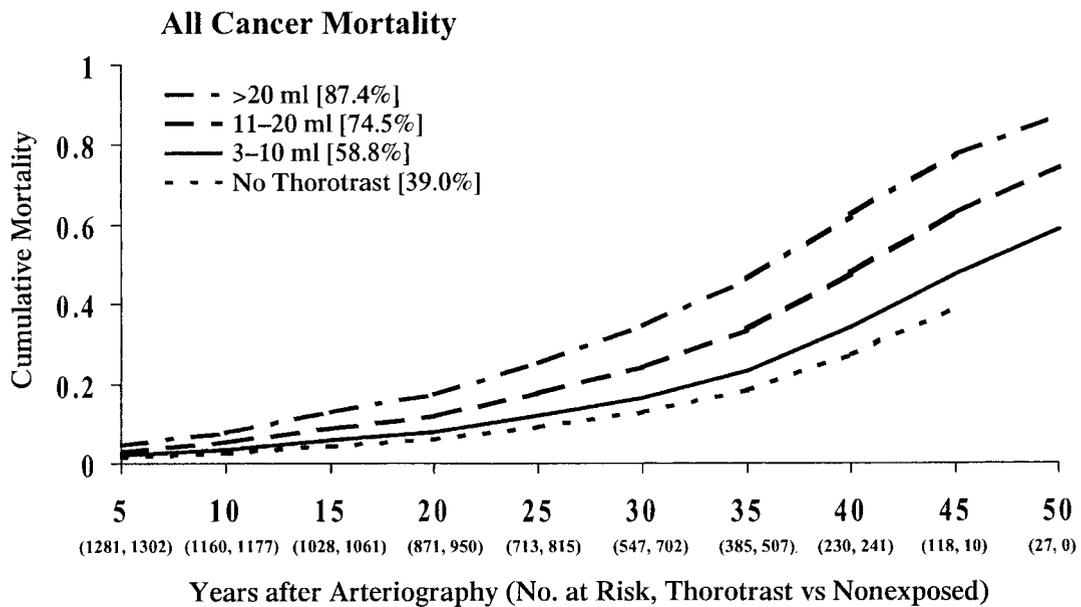


FIG. 1a. Cumulative mortality due to cancer among Thorotrast-exposed patients in relation to the injected dose of Thorotrast and years since arteriography (*P* for nonhomogeneity in dose category = 0.0001). The figure includes only those patients (*n* = 1,377) for whom the injected volume of Thorotrast was recorded and for whom extravasation did not occur. Data are also shown for a comparison group of 1,407 patients who underwent cerebral angiography with a nonradioactive contrast medium. Percentages in brackets indicate the actuarial risk for all cancer mortality at 50 years for Thorotrast patients and at 45 years for the comparison group.

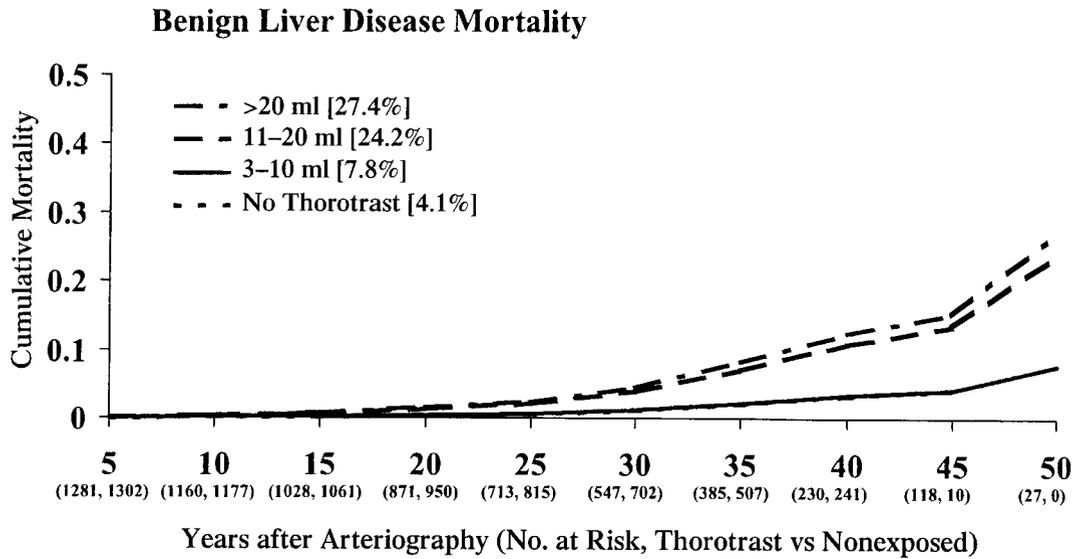


FIG. 1b. Cumulative mortality due to benign liver disease among Thorotrast-exposed patients in relation to the injected dose of Thorotrast and years since arteriography (P for nonhomogeneity in dose category = 0.0001). Figure includes only those patients ($n = 1,377$) for whom the injected volume of Thorotrast was recorded and for whom extravasation did not occur. Data are also shown for a comparison group of 1,407 patients who underwent cerebral angiography with a nonradioactive contrast medium. Percentages in brackets indicate the actuarial risk for all liver disease mortality at 50 years for Thorotrast patients and at 45 years for the comparison group.

have resulted in killing of transformed cells, and the impact of tissue necrosis and regeneration (especially of the liver) on subsequent risk from the protracted exposure. Thus, for simplicity, our analyses were based primarily on the volume of injected Thorotrast to facilitate comparisons with other studies. Even then, volumes of Thorotrast obtained from medical records may be overestimates compared to

data obtained by whole-body counting (18). Thorotrastomas occurred not infrequently and resulted in local deposits of Thorotrast that were not distributed systemically. Although Thorotrastomas were noted in only a small percentage of patients in our series, this assessment was based on a retrospective review of records, and ascertainment was likely not complete.

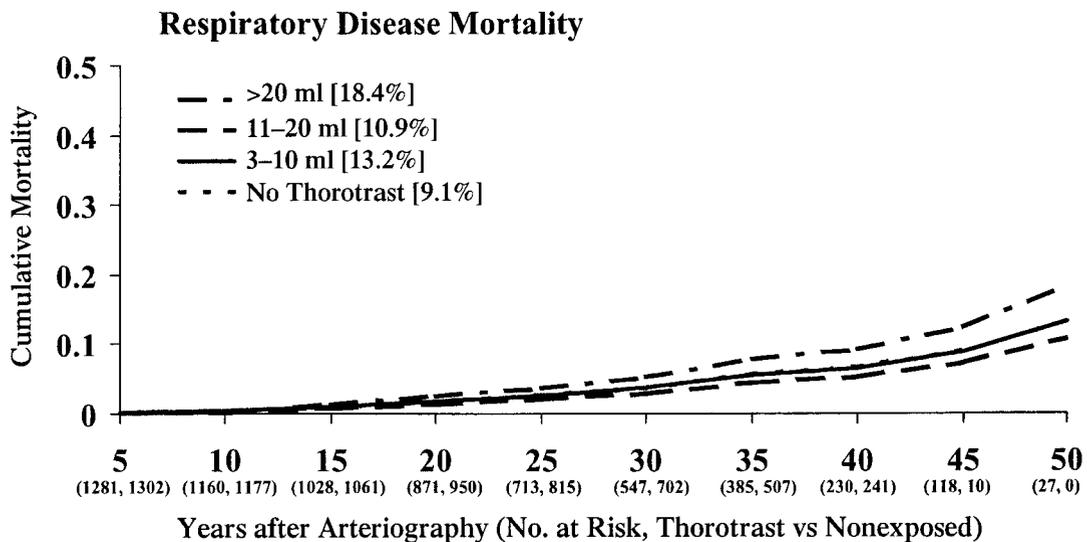


FIG. 1c. Cumulative mortality due to respiratory disease among Thorotrast-exposed patients in relation to the injected dose of Thorotrast and years since arteriography. Figure includes only those patients ($n = 1,377$) for whom injected volume of Thorotrast was recorded and for whom extravasation did not occur. Data are also shown for a comparison group of 1,407 patients who underwent cerebral angiography with a nonradioactive contrast medium. Percentages in brackets indicate the actuarial risk for all respiratory disease mortality at 50 years for Thorotrast-exposed patients and at 45 years for the comparison group.

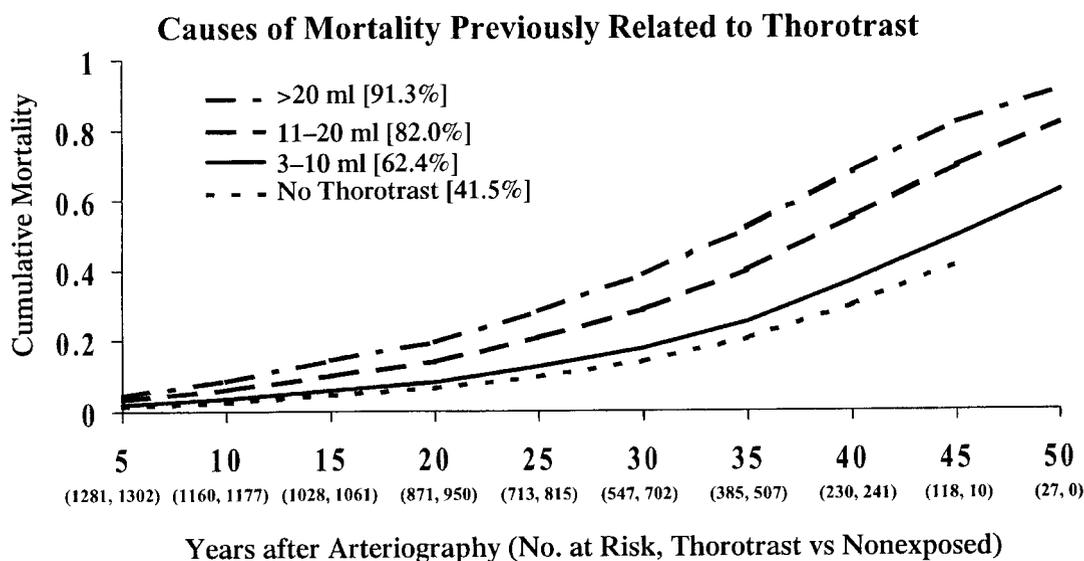


FIG. 1d. Cumulative mortality due to causes previously related to Thorotrast among exposed patients in relation to the injected dose and years since arteriography (P for nonhomogeneity in dose category = 0.0001). Figure includes only those patients ($n = 1,377$) for whom injected volume of Thorotrast was recorded and for whom extravasation did not occur. Data are also shown for a comparison group of 1,407 patients who underwent cerebral angiography with a nonradioactive contrast medium. Percentages in brackets indicate the actuarial risk for all Thorotrast-related mortality at 50 years and at 45 years for the comparison group.

Despite the intrinsic weaknesses of Thorotrast studies with regard to precise estimates of radiation risks, patients have been studied effectively in several other countries, including Germany (19), Portugal (20) and Japan (21). In the German cohort, patients ($n = 2,326$) underwent either cerebral (70%) or other (30%) types of angiography; comparison subjects were matched by age and sex, and consisted of a diverse group of hospital patients who were not matched with regard to index disease or hospital department and most of whom did not undergo angiography. All Thorotrast-exposed and comparison patients were followed successfully.

The Portuguese series 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 (20). 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 followed successfully.

In the combined Japanese study (21), 412 of 416 Thorotrast-exposed male patients were followed through 1998. All subjects were injected with Thorotrast intravascularly for the diagnosis of war-related trauma, but it was not clear how many, if any, had cerebral angiography. The comparison group included war-wounded males matched to the Thorotrast-exposed patients by age and time of hospitalization, without regard to angiography status. Selected cancer mortality, liver cirrhosis and all-cause mortality were eval-

uated for the combined cohort, with selected causes of mortality analyzed for a subset of patients ($n = 255$) (22). Our findings are reviewed below and compared with those reported recently in these other Thorotrast series.

Hepatosplenic Effects

The sites of major organ deposition of Thorotrast include the liver, spleen and bone marrow, which retain approximately 60%, 20% and 12% of an injected dose, respectively (23). Smaller amounts remain in calcified bone (3%) (23) and lung (0.7%) (24). Radiation dose is related to the site of Thorotrast deposition and exposure time, leading to the expectation that deaths due to hepatic causes, in particular, would be in excess. The dose to the liver is estimated to be about 40 cGy per year from a typical injection of Thorotrast (23), resulting in a cumulative dose of 16 Gy at 40 years. The significant excesses of death due to benign liver disease in our series, which increased with injected volume of Thorotrast, are due in large part to liver cirrhosis (19, 21, 25); the 6.5-fold relative risk of death which we found was comparable in magnitude to excesses observed in Portugal (RR 5.7) (20), Japan (RR 8.6 and RR 7.5) (21, 22), and Germany (RR 6.0) (19). Gender differences in mortality from benign liver disease were not evaluated for the Portuguese and German cohorts, which included both females and males, and could not have been addressed in the Japanese cohorts, which included only males. The 3-fold gender difference (females:males) in relative risk of mortality from benign liver disease that we observed has not been noted previously. Since the amount of injected Tho-

rotrast was similar for males and females in our study, the large risks could reflect the smaller liver volumes of females, but may also reflect the different background rates for this disease in men and women. The cumulative rate of liver cirrhosis in the German series of Thorotrast patients was also dependent on injected dose (19), and a dose-related increase in liver cirrhosis was reported among atomic bomb survivors (26).

Thorotrast exposure results in eventual atrophy of the spleen and functional asplenia (3, 27), with subsequent compromise of the immune system; patients may also experience a functional reticuloendothelial blockade and immune abnormalities (28). However, no significant excess mortality due to infections was apparent in either the Portuguese (20) or Japanese (22) series, but the possible effects of Thorotrast dose were not addressed. In our series, the relative risk of death due to infection was not increased significantly for any category of cumulative radiation dose, and no excess overall risk was observed. Further, the risk of death due to infection was higher for the nonexposed patients than for the Thorotrast-exposed patients. Thus, although a biological rationale for an effect of Thorotrast on the immune system may exist, it does not appear to translate convincingly into an increased risk of death due to infection.

Benign Hematological Disease

Relative to the comparison cohort, subjects exposed to Thorotrast also had significantly increased mortality due to benign blood diseases, which includes bone marrow failure and aplastic anemia. Thorotrast deposits throughout the red marrow (29), where it conceivably irradiates all cellular elements, inducing both leukemia (30) and bone marrow failure. The annual absorbed dose to bone marrow from a 25-ml injection of Thorotrast has been estimated as 10 cGy (23), which would result in a dose of 3 to 4 Gy over 30 to 40 years. Compared to the general population, excess deaths from benign blood diseases occurred throughout most follow-up periods in our survey, likely reflecting the ongoing radiation exposure. The lengthy interval between Thorotrast administration and death due to benign hematological disorders is similar to the average latent period of 8 to 40 years for the development of leukemia in these patients (31). It is possible that infection due to leukopenia may also have played a role in the deaths of some subjects. Significantly elevated mortality due to benign hematological diseases was recently observed in the Portuguese Thorotrast study (20).

Cytogenetic studies of patients administered Thorotrast years ago indicate that about 30% of all peripheral blood lymphocytes contain one or more chromosome aberrations (in contrast to about 1% in a normal population), the majority being stable-type aberrations such as translocations (32). This suggests that Thorotrast patients continue to accumulate a substantial population of cytogenetically aber-

rant lymphoid stem cells as a result of chronic exposure to α particles, and that while the arrangements are complex, there is a meaningful proportion of aberrations that are not unstable, resulting in eventual cell death. Further, cytogenetic studies did not find chromatid-type aberrations in lymphocyte metaphases (32, 33), providing little evidence for the continuing expression of the genomic instability that has been reported in human hematopoietic stem cells exposed to α particles *in vitro* (34).

Respiratory Disorders

Radon-220, a decay product of both radium and thorium, has been detected in the exhaled breath of Thorotrast patients (35). The temporal pattern of elevated risks which we observed for death due to respiratory disease and association of increased risk with cumulative radiation dose are provocative, and are consistent with a possible relationship with the constant exhalation of radon. Cumulative mortality due to respiratory disease remained highest over time for those patients who received the largest doses (>20 ml) of Thorotrast, and who presumably exhaled the largest amounts of radon. Radiation at high therapeutic doses is associated with lung injury, including interstitial fibrosis (36); whether pulmonary damage is incurred at the chronic low doses delivered in Thorotrast patients (5.3 mGy/year) (37) is not known, but it seems unlikely. Chronic interstitial fibrosis, eventually resulting in death, is a well-established complication of radon exposure in uranium miners who inhaled enormous levels of radon decay products (38), but the role of other factors must also be considered. Interstitial fibrosis has been reported in association with lung cancer in one Thorotrast-exposed patient (39), and one Thorotrast subject was also found with pulmonary fibrosis at 45 years after thoracic fistulography (40). In the updated follow-up of Thorotrast-exposed Portuguese patients (20), a significantly increased 3.8-fold risk of death due to respiratory diseases was noted; however, no clear trend with time since Thorotrast injection was apparent.

Cancer

Excess cancer deaths attributable to Thorotrast increased throughout the period of observation and remained elevated for 50 years after Thorotrast injection, indicating that its carcinogenic effects persist for life. All Thorotrast studies have reported significantly elevated risks of cancer mortality, in particular liver cancer (11, 12, 19–21). Minimal latent periods for liver cancer in Thorotrast-exposed patients are lengthy, ranging from 16 to 22 years after initial injection (19, 41, 42). External radiation has been linked with an increased risk of liver cancer (primarily hepatocellular carcinoma) in the atomic bomb survivors, although it is likely that viral cofactors play an important, if not necessary, role (43). In contrast, investigations of cancer incidence among Thorotrast-exposed patients have shown that the 120-fold increased risk of liver cancer (44) is due large-

ly to angiosarcomas and cholangiocarcinomas (42, 45). Hepatic angiosarcoma, a rare subtype, has also been linked with exposure to arsenic (46) and vinyl chloride (46) and perhaps with the long-term use of androgenic-anabolic steroids (47). Molecular analyses of the *TP53* gene in angiosarcomas among Thorotrast patients have found mutations in some series (48), but not others (11), and multiple point mutations in *KRAS2* have been reported in sporadic and Thorotrast-associated angiosarcomas (49). Numerous molecular mechanisms are involved in carcinogenesis, and comprehensive genetic profiles of Thorotrast-induced liver tumors compared with sporadic liver neoplasms are needed.

Other Effects

Mortality due to other types of digestive disease and genitourinary disorders was found to increase significantly with the increasing cumulative radiation dose surrogate for Thorotrast. A nonsignificant overall 60% excess of deaths due to other digestive diseases was observed, which differs from the significantly elevated 4.5-fold risk of mortality due to these conditions observed recently by Portuguese investigators (20). The observation that small amounts of Thorotrast are excreted through the kidneys (50) suggests that long-term exposure to α -particle radiation may have contributed to diseases of genitourinary sites (51).

The elevated risk of death due to causes of mortality not previously related to Thorotrast and the patterns with time after arteriography and injected volume suggest that Thorotrast-induced sequelae may extend beyond those documented previously in the literature. Some of these effects might include respiratory disease, other types of digestive disease besides liver cirrhosis, and genitourinary disease, as reviewed earlier. The strength of this possibility is mitigated by the fact that many of the patients studied were seriously ill when given Thorotrast and that these underlying illnesses may have contributed to the excess mortality.

Comments

A number of series of Thorotrast patients have been followed extensively (52). Most subjects, like those in our investigation, have been studied to the end of life for all practical purposes. Only 94 (5.4%) of Thorotrast patients were known to be alive at the closure of the study. This multicenter survey in the United States, Sweden and Denmark was undertaken to learn whether any additional insights into high-LET radiation carcinogenesis could be gleaned. It is important to note that the increased risk of cancer persists for life, which is not unexpected since the thorium remains in the body and continually exposes tissue, especially liver and active bone marrow. The excess probability of excess cancer mortality approaches 50%, indicating that Thorotrast might be one of the most carcinogenic substances evaluated to date. Thus clinicians should be apprised of the risks of cancer and other disorders incurred by these unfortunate subjects, whose complications contin-

ue to be described in the medical literature (3–7). It is evident from our survey and from the results of other Thorotrast studies that low-dose chronic exposure to α particles can accumulate to a large organ dose to sensitive tissues and result not only in a very high risk of cancer, but increased mortality from selected non-cancer causes as well, especially of the liver and blood-forming organs.

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