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Mortality among Thorotrast-exposed patients and an unexposed comparison group in the German Thorotrast study ☆

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ABSTRACT

Thorotrast was the brand name of a stabilised colloidal solution of thorium dioxide which was used preferentially as an X-ray contrast medium for arteriography between 1930 and 1950. The administration of the medium led to lifelong chronic α-particle irradiation by thorium decay products, mainly in the organs of deposition. Several epidemiological follow-up studies were set up after recognition of these side-effects among which the German study was the largest. After an extended follow-up, by 2004 only nine out of 2326 originally exposed subjects were still alive (while 151 of the comparison group, which originally numbered 1890 subjects, survived) and partially more than 70 years observation and chronic exposure time could be studied allowing for further observations to be made about long-term mortality effects of Thorotrast exposure. Median life-expectancy was shortened by 14 years and mortality increased, affecting total mortality (SMR = 287 for males, SMR = 387 for females) as well as cause-specific, especially liver cancer (SMR = 16,695 and SMR = 12,680, respectively), and the haematopoietic system (SMR = 556 and SMR = 504, respectively), but not lung cancer. Mortality (total and selected cause-specific) increased with cumulative time since first exposure.

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1. Introduction

Thorotrast was the brand name of a stabilised colloidal solution of thorium dioxide which was used as an X-ray contrast medium for arteriography between 1930 and 1950. Since the intravascular administration led to a lifelong storage of thorium dioxide particles in the organs of the reticuloendothelial system, and thorium-232 is a radioactive agent with a half-time of 1.4×10^{10} years, the administration of the medium implied a lifelong chronic α-particle irradiation by thorium decay products in the organs of deposition, from the daughter products of radon-220 in the lungs, and from radium-224 and its decay products in the skeletal system. Due to these side effects, the use of the contrast medium was banned and its production stopped in 1949/50.[1]

The first epidemiological Thorotrast study was started in Denmark in 1949.[2] Further studies were initiated in Portugal[3] and Japan.[4] The German study started in 1967 and comprised of 2326 exposed patients and 1890 unexposed control patients from the same hospitals. The scope of the study was to quantify the internal long-term exposure and to relate it to the observed health effects.[5]

☆ In memoriam - Prof. Dr. Kurt Wegener, pathologist in the German Thorotrast study group since 1968 who died December 13, 2007.

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The results published so far from the German study were based on an internal comparison between the Thorotrast-exposed patients and the control group and referred to the best available information including hospital records, histo-pathological findings, autopsy reports and death certificates. An evaluation based on the external comparison of the mortality in the two groups to the mortality of the German population was not yet conducted. Such an analysis would, however, be reasonable to obtain an insight into the cause-of-death profile of the two groups, especially the unexposed group which also consisted of hospital patients and cannot be considered representative for the entire German population.

In the present paper, and for the first time, the overall and cause-specific mortality among the Thorotrast-exposed patients and the unexposed comparison group were compared with the mortality experience in the general German population. The scope of this investigation was to examine whether the mortality in the control group deviated from that of the general population, and, if so, how it might have affected the risk assessment of the Thorotrast exposure.

2. Material and methods

2.1. Study population

The design of the study has been described elsewhere.[1–5] Names and addresses of the 2326 patients who had been examined with Thorotrast for cerebral angiography (about 70%) or arteriography of the upper and lower limbs (about 30%) were retrospectively collected since 1968 from records of 31 hospitals in former West Germany and Vienna (Austria). The comparison group of 1890 subjects was selected from patients of the same hospitals. Selection criteria included being diagnosed or treated at the same time as the Thorotrast-exposed patients, having the same sex and age, having not received intravascular injection of Thorotrast, and bearing a family name with the initial letter 'B'. Excluded from the study were those Thorotrast-exposed patients and control subjects who died within 3 years after administration of Thorotrast or hospitalisation. Since Thorotrast was administered mainly in the late 1930 s and 1940 s, most of the included subjects were recruited from that time.

2.2. Methods of follow-up

2.2.1. Past follow-ups

Since at the start of the project in 1968 many Thorotrast-exposed patients and some of the control subjects had already died, setting up the study involved the collection of hospital records on cause of death, post-mortem examinations and death certificates. The patients who were still alive at that time (899/662 exposed/control subjects) have been invited, every 2 years, for outpatient examination into the German Cancer Research Centre offering clinical and radiological examinations to detect diseases – mainly liver cancer – at an early stage. In case of death of these patients, the responsible family physicians, hospitals and pathologists were asked for the cause of death and prevalent diseases. If no information was available from these sources, the cause of death as recorded officially by the health authorities was used.

2.2.2. Recent follow-up

Since the last follow-up dated back several years, it was decided to update the vital status of the cohorts and the cause-of-death information (last information: 48 exposed subjects alive and 239 subjects of the comparison group). Since for many patients the official cause of death was not available (from the procedure described above), and a mortality comparison with the general population would be inadequate using other sources of information on cause of death for the study participants than for the reference population, an update of causes of death for all study participants was undertaken in 2005.

2.3. Statistical methods

The analysis was carried out by calculating standardised mortality ratios (SMRs) using the mortality rates of West Germany from the years 1952–2002 as reference[6] (see also the internet update at www.canceratlas.de). Person-years at risk, numbers of cause-specific deaths and reference rates for computing the expected numbers were subdivided into nine calendar periods and 22 age groups. SMRs are given as percentages, i.e. reference is 100. Confidence limits were calculated using the method of Breslow and Day[7], page 70. Relative risks (RR) between the exposed and unexposed cohorts were computed as the ratio between the two respective SMRs as outlined in[7], page 94 with 1 as reference. For the related 95%-confidence limits the exact method was used. For survival analysis, the life-table of 1950/51, as published by the Federal Statistical Office of Germany, and relative survival, as outlined in[8], 231 ff, were used.

3. Results

By the end of 2004, nine out of 2316 Thorotrast-exposed patients and 151 out of 1890 comparison patients (3.8% of the original cohorts) were still alive (Table 1). For 90% of the overall 4046 deceased cohort members, the death certificates were available. Information was missing for 9.2% of the deceased subjects, and lost to follow-up were 0.2% of all cohort members. The comparison group was about 4 years older, on average, than the Thorotrast-exposed cohort.

Among the Thorotrast-exposed patients, a substantial number were hospitalised due to diagnostics for a brain tumour, followed by conditions due to accidents, injuries etc. and diseases of the circulatory or nervous system. Among the patients of the comparison cohort, conditions due to accidents, injuries etc. were a relevant reason for hospitalisation, followed by diseases of the digestive organs and the nervous system. However, for one third of this group the reason for hospitalisation was unknown.

Among males (Table 2), the total mortality was elevated in both cohorts with a stronger increase in the exposed (SMR = 287) than in the unexposed cohort (SMR = 153) resulting in a significantly increased relative risk (RR = 1.9). Both cohorts shared diseases for which mortality was increased, such as benign neoplasms including MDS, some with unknown characteristics, and in the majority, some forms of brain tumour (SMR = 1116 and SMR = 300, respectively), diseases of the nervous system (SMR = 1169 and SMR = 493), the blood and

Table 1 – Characteristics of the Thorotrast-exposed cohort and the comparison cohort (follow-up by end of 2004)

	Thorotrast-exposed cohort	Comparison group	Total	
	N	N	N	%
Alive	9	151	160	3.8
Men	*6*	*99*	*105*	
Women	*3*	*52*	*55*	
Deceased	2313	1733	4046	96
Men	*1709*	*1305*	*3014*	
Women	*604*	*428*	*1032*	
Death certificate available	2129	1512	3641	90
Information from family members etc.	13	19	32	0.8
Missing information	171	202	373	9.2
Lost to Follow-up	4	6	10	0.2
Men	*2*	*4*	*6*	
Women	*2*	*4*	*6*	
Total	2326	1890	4216	100
Men	*1717*	*1408*	*3125*	*74*
Women	*609*	*482*	*1091*	*26*
Age distribution at entry into the study				
0 – 9	*43*	*33*	*76*	*1.8*
10 – 19	*235*	*163*	*398*	*9.4*
20 – 29	*649*	*455*	*1104*	*26*
30 – 39	*598*	*446*	*1044*	*25*
40 – 49	*503*	*419*	*922*	*22*
50 – 59	*235*	*253*	*488*	*12*
60 – 69	*57*	*96*	*153*	*3.6*
70 +	*6*	*25*	*31*	*0.7*
Major suspected diagnosis according to the reason for angiography (Thorotrast group) or hospitalisation (comparison group)				
Benign neoplasm and neoplasms with unknown characteristics (primarily brain tumours)	*715*	*23*		
Injuries. accidents and other external conditions	*422*	*324*		
Psychiatric diseases	*43*	*100*		
Diseases of the nervous system	*318*	*157*		
Diseases of the circulatory system	*404*	*51*		
Diseases of the digestive organs	*–*	*181*		
Others				
Unknown	*261*	*667*		

metabolic diseases (SMR = 341 and SMR = 328), and accidents and poisoning ('unnatural diseases', SMR = 168 and SMR = 256) leading to relative risks which were increased for neoplasms (RR = 3.7) and diseases of the nervous system (RR = 2.4), near reference for haematological diseases (RR = 1.0) or decreased for 'unnatural diseases' (RR = 0.7). Mortality from malignant neoplasms, diseases of the circulatory system and digestive organs were specifically elevated in the exposed cohort but not in the unexposed, providing relative risks of RR = 3.7, RR = 1.4 and RR = 5.0, respectively.

Among females (Table 3), the total mortality was also elevated in both cohorts, and the increase was, corresponding to males, stronger in the exposed (SMR = 387) than the unexposed cohort (SMR = 212) yielding a significantly increased relative risk (RR = 1.8). However, the underlying patterns of mortality were different from those among males in as far as mortality was increased for most disease categories in both cohorts. With few exceptions (infectious diseases, unnatural causes of death) the relative risk of these causes of death was higher for the exposed compared to the unexposed women.

Underlining the results on total mortality, the survival curves for the exposed (Fig. 1a) and the unexposed cohort (Fig. 1b) showed a substantially decreased survival in comparison to that of the general population ($p < 0.0001$ in both instances). The expected median survival time in the exposed cohort in case of no exposure would have been 41 years, while 27 years have been observed. The corresponding numbers for the unexposed cohort were 38 years expected and 24 years observed. The survival did not materially change if the deaths from liver cancer were excluded from the analysis (data not shown in tables or figures).

Mortality from liver cancer was by far the most excessive amongst all the cancer sites in exposed males (SMR = 16,695, Table 4) providing a relative risk of RR = 71, followed by cancers of the gallbladder and bile ducts (SMR = 1656, RR = 8.1). However, most other sites also showed elevated mortality from cancers of the upper digestive tract, sites other than the liver and gall bladder in the lower digestive tract and respiratory organs, to malignancies of the haematopoietic system. Notice that myelodysplastic syndromes (MDS) were subsumed to 'benign neoplasms' (ICD-10 D46) and also showed an elevated SMR (data not shown). Interestingly, lung cancer mortality was not increased. In the unexposed control group, only mortality from liver cancer, some forms of insufficiently specified

Table 2 – Standardised mortality ratio (SMR) with 95% confidence intervals (95% CI) for the Thorotrast-exposed cohort and the comparison cohort based on the three-character categories of ICD-10 of all causes of death / males

Causes of death	ICD-10	ICD-9	Thorotrast-exposed group				Comparison group				Relative Risk	
			O	E	SMR	95% CI	O	E	SMR	95% CI	RR	95% CI
Total mortality	A00-Z99	001-999	1709	596	287	273-301	1305	853	153	145-162	1.9	1.7-2.0
Infectious diseases	A00-B99	001-139	17	15.5	110	68-177	24	16.4	147	98-219	0.7	0.4-1.5
Malignant neoplasms	C00-C97	140-208	542	136	398	366-433	211	194	109	95-125	3.7	3.1-4.3
Benign neoplasm and neoplasms with unknown characteristics	D00-D48	210-239	64	5.7	1116	873-1426	22	7.3	300	198-456	3.7	2.3-6.4
Diseases of the blood and blood-forming organs. endocrine. nutritional and metabolic diseases	D50-E90	240-289	50	14.7	341	259-450	67	20	328	259-417	1.0	0.7-1.5
Mental and behavioural diseases	F00-F99	290-319	3	3.1	95	31-296	6	4.2	143	64-317	0.7	0.1-3.2
Diseases of the nervous system. eye and ear	G00-H95	320-389	95	8.1	1169	956-1430	56	11.4	493	380-641	2.4	1.7-3.4
Diseases of the circulatory system	I00-I99	390-459	363	242	150	135-166	397	380	104	95-115	1.4	1.2-1.7
Diseases of the respiratory system	J00-J99	460-519	48	43	111	84-148	82	68	120	97-149	0.9	0.6-1.3
Diseases of the digestive system	K00-K93	520-579	263	41	641	568-724	62	49	127	99-163	5.0	3.8-6.8
Diseases of the genitourinary system	N00-N99	580-629	20	14.5	138	89-214	29	20	142	99-204	1.0	0.5-1.8
Diseases of the skin and subcutaneous tissue	L00-M99	680-739	3	2.0	152	49-471	3	2.6	117	38-362	1.3	0.2-9.7
Congenital malformations. deformations and chromosomal abnormalities	Q00-Q99	740-759	1	0.4	276	39-1960	0	0.3			-	
Insufficiently coded causes of death	R00-R99	780-799	152	17.7	861	734-1009	216	28	770	674-880	1.1	0.9-1.4
Injuries. accidents and other external causes of death	S00-T98	800-999	88	53	168	136-207	130	51	256	216-304	0.7	0.5-0.9

Table 3 – Standardised mortality ratio (SMR) with 95% confidence intervals (95% CI) for the Thorotrast-exposed cohort and the comparison cohort based on the three-character categories of ICD-10 of all causes of death / females

Causes of death	ICD-10	ICD-9	Thorotrast-exposed group				Comparison group				Relative Risk	
			O	E	SMR	95% KI	O	E	SMR	95% KI	RR	95% CI
Total mortality	A00-Z99	001-999	604	156	387	357-419	428	202	212	192-233	1.8	1.6-2.1
Infectious diseases	A00-B99	001-139	9	2.1	426	222-819	11	2.3	478	265-863	0.9	0.3-2.4
Malignant neoplasms	C00-C97	140-208	165	42	395	339-460	80	46	174	140-217	2.3	1.7-3.0
Benign neoplasm and neoplasms with unknown characteristics	D00-D48	210-239	53	2.1	2579	1971-3376	6	2.1	281	126-626	8.8	3.8-25
Diseases of the blood and blood-forming organs. endocrine. nutritional and metabolic diseases	D50-E90	240-289	32	6.2	520	368-735	28	7.2	386	267-559	1.3	0.8-2.3
Mental and behavioural diseases	F00-F99	290-319	0	0.8			2	1.1	184	46-735	-	
Diseases of the nervous system. eye and ear	G00-H95	320-389	38	2.5	1495	1088-2055	26	3.0	865	589-1271	1.8	1.0-3.0
Diseases of the circulatory system	I00-I99	390-459	123	67	183	154-219	133	98	136	115-162	1.3	1.0-1.7
Diseases of the respiratory system	J00-J99	460-519	17	7.3	232	144-373	20	11.0	181	117-281	1.3	0.6-2.6
Diseases of the digestive system	K00-K93	520-579	73	9.3	784	623-986	24	10.5	229	153-341	3.4	2.1-5.7
Diseases of the genitourinary system	N00-N99	580-629	5	3.3	150	62-360	8	3.6	225	112-450	0.7	0.2-2.4
Diseases of the skin and subcutaneous tissue	L00-M99	680-739	2	1.0	194	49-776	3	1.2	247	80-764	0.8	0.1-7.0
Pregnancy. childbirth and the puerperium	O00-O99	630-676	1	0.6	176	25-1252	1	0.4	268	38-1905	0.7	0.0-52
Insufficiently coded causes of death	R00-R99	780-799	66	4.6	1432	1125-1823	57	8.6	664	512-861	2.2	1.5-3.1
Injuries. accidents and other external causes of death	S00-T98	800-999	20	7.3	274	177-425	29	7.7	377	262-543	0.7	0.4-1.3

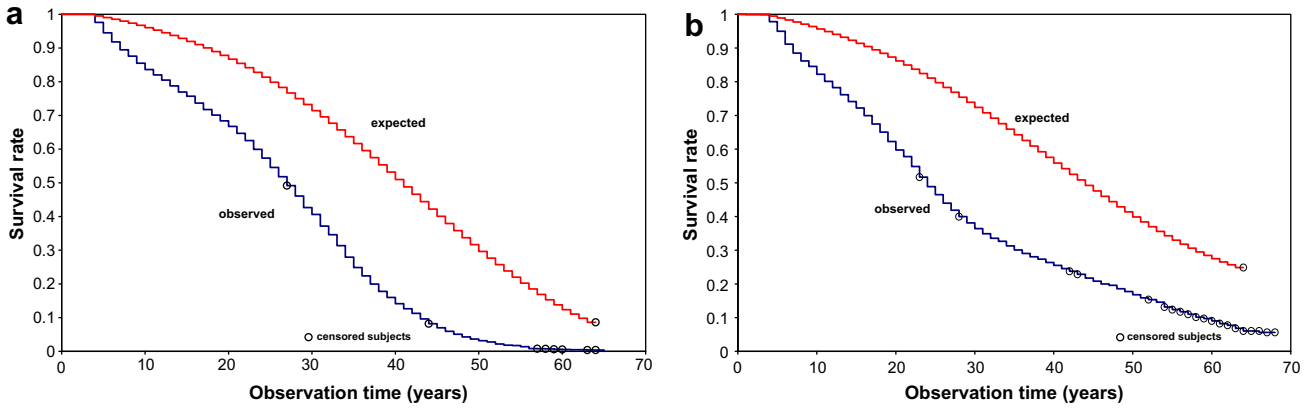

Fig. 1 – Observed and expected survival in (a) the Thorotrast exposed cohort and (b) the unexposed cohort of the German Thorotrast study.

sites and myeloid leukaemia was increased, partially based on low numbers.

Liver cancer was also, among exposed females (Table 5), the cancer site with by far the strongest elevation of mortality (SMR = 12,680). Most other cancer sites also showed increased mortality (e.g. connective tissue, genitourinary organs, brain and nervous system) based, however, mostly on very low numbers. In the unexposed group, mortality from liver cancer was also in excess, but many other cancer sites than those among males also showed an increased mortality (e.g. respiratory organs, bones and connective tissue, genitourinary organs, haematopoietic system). Due to the low numbers of observed cases for many cancer sites, several relative risks could not be calculated and elevated RRs frequently could not be confirmed statistically. Liver cancer (RR = 34) and cancers of the brain and nervous system (RR = 17.0) were the only sites for which increased relative risks could be confirmed statistically.

The analysis of overall and selected cause-specific mortality by time since first exposure (Tables 6 and 7) shows that among males (Table 6) the overall mortality is elevated through about three decades in both cohorts so that relative risk for exposure is only slightly elevated. However, in the unexposed cohort, the SMR falls approximately to reference beyond 30 years of observation (SMR = 106); in the exposed cohort it increases to SMR = 403, providing a strongly increased relative risk of RR = 3.8. For cancer, the SMRs are near reference in the unexposed cohort during almost the entire observation time, while in the exposed cohort it increases after slightly elevated SMRs in the first 20 years of observation to SMR = 333 (20–29 years of observation) and SMR = 773 (30 years and more of observation time) resulting in relative risks of RR = 2.2 and RR = 7.7, respectively. SMRs for liver cancer are slightly elevated in the unexposed cohort throughout the observation time and strongly increasing in the exposed cohort yielding a sharply increasing relative risk after 10 or 20 years of observation. Also, diseases of the circulatory system show, after a decline of relative risk with increasing observation time, a moderate increase after 30 years and more of observation (RR = 1.5). Mortality patterns are similar for females (Table 7) though less statistically confirmed since numbers of observed cases per cell were much lower than for males.

4. Discussion

The present analysis provides, for the first time, a mortality evaluation of the German Thorotrast study including a comparison with the general German population. Additionally, it presents for the first time the long-term trends of Thorotrast-related cancer risk in the German cohort covering an observation time of up to 65 years.

The mortality-based approach makes the study comparable to the other published studies on Thorotrast-related cancer risk which also mostly used mortality as target endpoint. It also quantifies the most fatal consequence an exposure may have - death from the exposure. On the other hand, some limitations have to be recognised. The mortality statistics ignore serious disease present at time of death, if the immediate cause of death was unrelated to it. Furthermore, its precision is sometimes substantially lower than clinical diagnosis of an incident cancer. This unfortunately affects the cancer site of utmost interest in this project, liver cancer: in death certificates primary liver cancer is frequently not distinguished from liver metastasis of other cancer sites leading to artificially increased numbers of deaths from 'liver cancer'. To some extent, this is balanced out by the fact that it affects the control group as well. In any way, the results of the mortality evaluation should be seen as complementary to the published results on incidence, and the consistency examined (see below).

The comparison of the total and cause-specific mortality in the Thorotrast-exposed and the unexposed cohort with that of the general population in Germany shows broadly elevated SMRs in both cohorts. However, while the originally increased mortality declines with increasing observation time in the unexposed cohort, the mortality in the Thorotrast cohort stabilises only temporarily and increases thereafter continuously for decades. Correspondingly, median survival is shorter in both cohorts compared to what would be expected under 'normal' conditions, but survival worsens considerably in the exposed cohort over the decades of observation time,

Table 4 – Standardised mortality ratio (SMR) with 95% confidence intervals (95% CI) for the Thorotrast-exposed cohort and the comparison cohort for malignant neoplasms / males

Malignant neoplasms	ICD-10	ICD-9	Thorotrast-exposed group				Comparison group				Relative Risk	
			O	E	SMR	95% CI	O	E	SMR	95% CI	RR	95% CI
Lip. oral cavity and pharynx	C00-C14	140-149	6	1.8	330	148-735	3	2.6	114	37-354	2.9	0.6-17.9
Digestive organs and peritoneum	C15-C26	150-159	331	54	616	554-687	87	75	116	94-143	5.3	4.2-6.8
Oesophagus	C15	150	5	2.8	178	74-428	6	4.0	149	67-332	1.2	0.3-4.7
Stomach	C16	151	25	25	100	68-148	34	32	107	76-150	0.9	0.5-1.6
Colon	C17, C18	152.153	4	8.3	48	18.1-128	19	13.6	139	89-218	0.3	0.1-1.0
Rectum	C19-C21	154	6	6.3	95	43-211	8	9.0	89	45-178	1.1	0.3-3.5
Liver and intrahepatic bile ducts	C22	155	238	1.4	16695	14703-18957	6	2.5	238	107-529	71	32-195
Gallbladder and extraphepatic bile ducts	C23-C24	156	34	2.1	1656	1183-2318	6	3.0	200	90-446	8.1	3.4-23.6
Pancreas	C25	157	15	5.2	288	174-478	4	7.6	53	19.9-141	5.5	1.7-22.7
Peritoneum and retroperitoneum	C48	158	1	0.5	200	28-1420	1	0.6	177	25-1257	1.2	0.0-94
Digestive system not specified	C26	159	3	0.5	621	200-1925	3	1.0	310	100-960	2.0	0.3-14.9
Respiratory- and intrathoracic organs	C30-C39, C45	160-165	53	39	137	104-179	51	52	99	75-130	1.4	0.9-2.1
Larynx	C32	161	6	1.8	339	152-754	2	2.3	86	21-343	3.8	0.7-39
Trachea. bronchus. lung	C33-C34	162	42	37	114	84-154	49	49	101	76-133	1.1	0.7-1.7
Pleura	C38, C45	163	5	1.0	512	213-1230	0	1.2			-	
Bone. connective tissue. skin and breast	C40-C44, C46-C47, C49-C50	170-175	7	3.1	225	107-471	5	3.9	128	53-307	1.8	0.5-7.0
Bone and articular cartilage	C40-C41	170	7	1.1	636	303-1335	3	1.2	256	83-794	2.5	0.6-15.3
Connective tissue and soft tissue	C49	171	0	0.3			1	0.4	228	32-1622	-	
Melanoma	C43	172	0	1.2			1	1.4	72	10.2-513	-	
Male genital organs and urinary tract	C60-C68	179-189	29	10.8	269	187-387	29	24	119	82-173	2.2	1.3-3.8
Prostate	C61	185	18	8.8	205	129-325	18	18.6	97	61-154	2.1	1.0-4.3
Testis	C62	186	1	0.5	189	27-1343	0	0.5			-	
Bladder	C67	188	5	5.2	97	40-233	3	8.4	36	11.6-111	2.7	0.5-17.3
Kidney	C64-C66, C68	189	5	4.1	123	51-295	8	5.6	143	72-286	0.9	0.2-3.0
Malignant neoplasms of eye. brain. other parts of the nervous system. the thyroid and other endocrine glands and ill-defined or unspecified sites	C69-C80	190-199	59	12.0	490	379.9-632.9	23	16.3	141	93.9-212.6	3.5	2.1-5.9
Brain and unspecified parts of nervous system	C70-C72	191-192	19	2.0	933	595-1463	7	2.4	296	141-620	3.3	1.3-9.2
Thyroid gland	C73	193	1	0.5	207	29-1472	0	0.6			-	
Endocrine glands	C74, C75	194	3	0.2	1562	504-4843	1	0.2	456	64-3240	3.0	0.2-158
Other and ill-defined sites	C76	195	6	1.3	447	201-994	7	1.6	435	207-913	1.1	0.3-3.7
Without specification of site	C80	199	30	4.5	669	468-957	8	7.5	107	53-213	6.3	2.8-15.8
Lymphoid. haematopoietic and related tissue	C81-C96	200-208	46	8.3	556	416-742	11	11.3	97	54-176	5.7	2.9-12.2
Non-Hodgkin lymphoma	C82-C85; C96	200.202	7	1.6	441	210-925	3	2.5	119	38-368	3.6	0.8-22
Hodgkin lymphoma	C81	201	1	1.5	69	9.7-487	1	1.4	72	10.1-511	0.9	0.0-73
Multiple myeloma and immunproliferative diseases	C88, C90	203	6	1.3	464	208-1032	1	2.0	50	7.0-352	9.2	1.1-425
Lymphoid leukemia	C91	204	2	1.2	172	43-688	1	1.9	54	7.6-382	3.2	0.2-187
Myeloid leukemia	C92	205	11	1.6	675	374-1219	2	2.2	89	22-357	7.6	1.7-70
Monocytic leukemia	C93	206	3	0.1	3875	1250-12015	1	0.1	999	141-7091	3.0	0.2-158
Other leukemias of specified cell type	C94	207	1	0.1	1532	216-10878	0	0.1			-	
Leukemia of unspecified cell ytpe	C95	208	15	1.1	1330	802-2207	2	1.5	129	32-517	10.2	2.4-92
Malignant neoplasms of multiple primary sites	C97	199	11	-	-	-	2	-	-	-	-	
Total	C00-C97	140-208	542	136	398	366-433	211	194	109	95-125	3.7	3.1-4.3

Table 5 – Standardised mortality ratio (SMR) with 95% confidence intervals (95% CI) for the Thorotrast-exposed cohort and the comparison cohort for malignant neoplasms / females

Malignant neoplasms	ICD-10	ICD-9	Thorotrast-exposed group				Comparison group				Relative Risk	
			O	E	SMR	95% CI	O	E	SMR	95% CI	RR	95% CI
Lip. oral cavity and pharynx	C00-C14	140-149	2	0.2	978	245-3909	1	0.3	387	55-2748	3.0	0.2-177
Digestive organs and peritoneum	C15-C26	150-159	75	15.6	480	382-601	25	18.4	136	92-201	3.5	2.2-5.8
Oesophagus	C15	150	4	0.3	1473	553-3926	0	0.4			–	
Stomach	C16	151	8	5.7	141	70-281	10	6.4	156	84-289	0.9	0.3-2.5
Colon	C17, C18	152. 153	2	3.2	62	15.5-248	4	4.0	100	37-266	0.6	0.1-4.4
Rectum	C19-C21	154	2	1.8	112	28-449	2	2.0	102	26-407	1.1	0.1-15.3
Liver and intrahepatic bile ducts	C22	155	41	0.3	12680	9337-17221	2	0.5	439	110-1753	34	8.9-292
Gallbladder and extraphepatic bile ducts	C23-C24	156	7	1.7	411	196-863	2	1.9	107	27-427	3.9	0.7-39
Pancreas	C25	157	3	1.4	209	67-647	3	1.8	164	53-509	1.3	0.2-9.6
Peritoneum and retroperitoneum	C48	158	2	0.3	674	169-2694	0	0.3			–	
Digestive system not specified.	C26	159	6	0.2	3296	1481-7336	2	0.3	657	164-2627	4.5	0.8-46
Respiratory- and intrathoracic organs	C30-C39, C45	160-165	7	2.0	353	168-740	6	2.4	248	111-551	1.4	0.4-5.0
Larynx	C32	161	0	0.1			0	0.1			–	
Trachea. bronchus. lung	C33-C34	162	6	1.9	317	143-706	6	2.3	263	118-584	1.2	0.3-4.5
Pleura	C38, C45	163	1	0.2	482	68-3419	0	0.2			–	
Bone. connective tissue. skin and breast	C40-C44, C46-C47, C49-C50	170-175	15	8.4	180	108-298	15	8.5	176	106-292	1.0	0.5-2.2
Bone and articular cartilage	C40-C41	170	3	0.3	1041	336-3228	1	0.3	361	51-2560	3.0	0.2-158
Connective tissue and soft tissue	C49	171	2	0.1	2172	543-8683	0	0.1			–	
Melanoma	C43	172	1	0.3	292	41-2075	0	0.4			–	
Breast	C50	174	9	6.4	141	73-271	14	6.6	211	125-356	0.7	0.3-1.6
Female genital organs and urinary tract	C51-C68	179-189	11	1.6	686	380-1239	16	2.1	753	462-1230	0.9	0.4-2.1
Cervix uteri	C53	180	3	1.5	194	63-602	4	1.3	312	117-832	0.7	0.1-3.8
Corpus uteri	C54-C55	182	2	2.7	73	18.4-294	6	2.6	234	105-520	0.3	0.0-1.8
Ovary	C56	183	3	2.9	105	34-326	4	2.9	140	53-374	0.8	0.1-4.4
Other and unspecif. female genital organs	C57	184	0				1	1.4	69	9.7-490	–	
Urinary bladder	C67	188	2	0.5	377	94-1505	1	0.7	137	19.3-971	2.8	0.1-165
Kidney	C64-C66, C68	189	1	0.8	125	17.5-884	0	0.9			–	
Malignant neoplasms of eye. brain. other parts of the nervous system. the thyroid and other endocrine glands and ill-defined or unspecified sites	C69-C80	190-199	41	3.7	1120	824.5-1520.9	9	4.3	212	110-407	5.3	2.5-12.4
Brain and unspecified parts of nervous system	C70-C72	191-192	17	0.5	3320	2064-5340	1	0.5	185	26-1312	17.0	2.7-711
Thyroid gland	C73	193	2	0.3	637	159-2549	1	0.3	297	42-2109	2.0	0.1-118
Other and ill-defined sites	C76	195	6	0.5	1153	518-2566	3	0.5	574	185-1781	2.0	0.4-12.4
Without specification of site	C80	199	16	1.5	1097	672-1791	4	2	205	77-546	5.3	1.7-22
Lymphoid. haematopoietic and related tissue	C81-C96	200-208	11	2.2	504	279-910	6	2.5	241	108-536	2.1	0.7-6.9
Non-Hodgkin lymphoma	C82-C85, C96	200.202	2	0.4	523	131-2089	1	0.5	184	26-1306	2.5	0.1-148
Hodgkin lymphoma	C81	201	0	0.3			1	0.2	403	57-2862	–	
Multiple myeloma and immunoproliferative diseases	C88, C90	203	1	0.4	252	36-1790	1	0.5	198	28-1405	1.3	0.0-98
Lymphoid leukaemia	C91	204	1	0.2	416	59-2951	1	0.3	311	44-2208	1.5	0.0-118
Myeloid leukaemia	C92	205	5	0.5	993	413-2386	2	0.6	361	90-1443	3.0	0.5-32
Monocytic leukaemia	C93	206	1	0.0	4094	577-29065	0	0.0			–	
Other leukaemias of specified cell type	C94	207	0	0.0			0	0.0			–	
Leukaemia of unspecific cell type	C95	208	1	0.4	284	40-2013	0	0.4			–	
Primary tumours of multiple sites	C97	199	3	–	–	–	2	–	–	–		
Total	C00-C97	140-208	165	42	395	339-460	80	46	174	140-217	2.3	1.7-3.0

Table 6 – SMR among Thorotrast-exposed (part A) and comparison group (part B) by observation time since first exposure and relative risk (part C) / males

Causes of death	Observation time (years since first expo)[a]				Total
	< 10	10–19	20–29	30+	
Thorotrast-exposed group	269 / 102	280 / 148	471 / 175	689 / 171	
Total mortality	265	189	269	403	
	235 – 299	168 – 212	245 – 294	374 – 434	
Malignant neoplasms	27 / 20	41 / 32	133 / 40	341 / 44	
	135	128	333	773	
	93 – 197	94 – 174	281 – 395	695 – 860	
Diseases of the circulatory system	65 / 32	96 / 56	104 / 74	98 / 80	
	206	171	140	123	
	162 – 263	140 – 209	115 – 170	101 – 150	
Cancer of the liver and intrahepatic bile ducts	2 / 0.2	5 / 0.3	55 / 0.4	176 / 0.6	
	1004	1614	15188	31747	
	251 – 4014	672 – 3877	11660 – 19782	27387 – 36802	
Control group	250 / 115	291 / 164	319 / 157	445 / 418	
Total mortality	218	178	204	106	
	193 – 247	158 – 199	183 – 228	97 – 117	
Malignant neoplasms	20 / 23	36 / 33	51 / 34	104 / 103	
	87	108	149	101	
	56 – 134	78– 150	113 – 196	83 – 122	
Diseases of the circulatory system	34 / 40	78 / 66	118 / 68	167 / 206	
	84	118	174	81	
	60 – 118	95 – 148	145 – 208	70 – 94	
Cancer of the liver and intrahepatic bile ducts	1 / 0.2	0 / 0.3	3 / 0.3	2 / 1.7	
	437	–	976	120	
	62 – 3103	–	315 – 3025	30 – 479	
Relative risk					
Total mortality	1.2	1.1	1.3	3.8	
	1.0-1.4	0.9-1.3	1.1-1.5	3.4-4.3	
Malignant neoplasms	1.6	1.2	2.2	7.7	
	0.8-2.9	0.7-1.9	1.6-3.2	6.1-9.6	
Diseases of the circulatory system	2.4	1.4	0.8	1.5	
	1.6-3.8	1.1-2.0	0.6-1.1	1.2-2.0	
Cancer of the liver and intrahepatic bile ducts	2.0	–	13.8	249	
	0.1-118		4.5-69	68-2075	

a Description of cells: first line: observed/expected number of cases; second line: SMR; third line: confidence interval.

while it shows a relative improvement in the unexposed cohort.

The increased mortality in the early years of observation is likely to reflect illness which was the reason of hospitalisation and the diagnostic processes under investigation in both cohorts. This view is supported by the observation that in the unexposed cohort the effect of the hospitalisation on mortality disappeared and SMRs or survival rates approached levels as expected from the general population. On the other hand, it has to be recognised that the effect of the diseases which led to hospitalisation disappeared only after more than 20 years. The opposite trend in the Thorotrast cohort reflects apparent exposure-related mortality which begins to show up after a latency of about 20 years. The less pronounced decrease of survival in the first 20 years may be explained by the fact that about 35% of the patients were basically healthy soldiers hospitalised due to war-related gunshot wounds.

The extremely elevated mortality from liver cancer was the subject of repeated incidence-based analyses.[5] These comparisons indicated an incidence ratio of about 129 between the exposed and unexposed cohorts. In the present evaluation, mortality comparison to the general population resulted, for the exposed cohort, in a 166-fold increase in males and a 126-fold increase in females (combined SMR = 164 based on 279 cases versus 1.7 expected), while the relative risk comparison to the unexposed cohort provided RR = 71 (males) and RR = 34 (females).

The inconsistency between these two sets of figures arises from the fact that liver cancer mortality was also elevated in the unexposed cohort based on eight cases versus three expected, presumably related to the health conditions which led to hospitalisation in the unexposed cohort. Since liver diagnostics was not the subject of Thorotrast-based angiography, the two cohorts reflect different baseline risks for liver

Table 7 – SMR among Thorotrast-exposed (part A) and comparison group (part B) by observation time since first exposure and relative risk (part C) / females

Causes of death	Observation time (years since first exposure) [a]				Total
	<10	10–19	20–29	30+	
Thorotrast-exposed group	112 / 24	113 / 40	137 / 46	242 / 47	
Total mortality	460	286	301	517	
	382 - 554	238 - 344	255 - 356	456 – 586	
Malignant neoplasms	15 / 7.5	23 / 10.9	34 / 11.7	93 / 11.7	
	201	210	290	796	
	121 - 334	140 - 317	207 - 406	649 – 975	
Diseases of the circulatory system	22 / 7.7	31 / 15.8	28 / 20	42 / 23	
	287	196	139	179	
	189 - 436	138 - 279	96 - 201	132 – 242	
Cancer of the liver and intrahepatic bile ducts	0 / 0.0	0 / 0.1	7 / 0.1	34 / 0.1	
	–	–	7460	33632	
	–	–	3556 - 15648	24031 - 47069	
Control group	86 / 33	135 / 46	121 / 33	86 / 91	
Total mortality	264	295	367	95	
	213 - 326	249 - 349	307 - 438	77 - 117	
Malignant neoplasms	10 / 8.5	26 / 10.4	22 / 7.7	22 / 19.4	
	118	250	286	113	
	64 - 220	170 - 367	189 - 435	75 - 172	
Diseases of the circulatory system	19 / 12.7	43 / 20	38 / 15.3	33 / 49	
	150	212	249	67	
	96 - 235	158 - 286	181 - 342	48 - 94	
Cancer of the liver and intrahepatic bile ducts	0 / 0.1	2 / 0.1	0 / 0.1	0 / 0.3	
	–	2400	–	–	
	–	600 - 9596	–	–	
Relative risk					
Total mortality	1.7	1.0	0.8	5.5	
	1.3-2.3	0.7-1.3	0.6-1.1	4.3-7.1	
Malignant neoplasms	1.7	0.8	1.0	7.0	
	0.7-4.2	0.5-1.5	0.6-1.8	4.4-11.7	
Diseases of the circulatory system	1.9	0.9	0.6	2.7	
	1.0-3.7	0.6-1.5	0.3-0.9	1.7-4.4	
Cancer of the liver and intrahepatic bile ducts	–	–	–	–	

a Description of cells: first line: observed/expected number of cases; second line: SMR; third line: Confidence interval.

cancer. Thus, the SMR comparison to the general population appears the less biased quantification of Thorotrast-related mortality for liver cancer. It exceeds what was found previously with regard to males, while it corresponds fairly well with previous assessment for females.

For other cancer sites, the previous assessments provided ratios of 4.9 (gall bladder and bilary ducts), 2.4 (pancreas), 4.1 (plasmocytoma) and 3.3 (bone sarcoma). The comparison to the relative risks in Tables 4 and 5 indicate a similar pattern as for liver cancer, i.e. relative risks in the present evaluation which are slightly above the previous reports for males and similar or slightly below for females.

Interestingly, despite the lifelong exhaust of α-particles through the respiratory tract, we found no indication for an increased mortality from lung cancer. This observation appears inconsistent with environmental risk assessments which found α-radiation caused by environmental radon exposure associated with an increased lung cancer risk. This issue has already been raised in previous reports[9] and will be reconsidered in the frame of more specific analyses based on quantified radiation exposure within a subsequent paper.

Among the causes of death other than malignancies, the diseases of the digestive tract showed particularly strong elevations among the Thorotrast-exposed cohort based on large numbers. This group of diseases includes liver cirrhosis which is known as a non-malignant consequence of the Thorotrast-related radiation exposure.

The present results are largely consistent with recent reports from the Thorotrast cohorts in Denmark, Japan, Portugal and Sweden,[10–15] and the combined analysis of the Danish, Swedish and US cohorts,[16] though differences are apparent in details.

The baseline illness in both the exposed and the unexposed cohort is high, similar to the international cohort,[16] and most likely due to the underlying conditions having led to hospitalisation.

The mortality from liver cancer is, with SMR = 164, exorbitantly high and above the level found in the Portuguese

(RR = 42) or Swedish cohorts (standardised incidence ratio (SIR) = 39) and roughly similar to the incidence ratio observed in the Danish cohort (SIR = 126). The relative risk was lower in the Japanese study (RR = 18.2),[11,12] possibly due to a substantially higher baseline risk for liver cancer in this country. Also, the mortality from or incidence of brain tumours is elevated in the Danish (SIR = 28.0), Swedish (SIR = 3.1) and our (SMR = 3.3 for males and SMR = 17.0 for females) cohort, as is risk of leukaemia and lymphoma, though presentation of results does not allow for direct comparisons.

Mortality from pancreas cancer is elevated in our and the Swedish cohort (SIR = 2.9), but not or only weakly in the Danish cohort (SIR = 1.9). Stomach cancer mortality is not increased in our and the Danish cohort, but is in the Swedish cohort (SIR = 10.5), while mortality from cancers of the small intestine is increased in the Danish (SIR = 7.4) and Swedish (SIR = 12.0), but not in the German cohort. Also, the null result on lung cancer in this cohort is inconsistent with the findings of the other cohorts in as far as this cancer was non-significantly elevated in the Portuguese cohort (RR = 9.1) and significantly in the Danish cohort (SIR = 2.3). In the Swedish cohort, lung cancer was elevated in females (SIR = 4.6) but not in males (SIR = 0.9). All these organs are considered targets for Thorotrast depository, so that the different findings appear obscure and warrant explanation.

Differences in relative risk also occur among causes of death other than cancer. Thus, benign respiratory diseases led to an increased relative risk in the combined (RR = 1.4) and the Portuguese cohorts (RR = 4.3), but not in the German cohort (RR = 1.0). In direct comparison with the general population, the SMR for benign respiratory diseases is close to the reference for males (SMR = 111), but above reference for females (SMR = 232).

5. Conclusion

Consistent with other studies, the results of the present evaluation of the mortality patterns in the German Thorotrast study demonstrate a lifelong burden of illness related to Thorotrast exposure leading to a substantial shortening of life span, and a specifically elevated risk of neoplasms, which continues to increase even after decades. The inconsistent results for lung cancer warrant further investigation, especially in view of the current discussion on environmental radon-related lung cancer risk. The observation of increasing relative risks, even after decades (Tables 6 and 7), gives rise to subsequent dose-related analyses.

Conflict of interest statement

None declared.

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