

# Risk of Second Malignant Neoplasms Among Long-term Survivors of Testicular Cancer

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**Background:** We have quantified the site-specific risk of second malignant neoplasms among nearly 29 000 survivors ( $\geq 1$  year) of testicular cancer, taking into account the histologic type of initial cancer and the primary therapy used to treat it. **Methods:** The study cohort consisted of 28 843 men identified within 16 population-based tumor registries in North America and Europe; over 3300 men had survived more than 20 years. New invasive cancers were identified through a search of registry files. **Results:** Second cancers were reported in 1406 men (observed-to-expected ratio [O/E] = 1.43; 95% confidence interval = 1.36–1.51), with statistically significant excesses noted for acute lymphoblastic leukemia (O/E = 5.20), acute nonlymphocytic leukemia (O/E = 3.07), melanoma (O/E = 1.69), non-Hodgkin's lymphoma (O/E = 1.88), and cancers of the stomach (O/E = 1.95), colon (O/E = 1.27), rectum (O/E = 1.41), pancreas (O/E = 2.21), prostate (O/E = 1.26), kidney (O/E = 1.50), bladder (O/E = 2.02), thyroid (O/E = 2.92), and connective tissue (O/E = 3.16). Overall risk was similar after seminomas (O/E = 1.42) or nonseminomatous tumors (O/E = 1.50). Risk of solid tumors increased with time since the diagnosis of testicular cancer, yielding an O/E = 1.54 (O = 369) among 20-year survivors (two-sided *P* for trend = .00002). Secondary leukemia was associated with both radiotherapy and chemotherapy, whereas excess cancers of the stomach, bladder, and, possibly, pancreas were associated mainly with radiotherapy. **Conclusions:** Men with testicular cancer continue to be at significantly elevated risk of second malignant neoplasms for more than two decades following initial diagnosis. Patterns of excess second cancers suggest that many factors may be involved, although the precise roles of treatment, natural history, diagnostic surveillance, and other influences are yet to be clarified. [J Natl Cancer Inst 1997;89:1429–39]

The introduction of the heavy metal compound cisplatin into therapy protocols for testicular tumors in the early 1970s represents one of the major breakthroughs in cancer treatment (1). Testicular cancer is now largely curable, with a 5-year relative survival rate of more than 90% (2). In recent decades, radiotherapy fields to treat testicular cancer have also decreased in size, and lower doses are employed. Men who were treated with earlier, more aggressive approaches, however, remain at risk for possible late effects which have not been well-studied. In addition, concern has been raised about the possible carcinogenic

sequelae of cisplatin (3), which is retained in numerous tissues long after completion of treatment (4). Men with testicular cancer are generally in their 20s or 30s at diagnosis, and few studies have quantified the long-term risks of second cancers among large numbers of survivors, taking into account both histologic type of testicular tumor and initial therapy. In this investigation, we quantify the site-specific risk of second malignant neoplasms among almost 29 000 1-year survivors of testicular cancer, including 3306 20-year survivors, reported to a number of population-based cancer registries in North America and Europe. Previous studies, as summarized by Van Leeuwen (5), have shown that men with testicular cancer may be at increased risk of secondary leukemia, sarcoma, and cancers of the lung, gastrointestinal tract, and other urogenital sites.

## Patients and Methods

Patients diagnosed with a first primary cancer of the testis between January 1, 1935, and December 31, 1993, and who survived 1 or more years were identified within 16 population-based cancer registries in the United States (1935–1991), Canada (Ontario, 1964–1992), Sweden (1958–1992), Finland (1953–1993), Denmark (1943–1991), and The Netherlands (1971–1993). In the United States, patients were registered in the nine reporting areas of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program<sup>1</sup> (1973–1991) and the State Health Registry of New Jersey (1979–1991). Participating SEER registries, which include the states of Connecticut, Hawaii, Iowa, New Mexico, and Utah, and the metropolitan areas of Detroit, Atlanta, Seattle-Puget Sound, and San Francisco-Oakland, comprise approximately 10% of the U.S. population. Patients from earlier years of the Connecticut Tumor Registry (1935–1972) were also included in the survey.<sup>2</sup> Features of each cancer registry have been previously described (11).

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Information routinely collected by all participating cancer registries includes patient demographic data, tumor characteristics, and vital status. For our analyses, we defined three major histologic groups of testicular cancer: seminomatous or nonseminomatous germ cell tumors (GCT) and cancers of other or unspecified histologic type. Testicular lymphomas and extragonadal GCT were excluded from the cohort. Except for registries in Sweden and Ontario, the initial course of cancer therapy in broad categories is also recorded. We used this information to identify patients with testicular cancer whose primary therapy included radiotherapy and/or chemotherapy. Data on subsequent courses of treatment are not recorded by the cancer registries. Furthermore, no information is available with regard to specific drugs or dose schedules administered. Treatment for testicular cancer typically includes orchiectomy, with adjuvant regional radiotherapy or retroperitoneal lymph node dissection being used in the management of early stage seminomatous or nonseminomatous GCT, respectively (12). When used to treat nonseminomatous GCT, similar radiation fields but larger doses (45–55 Gy) are typically used than for seminomas (25–35 Gy) (12,13). Average doses of radiation received by various organs during standard radiotherapy for testicular tumors are provided in Appendix Table 1. Advanced testicular cancer is treated with chemotherapy, which has conventionally included various combinations of cisplatin, vinblastine, and bleomycin since the mid-1970s, with etoposide added in the 1980s (14). Before that time, cytotoxic therapy included dactinomycin, mithramycin, vinblastine, and bleomycin.

Cancer registry incidence files were searched for invasive primary cancers that developed at least 1 year after testicular cancer. Because contralateral testicular tumors were not uniformly recorded by all registries, these tumors were excluded from the analysis. To estimate the risk of second cancers, person-years (PY) of observation were compiled according to age and calendar year periods from 1 year after the date of testicular cancer diagnosis to the date of death, date of diagnosis of a second invasive cancer, or the study end date (December 31, 1994),<sup>3</sup> whichever occurred first. Cancer incidence rates specific for each registration region, age (within 5 years), sex (male), and 5-year calendar period intervals were multiplied by the accumulated PY at risk to estimate the number of cancer cases expected. The observed and expected numbers of second cancers from each registry were then summed. For Finland, Connecticut incidence rates were used, with no substantive effect on the pooled results. Statistical tests and 95% confidence intervals (CIs) were based on the assumption that cases followed a Poisson distribution. Tests for linear trend were conducted according to the methods described by Breslow et al. (15), with variation in second cancer risk across registries evaluated by tests of homogeneity (15). All reported *P* values are two-sided. Cumulative probabilities of developing second cancers over time were calculated using life table methods (16). To determine the absolute risk of second cancers, the expected number was subtracted from the number observed; the difference was divided by the PY of follow-up and then multiplied by 10<sup>4</sup> to yield the excess number of cancers expected per 10 000 men per year.

## Results

Nearly 29 000 1-year survivors of testicular cancer were identified; they were diagnosed at an average age of 35.2 years and followed for a mean of 10.2 years (Table 1). The numbers of patients followed for 10, 15, and 20 years were 12 003, 6526, and 3306, respectively. GCT (15 602 seminomas and 12 408 nonseminomas) accounted for 97% of the testicular cancers, with other histologic types comprising 1.6% of cases and morphology not specified for the remainder.

Second cancers, excluding those of the contralateral testis, developed in 1406 patients (observed/expected [O/E] = 1.43; 95% CI = 1.36–1.51) (Table 2). The absolute risk was 16 excess cancers per 10 000 men per year. Significantly elevated risks were observed for all second solid tumors (O = 1251; O/E = 1.35; 95% CI = 1.28–1.43), including cancers of the stomach, small intestine, colon, rectum, pancreas, prostate, kidney, bladder, thyroid, and connective tissue as well as malignant melanoma. A twofold risk of bone cancer that was not statistically significant was also seen. A large proportion of cancers of the small intestine (10 [83%] of 12) and pancreas (57 [86%] of 66), sites at which misclassification might be anticipated, was confirmed microscopically. Among 13 connective tissue cancers for which site was specified, nine occurred in areas likely to be included in radiotherapy fields. Significant excesses of acute lymphoblastic leukemia (ALL) (O/E = 5.20; 95% CI = 2.37–9.86), acute nonlymphocytic leukemia (ANLL) (O/E = 3.07; 95% CI = 2.02–4.47), and non-Hodgkin's lymphoma (NHL) (O/E = 1.88; 95% CI = 1.46–2.39) were also found. No cancer occurred at a frequency significantly below expectation. Risks for second cancers were significantly elevated in all registries, ranging from 1.34- to 1.62-fold, except in New Jersey (O/E = 1.16). Excesses of prostate cancer were restricted to the U.S. SEER Program and the Connecticut Tumor Registry, while risks for malignant melanoma and NHL ranged from deficits to excesses of more than fourfold across registries.

Risk of all second solid tumors was similar following semi-

**Table 1.** Characteristics of 1-year survivors of testicular cancer reported to population-based study registries\*

Registry	No. of patients	Average age, y†	Person-years of follow-up	Average follow-up, y	No. of second primary cancers‡
All registries (1935–1993)§	28 843	35.2	293 652	10.2	1406
U.S. SEER Program (1973–1991)	8656	33.5	68 011 (23%)¶	7.9	210
Denmark (1943–1991)	6089	36.7	77 078 (26%)	12.7	470
Sweden (1958–1992)	4175	36.8	48 379 (17%)	11.6	221
Ontario (1964–1992)	4067	34.5	40 977 (14%)	10.1	179
The Netherlands (1971–1993)	2040	35.3	21 061 (7%)	10.3	96
New Jersey (1979–1991)	1797	34.3	11 661 (4%)	6.5	30
Finland (1953–1993)	1256	35.8	13 025 (4%)	10.4	52
Connecticut (1935–1972)	763	36.8	13 461 (5%)	17.6	148

\*All patients were diagnosed with testicular cancer as a first primary cancer and survived 1 or more years. SEER = Surveillance, Epidemiology, and End Results.

†Average age at initial diagnosis of testicular cancer.

‡Numbers exclude contralateral testicular cancers.

§Calendar years of diagnosis of testicular cancer.

||The 28 843 first primary cancers of the testis consisted of 28 010 germ cell tumors (GCT) (15 602 seminomas and 12 408 nonseminomas) and 833 cancers of other or unspecified histology. Average age at diagnosis was 39.2 and 29.8 years and the mean follow-up was 10.9 and 9.3 years for men with seminomatous and nonseminomatous GCT, respectively.

¶Numbers in parentheses indicate the percentage of total person-years of follow-up contributed by the indicated registry.

**Table 2.** Observed and expected numbers of second malignant neoplasms among 1-year survivors of testicular cancer\*

	All patients†			GCT, seminoma‡		GCT, nonseminoma§	
	Obs.	O/E	95% CI	Obs.	O/E	Obs.	O/E
All second cancers	1406	1.43¶	1.36–1.51	1033	1.42¶	311	1.50¶
All solid tumors	1251	1.35¶	1.28–1.43	932	1.35¶	262	1.36¶
All buccal	42	0.99	0.71–1.34	29	0.94	12	1.23
Esophagus	20	1.33	0.81–2.06	16	1.42	2	0.65
Stomach	93	1.95¶	1.57–2.39	62	1.73¶	27	2.95¶
Small intestine	12	3.18¶	1.64–5.56	12#	4.35¶	0	(0.85)**
Colon	105	1.27¶	1.04–1.54	80	1.30¶	22	1.32
Rectum	77	1.41¶	1.11–1.76	65	1.58¶	10	0.92
Liver, gallbladder	26	1.46	0.95–2.13	16	1.19	8††	2.26
Pancreas	66	2.21¶	1.71–2.81	53	2.35¶	11	1.89
Larynx	19	0.92	0.55–1.43	14	0.91	5	1.14
Lung	201	1.03	0.89–1.18	158	1.07	35	0.92
Prostate	164	1.26¶	1.07–1.46	118	1.18	31	1.42
Kidney	55	1.50¶	1.13–1.95	41	1.50¶	11	1.41
Bladder	154	2.02¶	1.72–2.37	121	2.12¶	28	1.85¶
Melanoma	58	1.69¶	1.29–2.19	36	1.57¶	18	1.74¶
Eye	2	0.72	0.08–2.60	2	1.02	0	(0.69)
Brain and central nervous system	24	0.82	0.52–1.21	17	0.85	6	0.72
Thyroid	19	2.92¶	1.76–4.57	11	2.61¶	8	3.82¶
Bone	6	2.44	0.89–5.31	2	1.32	3	3.51
Connective tissue	22	3.16¶	1.98–4.78	16	3.46¶	5	2.40
Non-Hodgkin's lymphoma	68	1.88¶	1.46–2.39	46	1.83¶	20	2.09¶
Hodgkin's disease	13	1.26	0.67–2.15	8	1.32	5	1.26
Multiple myeloma	10	0.81	0.39–1.50	6	0.65	4	1.65
All leukemia	64	2.13¶	1.64–2.72	41	1.92¶	20	2.78¶
Acute lymphoblastic leukemia	9	5.20¶	2.37–9.86	5	5.01¶	3	4.53
Acute nonlymphocytic leukemia	27	3.07¶	2.02–4.47	14	2.26¶	12	5.45¶
Chronic lymphocytic leukemia	7	0.56	0.22–1.15	5	0.53	2	0.80
Chronic granulocytic leukemia	9	0.93	0.42–1.76	7	1.05	1	0.38
All other§§	86	0.94	0.75–1.16	63	0.96	20	0.91

\*CI = confidence interval; GCT = germ cell tumor; Obs. = Observed; and O/E = observed-to-expected ratio.

†Includes 28 843 patients diagnosed with a first primary cancer of the testis who survived 1 or more years.

‡International Classification of Diseases (ICD)-0 (68) morphology codes 9060–9063 (n = 15 602 patients).

§ICD-0 morphology codes 9070–9073, 9080–9085, 9100–9102 (n = 12 408 patients).

||Numbers exclude contralateral testicular cancers. Category of all solid tumors also excludes lymphohematopoietic disorders.

¶Two-sided  $P < .05$ .

#Histologic subtype was specified for 10 cancers (seven adenocarcinoma and three miscellaneous); site was indicated for nine cancers (five duodenum, two jejunum, and two ileum).

\*\*Numbers in parentheses = expected number of second cancers.

††Site was specified for all cancers (four extrahepatic bile duct, two liver, one gallbladder, and one Ampulla of Vater), with six of eight tumors histologically confirmed.

§§Includes all solid tumors not itemized in this table, i.e., second cancers of unknown or ill-defined primary site.

nomas (O/E = 1.35) or nonseminomatous GCT (O/E = 1.36), with little variation in the site-specific patterns. Increased risks for cancers of the small intestine and rectum were observed only for seminomas, while patients with nonseminomatous GCT showed elevated twofold risks for hepatobiliary cancer. There were twofold to sixfold excesses of ANLL and ALL after both types of GCT.

The risk of solid tumors is shown in Table 3 according to initial treatment, histologic type, and time since diagnosis of testicular cancer. Significant excesses of second cancer were observed at 5–9, 10–14, 15–19, and 20 or more years after diagnosis of testicular cancer, with strong evidence of an increasing risk with time ( $P$  for trend = .00002). Among 20-year survivors, 369 (O/E = 1.54) solid tumors were reported, with significant excesses for cancers of the stomach (O/E = 2.32), colon (O/E = 1.71), pancreas (O/E = 3.24), prostate (O/E = 1.40), kidney (O/E = 2.30), bladder (O/E = 2.76), and connective tissue (not shown in Table 3; O/E = 4.72; O = 5). Among 21 kidney cancers in 20-year survivors, 15 occurred in the renal parenchyma, five occurred in the renal pelvis or ureter,

and the site was not indicated for one case. Elevated risks of NHL, malignant melanoma, and tumors of the thyroid and connective tissue occurred over all time intervals after testicular cancer diagnosis (data not shown). The median duration between the diagnosis of testicular cancer and NHL was 9.1 years (range, 1–32 years), with a high percentage of microscopic confirmation for each tumor (99% and 93%, respectively). Fourteen of 19 thyroid neoplasms occurred 5 or more years after testicular cancer (median, 9.2 years; range, 1.8–21.5 years). Significantly elevated twofold to fourfold risks of leukemia were observed during the first two decades after testicular cancer diagnosis.

### Seminomas

Seminomas were associated with significant excesses of total second tumors in each follow-up interval after 5 or more years, and risk increased with time since initial diagnosis ( $P$  for trend = .002). Risks were significantly elevated among patients treated initially with radiotherapy alone (overall O/E = 1.45;  $P$

**Table 3.** Selected second malignant neoplasms according to site, initial treatment, and time since diagnosis of testicular cancer\*

Time since diagnosis	1-4 y		5-9 y		10-14 y		15-19 y		≥20 y	
No. of patients (all) entering interval	28 843		19 498		12 003		6 526		3 306	
Seminoma	15 602		10 991		6 941		3 979		2 123	
Nonseminoma	12 408		8 009		4 747		2 343		1 061	
Person-years† (all)	94 399		77 801		45 429		23 791		23 390	
Seminoma	52 636		44 342		26 864		14 868		15 273	
Nonseminoma	39 275		31 456		17 296		8 107		7 042	
Second cancer site(s)	Obs.	O/E	Obs.	O/E	Obs.	O/E	Obs.	O/E	Obs.	O/E
Solid tumors, all patients	195	1.09	253	1.24‡	239	1.38‡	195	1.47‡	369	1.54‡§
Seminoma	149	1.14	195	1.29‡	179	1.39‡	133	1.34‡	276	1.56‡§§
Radiotherapy alone	81	1.31‡	103	1.30‡	105	1.49‡	72	1.38‡	161	1.65‡,¶
Any chemotherapy#	3	0.84	5	1.70	0	(1.38)**	0	(0.66)	0	(0.34)
Nonseminoma	31	0.88	48	1.13	55	1.47‡	50	1.80‡	78	1.56‡,§
Radiotherapy alone††	7	1.41	12	1.55	23	2.52‡	20	2.05‡	39	1.85‡
Any chemotherapy‡‡	4	0.73	10	1.53	11	2.42‡	2	1.57	1	3.65
Stomach, all patients	10	1.06	15	1.43	23	2.59‡	17	2.48‡	28	2.32‡,§§
Seminoma	7	1.00	11	1.39	14	2.08‡	10	1.92	20	2.20‡,¶
Radiotherapy alone	3	0.90	5	1.20	9	2.43‡	8	2.85‡	9	1.75
Nonseminoma	3	1.75	3	1.50	9	5.10‡	5	3.75‡	7	2.99‡
Radiotherapy alone	0	(0.37)	2	4.24	8	15.49‡	2	3.92	4	3.93‡
Colon, all patients	15	0.96	17	0.96	21	1.38	14	1.19	38	1.71‡,§§
Seminoma	13	1.13	13	0.97	12	1.06	11	1.25	31	1.89‡,§§
Radiotherapy alone	8	1.50	7	1.02	4	0.65	2	0.43	18	1.96‡
Nonseminoma	2	0.70	3	0.85	8	2.52‡	3	1.25	6	1.28
Radiotherapy alone	0	(0.41)	1	1.56	3	3.96	2	2.45	3	1.50
Rectum, all patients	13	1.30	15	1.30	14	1.39	19	2.37‡	16	1.06
Seminoma	12	1.61	12	1.38	12	1.58	15	2.47‡	14	1.25
Radiotherapy alone	6	1.65	10	2.13‡	8	1.86	7	2.11	10	1.55
Nonseminoma	1	0.55	2	0.88	1	0.48	4	2.48	2	0.65
Radiotherapy alone	0	(0.33)	1	2.05	0	(0.57)	3	4.87	2	1.46
Pancreas, all patients	7	1.30	6	0.96	14	2.54‡	12	2.72‡	27	3.24‡,§
Seminoma	7	1.73	4	0.84	12	2.88‡	8	2.39‡	22	3.53‡,§§
Radiotherapy alone	4	2.19	1	0.41	8	3.58‡	2	1.14	17	4.79‡,§§
Nonseminoma	0	(0.95)	2	1.67	2	1.80	2	2.27	5	2.98
Radiotherapy alone	0	(0.16)	1	4.01	0	(0.30)	2	6.06	3	4.06
Prostate, all patients	30	1.36	40	1.57‡	21	0.90	16	0.84	57	1.40‡
Seminoma	21	1.27	32	1.61‡	17	0.94	11	0.74	37	1.20
Radiotherapy alone	9	1.37	16	1.76‡	9	1.02	8	1.19	21	1.48
Nonseminoma	3	1.03	4	1.04	3	0.74	3	0.90	18	2.35‡,§§
Radiotherapy alone	0	(0.31)	1	2.04	0	(0.74)	1	1.12	7	2.61‡
Kidney, all patients	13	1.88	6	0.74	9	1.28	6	1.10	21	2.30‡
Seminoma	10	1.94	6	0.98	5	0.95	6	1.48	14	2.08‡
Radiotherapy alone	6	2.56	5	1.63	5	1.83	3	1.48	6	1.65
Nonseminoma	1	0.74	0	(1.72)	4	2.55	0	(1.20)	6	3.03‡
Radiotherapy alone	0	(0.20)	0	(0.32)	0	(0.38)	0	(0.41)	3	3.70
Bladder, all patients	13	0.98	28	1.80‡	28	2.04‡	23	2.07‡	62	2.76‡,§
Seminoma	10	1.01	23	1.96‡	22	2.13*	15	1.79	51	3.04‡,§
Radiotherapy alone	6	1.30	14	2.24‡	13	2.22‡	8	1.71	32	3.24‡,§§
Nonseminoma	3	1.23	4	1.31	6	2.12	7	3.12‡	8	1.76
Radiotherapy alone	1	2.66	0	(0.63)	1	1.28	1	1.12	5	2.41

**Table 3—continued.** Selected second malignant neoplasms according to site, initial treatment, and time since diagnosis of testicular cancer\*

Second cancer site(s)	Obs.	O/E								
Leukemia, all patients	24	3.61‡	13	1.89‡	11	2.02‡	10	2.50‡	6	0.85
Seminoma	17	3.76‡	4	0.83	6	1.54	9	3.08‡	5	0.96
Radiotherapy alone	9	4.27‡	1	0.40	3	1.43	4	2.60	4	1.34
Any chemotherapy	2	16.24‡	0	(0.09)	0	(0.04)	0	(0.02)	0	(0.01)
Nonseminoma	6	3.51‡	7	4.05*	5	3.77*	1	1.11	1	0.66
Radiotherapy alone	1	4.59	2	6.71	1	3.20	0	(0.32)	0	(0.66)
Any chemotherapy	2	6.61	4	14.13‡	0	(0.16)	0	(0.04)	0	(0.01)

\*Includes 28 843 men who were diagnosed with testicular cancer as a first primary cancer and survived 1 or more years. Numbers include 15 602 men with seminomas and 12 408 men with nonseminomatous germ cell tumors (GCT). Results are also stratified on the basis of initial course of therapy for 20 601 patients reported to cancer registries in Denmark, Finland, the Netherlands, New Jersey, and to the National Cancer Institute's Surveillance, Epidemiology, and End Results Program. Obs. = observed number of second cancers; and O/E = observed-to-expected ratio of second cancers.

†Indicates number of person-years within interval.

‡Two-sided  $P < .05$ .

§Two-sided  $P$  for trend  $< .01$ .

||Includes 7476 men with seminomas who received radiotherapy alone as primary treatment. Patients may have subsequently been given chemotherapy, but these data are not available.

¶Two-sided  $P$  for trend = .05.

#Includes 560 men with seminomas whose primary treatment included chemotherapy alone ( $n = 365$ ) or chemotherapy and radiotherapy ( $n = 195$ ). Because of the small numbers of patients and second cancers ( $n = 8$ ) in this category, site-specific risks for solid tumors are not provided.

\*\*Numbers in parentheses indicate the expected number of second cancers.

††Includes 1365 men with nonseminomatous GCT of the testis who received radiotherapy alone as primary treatment. Patients may have subsequently been given chemotherapy, but these data are not available.

‡‡Includes 2803 men with nonseminomatous GCT of the testis whose primary treatment included chemotherapy alone ( $n = 2448$ ) or chemotherapy and radiotherapy ( $n = 355$ ). Because of the small numbers of patients and second cancers ( $n = 28$ ) in this category, site-specific risks for solid tumors are not provided.

§§Two-sided  $P$  for trend  $< .05$ .

for trend = .05) but not chemotherapy (overall O/E = 0.90; O = 8); however, the number ( $n = 560$ ) of patients in the chemotherapy group was small and site-specific risks are not shown in Table 3. Significantly increased risks for cancers of the colon and kidney were restricted to 20-year survivors, while significant excesses of stomach and pancreas cancers were observed in all intervals 10 years or more after the diagnosis of seminoma. Significantly elevated risks of bladder cancer occurred 5–9 years after seminoma diagnosis, and these risks increased to threefold in later time periods ( $P$  for trend = .002), with excesses confined to those who initially received radiotherapy. Cancers of the small intestine occurred throughout follow-up (median, 11.5 years; range, 3–42.6 years). Significantly increased risks for leukemia were associated with regimens including chemotherapy (overall O/E = 7.20; O = 2) or with radiotherapy alone (overall O/E = 1.87; O = 21).

### Nonseminomas

During the 1–4- and 5–9-year intervals after the diagnosis of nonseminomatous tumors, second solid tumors did not exceed expectation, but an upswing in risk (50%–80% excess) was observed in later periods ( $P$  for trend = .001). A significantly increased risk occurred among patients who initially received radiotherapy alone (overall O/E = 1.92; O = 101) with twofold excesses after a follow-up of 10 or more years ( $P$  for trend = .66). Because only 28 solid tumors (O/E = 1.55) occurred among patients ( $n = 2803$ ) given any chemotherapy, site-specific risks are not presented. The significant excesses of cancers of the prostate (O/E = 2.35) and kidney (O/E = 3.03) following nonseminomatous tumors were confined to 20-year survivors, whereas twofold to threefold risks of bladder cancer and threefold to fivefold risks of stomach cancer were observed after 10 or more years. Excess hepatobiliary cancers were ob-

served in all follow-up periods after 5 years, with significantly increased risks in the 15–19-year interval (not shown in Table 3; O/E = 5.70; O = 3). Risks of leukemia were increased with radiotherapy alone (overall O/E = 2.21; O = 4) or any chemotherapy (overall O/E = 7.56; O = 6).

### Cumulative Risk

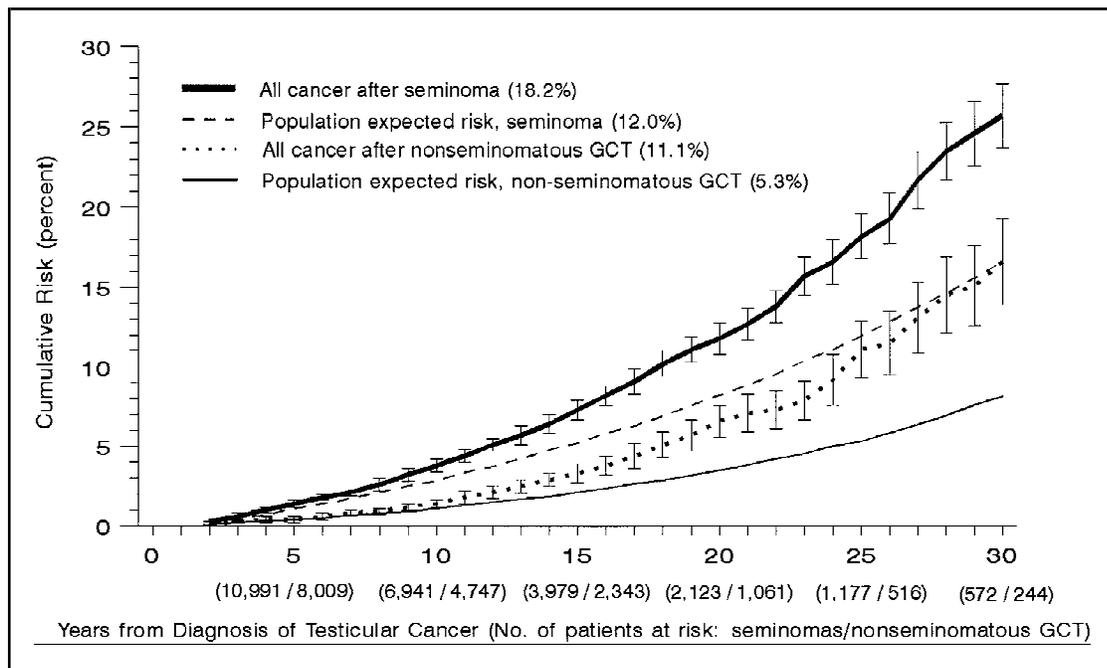
The actuarial risks of developing any second cancer, excluding tumors of the contralateral testis, 25 and 30 years after the diagnosis of testicular cancer were 15.7% and 22.6%, respectively. The corresponding population expected risks were 9.3% and 13.1%, respectively. As shown in Fig. 1, the cumulative risk of second cancer at 25 years was greater for men with seminomas (18.2%; 95% CI = 16.8–19.6) than for men with nonseminomatous tumors (11.1%; 95% CI = 9.3–12.9). The differences likely reflect the younger average age of the patients with nonseminomatous tumors (29.8 years versus 39.2 years), since the excess cumulative risks were similar.

The risks of leukemia are presented according to calendar year of diagnosis and histologic type of testicular tumor in Table 4. Large, significantly elevated risks followed any chemotherapy in the period 1975–1993 for seminomas and nonseminomatous tumors (O/E = 14.93 and 11.45, respectively). Before the widespread use of chemotherapy (1935–1974), overall risks of leukemia were increased threefold after both types of testicular tumor.

### Discussion

Our cohort study of second malignant neoplasms following testicular cancer had the advantage of large numbers of 10- and 20-year survivors, along with information on tumor histology and type of initial therapy. More than 1400 second cancers provided the basis for site-specific estimates of risk. For all solid

**Fig. 1.** Cumulative risk of second malignant neoplasms among 28 010 1-year survivors of testicular germ cell tumors (GCT). Percentages in parentheses indicate the actuarial risk at 25 years. Within the figure, 95% confidence intervals for point estimates are shown by short vertical lines.



tumors, excluding those of the contralateral testis, there were significantly elevated risks among 5-, 10-, 15-, and 20-year survivors, with clear evidence of an increasing risk with time. In addition, significant excesses of leukemia were found, including ALL (fivefold) and ANLL (threefold), along with NHL. Within our cohort, approximately one in five men (22.6%) with testicular tumors would be expected to develop a second primary cancer within 30 years compared with about one in eight men (13.1%) in the general population, representing an excess of about 10%.

Increased risks of second malignant neoplasms appeared to occur according to one of several patterns. For leukemia, elevated risks were observed within two decades after testicular cancer diagnosis; however, afterwards, the risks decreased to expectation. For several solid tumors, (e.g., stomach, bladder, pancreas, and colon), there was an increasing risk over time, suggesting the late effects of treatment. For other cancers (e.g., connective tissue and thyroid tumors, malignant melanoma, and NHL), elevated risks were observed throughout follow-up or exhibited no discernible trends (e.g., kidney). A discussion of the site-specific patterns of risk follows, with attention to the particular type of GCT.

### Leukemia

With 64 secondary leukemias after testicular cancer, our risk estimates are based on substantial numbers. For men diagnosed with testicular cancer between 1975 and 1993, a fourfold risk of secondary leukemia was detected overall, with 11- to 15-fold risks after chemotherapy. In recent clinical surveys of patients with testicular cancer, estimates of leukemia risk after chemotherapy have ranged from 20- to 300-fold, with figures typically based on one to six cases per report (9,17-21). Etoposide seems to be especially leukemogenic (18-21), although the effects of cumulative dose and schedule as well as the effects of other cytotoxic agents and radiotherapy remain to be clarified. The elevated risk of leukemia in our survey included not only ANLL

**Table 4.** Risk of secondary leukemia according to calendar year of diagnosis of testicular cancer\*

Calendar year of diagnosis	No. of patients	Secondary leukemia†		
		Obs.	O/E	95% CI
1935-1974				
All patients	6752	27	2.74‡	1.80-3.99
Seminoma	4001	19	2.70‡	1.63-4.22
Radiotherapy only§	2113	12	3.28‡	1.69-5.72
Any chemotherapy	34	0	(0.03)¶	0-141
Nonseminoma	2433	4	3.36	0.90-8.60
Radiotherapy only	900	1	1.14	0.01-6.37
Any chemotherapy	139	0	(0.05)	0-76
1975-1993				
All patients	22 091	30	3.96‡	2.67-5.65
Seminoma	11 601	17	3.46‡	2.01-5.54
Radiotherapy only	5363	6	2.53	0.93-5.52
Any chemotherapy	526	1	14.93‡	1.68-54
Nonseminoma	9975	12	5.09‡	2.63-8.89
Radiotherapy only	465	2	12.66‡	1.42-46
Any chemotherapy#	2664	6	11.45‡	4.18-25

\*Includes 28 843 patients with a first primary cancer of the testis who survived 1 or more years. Results are also stratified on the basis of initial course of therapy for 20 601 patients reported to cancer registries in Denmark, Finland, The Netherlands, New Jersey, and the National Cancer Institute's Surveillance, Epidemiology, and End Results Program. CI = confidence interval; O/E = observed-to-expected ratio; and Obs. = observed.

†Numbers exclude patients with secondary chronic lymphocytic leukemia (CLL) (n = 7).

‡Two-sided  $P < .05$ .

§This category includes patients who received radiotherapy alone as primary treatment. Patients may have subsequently been given chemotherapy, but these data are not available.

||This category includes 34 patients whose primary therapy included chemotherapy alone or chemotherapy and radiotherapy.

¶Numbers in parentheses indicate the expected number of second non-chronic lymphocytic leukemias.

#Includes 2664 patients whose primary treatment included chemotherapy alone (n = 2373) or chemotherapy and radiotherapy (n = 291).

but also ALL, for which data are sparse in previous studies of testicular cancer. ALL is increasingly recognized as therapy related (22,23) and may comprise 5%–10% of secondary acute leukemias (22). The cytogenetic translocation (4;11)(q21;q23), involving the region targeted by drugs such as etoposide that interact with DNA-topoisomerase II (24), has been reported in secondary ALL (25), including one patient with testicular cancer (26).

Although patients with mediastinal nonseminomatous GCT are inherently prone to develop secondary leukemia (27), such a relationship has not been reported for testicular tumors. In patients with mediastinal GCT and leukemia, both cancers have the cytogenetic abnormality i(12p), which is pathognomonic of GCT (28), suggesting derivation from a common progenitor cell (27). In contrast, cytogenetic studies of leukemias that follow testicular GCT have not revealed i(12p); they show instead abnormalities characteristic of treatment-related ANLL (19,29–31).

### **Non-Hodgkin's Lymphoma**

Although 7% of testicular tumors in older men are NHL (32), the average age in our cohort was quite young, and we excluded any patients with testicular lymphoma. The large proportion of microscopic confirmation of tumors in our study argues against diagnostic error as an explanation for the excess risks (O/E = 1.88); however, residual misclassification could have contributed to the variations in NHL risk observed across registries. Since increased risks of testicular cancer are not observed after NHL (33,34), it is unlikely that shared etiologic influences play a major role. Excess risks of secondary NHL in our study were apparent throughout follow-up and did not appear related to initial treatment. Furthermore, radiation exposure has not been convincingly linked with the development of lymphoma (35). Although immunologic defects, such as those observed in patients with Hodgkin's disease (36), have been implicated as a risk factor for NHL, immunosuppressive states are not pronounced in patients with testicular cancer.

### **Stomach Cancer**

Elevated risks of stomach cancer, which were observed after both types of testicular GCTs in our series, are well documented among atomic bomb survivors (37) and after irradiation for peptic ulcer disease (RR = 2.8) (38), cervical cancer (RR = 2.1) (39), and Hodgkin's disease (O/E = 10) (36). The stomach is located in the treatment field during standard irradiation of para-aortic lymph nodes for testicular cancer, so that the pattern of increasing risk in our series is consistent with a radiogenic effect. Moreover, large doses (mean, 13–26 Gy) of radiation can be delivered to the stomach during therapy for testicular cancer (Appendix Table 1). In previous studies, a significant eightfold increase in the risk of stomach cancer (n = 2) has been associated with infra- and supra-diaphragmatic irradiation for testicular tumors (40), and a fourfold to fivefold increase in risk has been associated with abdominal radiotherapy (n = 10) (9). Our study extends the findings of van Leeuwen et al. (9) and Moller et al. (8), whose patients are included in the current series with updated follow-up, by demonstrating that the excess risks of stomach cancer persist for at least two decades after the diagnosis of testicular cancer. Following irradiation for peptic ulcer

disease, there were significant excesses of stomach cancer extending beyond 30 years (38).

### **Bladder Cancer**

In our survey of patients with testicular cancer, significant twofold increased risks of bladder cancer were observed. Bladder cancer is recognized as a radiogenic neoplasm (37), with a highly significant dose-response relationship in the largest study to date (39). Elevated risks for bladder cancer have been reported following radiotherapy for NHL (41) and for cancers of the cervix (39) and ovary (42). Excess bladder tumors have been noted in some earlier follow-up surveys of testicular cancer (6,8,10), which included some patients in our series, but other studies have been negative (7,9). It is not clear why elevated risks of bladder cancer were observed as early as 5–9 years after the diagnosis of testicular cancer, especially since cyclophosphamide, a known bladder carcinogen (41), is not typically used in the therapy for GCT. Whether cisplatin, a radiation enhancer (43), contributes to a shortened latency period for radiogenic bladder cancer has not been evaluated.

### **Pancreas Cancer**

Twofold increased risks of pancreas cancer occurred among patients with testicular cancer in our series. The pancreas is not considered particularly susceptible to the carcinogenic effects of ionizing radiation (37), except when very high doses (e.g., on the order of 13 Gy) are given (38). The pattern of increasing risk with time, with excesses mainly in patients who received initial radiotherapy, suggests a radiogenic effect, consistent with the location of the pancreas in the radiation field (mean dose, 17–34 Gy) during standard therapy for testicular cancer. Excess pancreas cancers were observed in earlier surveys (6,8,9), but our extended follow-up points to threefold increased risks persisting 20 or more years after the diagnosis of testicular cancer. Although medical surveillance or misclassification of tumors might be involved to some extent, these potential biases are unlikely to explain the temporal patterns or treatment-specific effects we observed.

### **Colorectal Cancer**

A significantly elevated risk of colon cancer after testicular cancer, which we noted in our study (O/E = 1.27), has not been reported previously. Although the upward trends in risk with time for all patients and for those with seminoma in our series were statistically significant, similar trends were not apparent among patients who initially received radiotherapy. Moreover, the distribution of excess risks of colon cancer after nonseminomatous GCT seemed erratic. High-dose radiotherapy has been linked to colon cancer in some studies (37) but not others (39,44), and the large intestine receives nonuniform radiation exposure (mean dose, 1.4–12.4 Gy) during standard treatment of testicular seminoma. Excess rectal cancers in our series were restricted to patients with seminoma, with temporal patterns that were not consistent with the late effects of treatment. A significant relationship between radiation dose and rectal cancer, however, was reported following cervical cancer (39).

### **Connective Tissue Cancer**

Cancer of the connective tissue, a rare disease, occurred in only 22 men (O/E = 3.16) in our study, 13 of whom were

included in a previous report (45). In general, radiogenic sarcomas tend to arise after high therapeutic doses (46) and have not been observed among atomic bomb survivors (37). Sarcomas may occur as early as 14 months after radiotherapy (47), with some evidence that latency may be inversely related to dose (47,48). In children treated with radiotherapy for retinoblastoma, a dose-response relationship with soft tissue sarcoma was recently reported, with no evidence of increased risk below 10 Gy (49). It is noteworthy that nonseminomatous GCT and their metastases may contain sarcomatous elements (50,51) that could be mistaken for connective tissue cancer, but most sarcomas in our series occurred after seminoma and were located at sites likely to be included in the radiation field.

### Thyroid Cancer

Patients in our survey demonstrated a significant threefold increased risk of second thyroid cancers. During regional radiotherapy for testicular cancer, very low doses of radiation (0.2–0.4 Gy) may be delivered to the thyroid gland, which is especially sensitive to the carcinogenic effects of radiation, particularly when exposure occurs in early life (37). Prophylactic mediastinal irradiation for testicular cancer (40) would increase the dose to the thyroid; however, it is not clear whether a meaningful number of patients in our series received this treatment. Although radiotherapy may have contributed to late excesses of thyroid cancer among men with testicular tumors in our series, the finding of increased risks throughout follow-up suggests an effect of medical surveillance or possibly of shared etiologic factors (52). It is noteworthy that men with thyroid cancer reported to the SEER Program have shown an elevated risk of testicular cancer (O/E = 2.68; O = 5) (Travis LB, Curtis RE: unpublished data).

### Malignant Melanoma

A significantly increased risk (O/E = 1.69) of malignant melanoma was apparent in our series. Excesses of malignant melanoma after testicular cancer were previously reported by Kaldor et al. [(7), including some of the patients in our survey] and by Fossa et al. (40). Increased risks may, in part, reflect the association of both tumors with higher social class, while expected numbers used in the calculation of risks derive from the general population. The possibility of shared etiologic factors is suggested by the excesses of testicular cancer reported after melanoma in the SEER Program (O/E = 1.65, O = 8). Variations in melanoma risk across registries may reflect differences in reporting practices, diagnostic surveillance, or other factors.

### Kidney Cancer

Significant excesses of kidney cancer occurred among 20-year survivors of testicular cancer in our series (O/E = 2.30), but an increasing trend over time was not apparent. Although the kidney is considered relatively resistant to radiogenic cancer (37), radiotherapy for cervical cancer, in which kidney doses averaged 2 Gy, was associated with significant excesses of kidney cancer after 20–29 years (O/E = 1.5) and 30 or more years (O/E = 1.9) of follow-up ( $P$  for trend = .015) (44). Larger doses (average, 8–16 Gy) of radiation may be delivered to the kidney during therapy for testicular cancer. Whether chemo-

therapeutic agents used to treat testicular cancer (e.g., bleomycin and cisplatin) contribute to the excess risk in long-term survivors is not known. Bleomycin (53) can induce renal adenocarcinomas in laboratory rats, while cisplatin is a nephrotoxic agent that may enhance radiation effects (43).

### Prostate Cancer

The excess risk of prostate cancer among men with nonseminomatous GCT was confined to 20-year survivors (O/E = 2.35). The prostate gland, however, is relatively resistant to radiation-induced carcinogenesis (37), and no trend was apparent following treatment of seminomas, despite the large doses of radiation delivered to the prostate. Furthermore, since increased overall risks for prostate cancer were limited to specific registries, our findings may reflect a chance event associated with multiple comparisons or heightened medical surveillance of genitourinary conditions.

### Other Cancers

Increased risks of hepatobiliary cancer in our series were restricted to men with nonseminoma (O/E = 2.26). The liver retains the largest amount, approximately 2%, of administered cisplatin (54). Although this cytotoxic agent has been linked with the development of hepatic dysplasia and, possibly, with hepatocellular carcinoma in laboratory animals (55), most hepatobiliary cancers among patients with nonseminoma in our study involved the biliary tract. Hypercholesterolemia has been reported (56) following platinum-based chemotherapy for testicular cancer, but it is unclear whether this treatment predisposes to cholesterol gallstones, the major risk factor for biliary tract cancer. The increased body weight and hormonal alterations following testicular cancer therapy (57,58) may also increase the risk of biliary tract cancer (59).

The elevated risks (O/E = 4.35) of small bowel cancer among patients with seminoma in our series, with no cases reported after nonseminomatous GCT, deserve further investigation. Carcinoid tumors typically comprise about 30% of cancers in the small intestine (60), but none were observed in our series. Instead, the predominant small bowel tumor consisted of adenocarcinomas, which have been reported in several genetic syndromes, including familial adenomatous polyposis (61), hereditary nonpolyposis colorectal cancer (62), and Peutz-Jeghers syndrome (63). Testicular tumors have been reported in men with Peutz-Jeghers syndrome, but these neoplasms are typically sex cord tumors (64,65). Cancers of the small intestine reported to the SEER Program have been followed rarely by testicular cancer (O/E = 6.87; O = 1), and the small bowel seems relatively resistant to radiation-induced carcinogenesis (37,39).

### Comment

The significantly increased risks of second malignant neoplasms among men with testicular cancer in our series, particularly among 20-year survivors, is noteworthy. Although treatment regimens have changed in recent decades with the introduction of smaller radiation fields and lower doses, late effects of therapy administered to men decades ago continue to emerge. Given the relatively young age at which testicular cancer is treated, patients probably remain at risk for late sequelae for a lifetime. Moreover, excesses of many solid tumors do not

appear until 10 or more years after the diagnosis of testicular cancer, when patients may no longer be under routine medical surveillance. Our findings should prompt clinicians to follow patients with testicular cancer for life, even those cured decades ago. In future studies, radiation doses delivered to second cancer sites should be quantified in individual patients along with the doses of specific chemotherapeutic agents to clarify the role of treatment effects. It is also important to evaluate interactions of therapy with other environmental and genetic determinants of site-specific cancer risk.

For patients with testicular cancer treated in the modern era of chemotherapy, additional follow-up is needed to identify the risks of second cancers. Cisplatin, which has served as the cornerstone of successful therapy for testicular cancer for several decades, does not require metabolic activation and reacts directly with DNA. Although serum levels of cisplatin-DNA adducts correlate well with response to cancer treatment (66), their persistence in numerous tissues long after treatment is completed (4) has raised concerns about late effects. Cisplatin causes solid tumors in laboratory animals (53), and it will be important to determine whether it enhances the carcinogenic potential of radiotherapy (43).

Our results should be interpreted within the framework of the strengths and weaknesses of cancer registry-based data. Taken together, the centers included in our survey provide substantial numbers of subjects to permit the quantification of second cancer risk according to anatomic site, and the population-based nature of our study minimizes biases resulting from selection or referral patterns associated with clinical or hospital series. Because underreporting of second cancers may occur among patients who migrate from the catchment area of the registries, our estimates of increased risk may be conservative. However, migration is not an issue in Scandinavian countries, which have nationwide registration. In viewing our results, it should be noted that specified treatment categories reflect only initial management and not salvage therapy. Furthermore, the large number of comparisons in the analyses of multiple primary cancers will generate some statistically significant associations by chance alone.

Nevertheless, our results provide a reasonable estimate of the overall risk of second cancers following the diagnosis of testicular tumors and highlight the need to define better the role of treatment, natural history, medical surveillance, and other factors in the development of second malignant neoplasms. Since little is known regarding the etiology of testicular cancer (67), which is increasing in incidence at a rate of 2%–3% per year (2), the study of second cancers assumes even greater importance for insights into shared etiologic influences as well as into therapy-related and diagnostic factors. In future studies of cancer risk after testicular tumors, it will be important to consider histologic type, radiation dose to involved organs, chemotherapeutic regimens, and risk factor data to clarify the mechanisms underlying the associations. Our findings also underscore the importance of weighing the adverse effects of cancer therapy against the gains in survival. Despite the high cure rate in testicular cancer, it is important to monitor the carcinogenic potential of therapy throughout life and to develop approaches aimed at preventing second cancers.

**Appendix Table 1.** Estimated dose to selected organs and sites following typical radiation treatment for testicular germ cell tumors\*

Organ or site	Average total dose, Gy	
	Seminoma	Nonseminoma
Stomach	13.1	26.2
Small intestine	12.5	25.0
Colon	1.4–12.4	2.9–24.9
Rectum	12.5	24.9
Liver	10.7	21.4
Gallbladder	6.7	13.4
Pancreas	16.7	33.8
Prostate	22.5	45.0
Kidneys	7.8	15.6
Bladder	22.5	45.0
Thyroid	0.2	0.4
Active bone marrow	8.0	16.0

\*Radiation doses to target organs were estimated using methods described by Stovall et al. (69). Treatment simulation was based on standard anterior–posterior (AP)/posterior–anterior para-aortic fields and AP inguinal–iliac fields, with total administered doses of 25 and 50 Gy, respectively, for patients with seminomas and nonseminomatous germ cell tumors, as described by Castro et al. (70).

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## Notes

<sup>1</sup>*Editor's note:* SEER is a set of geographically defined, population-based tumor registries in the United States, operated by local nonprofit organizations

under contract to the National Cancer Institute (NCI). Each registry annually submits its cases to the NCI on a computer tape. These computer tapes are then edited by the NCI and made available for analysis.

<sup>2</sup>A portion of patients with testicular cancer reported to the U.S. SEER Program (1973-1991) and to cancer registries in Connecticut (1935-1972), Denmark (1943-1987), Finland (1953-1979), Ontario (1964-1982), Sweden (1958-1972), and The Netherlands Cancer Institute (1977-1985) were included in previous reports (6-10), with follow-up for the current study extended through December 31, 1992, for Denmark and registries that participate in the SEER Program; December 31, 1993, for Ontario and Sweden; and December 31, 1994, for Finland and The Netherlands.

<sup>3</sup>Study end date varied slightly according to registry, as described in the previous footnote. Patients reported to the State Health Registry of New Jersey were followed through December 31, 1993.

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We thank George Geise for computer support and data management; Dennis Buckman, Nelson Chong, Niels Christensen, Dr. Par Sparen, and Sandy Wilcox for assistance and provision of data files; Susan Smith for estimation of radiation doses; Virginia Hunter for field work; and Denise Duong and Rebecca Albert for typing support.

Manuscript received April 10, 1997; revised July 13, 1997; accepted July 28, 1997.