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Incidence of Second Primary Cancer Following Testicular Cancer

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The incidence of second primary cancers was investigated in 6187 Danish men diagnosed with testicular cancer in the period 1943–1987. During the course of 59 000 person years, 459 subsequent primary cancers occurred. The relative risks were significantly increased for leukaemia, gastric cancer, pancreatic cancer, bladder cancer, non-melanoma skin cancer and kidney cancer. Increased incidence was furthermore suggested for cancer of the rectum, prostate and lung. The increased incidence of leukaemia appeared in the first 10 years after testicular cancer diagnosis. The excess incidence for gastric cancer, pancreatic cancer, rectal cancer and lung cancer was strongest 10–19 years after testicular cancer, while the relative risk of non-melanoma skin cancer and prostate cancer increased throughout the period of follow-up. The increased incidence of cancer in this cohort is most likely an effect of radiotherapy used for testicular cancer. It is proposed that the different incidence patterns over time after testicular cancer diagnosis reflect differences in the growth rate of tumours originating in different tissues.
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INTRODUCTION

THE STUDY of multiple primary cancers occurring in the same person may yield an insight into (a) carcinogenic effects of cancer treatment, e.g. where the treatment of the first cancer is the cause of the second, and (b) cancer aetiology, e.g. where two different cancers have similar aetiology and hence appear together as a consequence of the same exposures [1].

The introduction of radiotherapy for seminoma, and more recently of chemotherapy for seminoma and non-seminoma, have resulted in a large number of long-term survivors after testicular cancer [2, 3]. The occurrence of leukaemia after chemotherapy for testicular cancer and other tumours has been studied previously [4, 5]. Follow-up studies of testicular cancer patients have indicated the possibility of increased incidence of cancer at a multitude of sites: digestive organs, urinary system, connective tissue, lung and skin [6–9].

The analysis presented here describes the incidence of second primary cancers occurring after a diagnosis of testicular cancer in Denmark in the period 1943–1987. The analysis of secondary sarcomas in the cohort is described in a separate paper [10]. Occurrence of contralateral testicular cancer is not described here, because of known under-registration of multiple primary tumours originating in the same organ, and, furthermore, only cancer diseases for which 10 or more cases occurred during the period of follow-up are analysed in detail.

A Danish study of bilateral testicular cancer, based on active case identification in clinical records, was published recently [11]. The Danish experience of secondary primary cancer in testicular cancer patients has previously been described from 1943–1980 [12]. The present report extends the follow-up with an additional period of 7 years, and expands the person time experience under risk from 36 000 to 59 000 person years. Compared with the collaborative study involving 113 000 person years reported by Kaldor *et al.* [6], in which the Danish data from 1950 to 1980 were included, the present study is smaller in terms of person years, but the mean duration of follow-up is longer than in the collaborative study (9.5 vs. 7.3 years).

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MATERIALS AND METHODS

The Danish Cancer Registry has recorded all cases of cancer in the Danish population since 1943 and classified these according to the 7th revision of the International Classification of Diseases (ICD) [13]. The unit of registration is a malignant tumour, and when two supposedly independent cancers occur in the same individual, two separate records exist in the registry holding among other variables the identification number of the person, date of diagnosis, diagnosis, date of death or emigration. The sources of information are notifications from clinical departments, practitioners and notifications based on autopsy reports. Active case identification is achieved by annual record linkages with the Danish Register of Deaths, and cases known from death certificates only are included in the Registry. The Danish Cancer Registry includes in addition to the ICD information about morphology for each tumour.

A total of 6 187 men diagnosed with testicular cancer in the period 1943–1987 were identified in the registry files. In the course of 58 908 person years of follow-up (mean: 9.5 years), 459 second primary cancers occurred (Table 1). Testicular cancer cases were grouped into three broad categories: pure seminoma (3 256; 53%), non-seminoma (2 550; 41%), and other and unspecified types (381; 6%). The median age at the time of testicular cancer diagnosis was 39 years for men with seminoma, 29 years for men with non-seminoma, and 42 years for men with other and unspecified types. The mean duration of follow-up was 11.6 years for seminoma and 7.4 years for non-seminoma, and 5.9 years for other and unspecified types.

Table 1. Number of persons, person years and second primary cancers, and age distribution and duration of follow-up after initial diagnosis with testicular cancer in Denmark, 1943–1987

Histological type	Persons	Age (years) Median	Quartile range	Person years	Mean follow-up, years	Secondary cancers
Seminoma	3256	39	32–48	37747	11.6	337
Non-seminoma	2550	29	24–37	18922	7.4	98
Other and unspecified types	381	42	30–66	2239	5.9	24
Total	6187	35	27–44	58908	9.5	459

The incidence of different second primary cancers were observed in the person time experience from 1 month after the date of diagnosis with testicular cancer to death, immigration, or 31 December 1987, which ever occurred first. The incidence of second primary cancers in testicular cancer patients was compared with the corresponding incidence rates in the Danish population as a whole using indirect age-standardisation for age and calendar time [14]. Results are expressed by the relative incidence rate (RR) with the associated 95% confidence interval. The RR was considered significantly increased or decreased when the 95% confidence interval did not include the value 1.0.

RESULTS

Malignant neoplasms of several sites occurred with increased incidence among men with previous testicular cancer (Tables 2–4).

The relative risk of leukaemia was 4.6 (2.5–7.9) in the first 10 years. Thereafter, the incidence was close to the expected. Of the 18 leukaemia cases which occurred in the cohort, there were 7 acute myeloid, 1 acute lymphatic, 3 chronic myeloid, 4 chronic lymphatic, 2 unspecified acute, and 1 unspecified leukaemia. According to the information in the Danish Cancer Registry, only one of these men had been treated with chemotherapy.

The RR for gastric cancer increased to 3.2 (1.8–5.2) 10–19 years after testicular cancer diagnosis. After 20 years the RR decreased again. A similar pattern was suggested for pancreatic cancer which increased to 3.1 (1.4–6.0) 10–19 years after testicular cancer diagnosis and then decreased slightly to 2.6 (1.2–4.9). Although both lung cancer and rectal cancer occurred with an incidence close to the expected overall, the data suggested a pattern resembling gastric and pancreatic cancer. The RR of lung and rectal cancer 10–19 years after testicular cancer diagnosis was not significantly increased [lung: 1.4 (0.9–2.1); rectum: 1.8 (0.8–3.4)]. In both sites, a χ^2 test for deviation from linearity was statistically significant.

Cancers of the prostate and the bladder, and non-melanoma skin cancer tended to increase in incidence throughout the period of follow-up. Non-melanoma skin cancer and cancer of the bladder were both significantly increased overall (about 2-fold), and both showed a tendency for increasing RR with time after testicular cancer diagnosis. The trends were, however, not statistically significant. Conversely, prostatic cancer was not significantly increased overall but showed a significantly increasing trend in RR. In the first 19 years, the incidence was below the expected, but increased thereafter to 1.8 (1.1–2.7).

The sub-site distribution of non-melanoma skin cancer occurring in the cohort was compared with the distribution among 50–69 year old men in Denmark (Table 5). The cases which occurred after testicular cancer diagnosis were more often than

Table 2. Number of cases (n), relative risks (RR) and 95% confidence intervals (CI) for second primary cancer after initial diagnosis with testicular cancer

	n	RR	95% CI
All sites	459	1.6	1.5–1.8
Stomach	34	2.1	1.4–2.9
Colon	28	1.5	1.0–2.1
Rectum	17	1.0	0.6–1.6
Pancreas	21	2.3	1.4–3.5
Lung	52	0.9	0.7–1.2
Prostate	27	1.2	0.8–1.7
Kidney	21	2.3	1.4–3.4
Bladder	47	2.1	1.5–2.8
Melanoma	10	1.8	0.9–3.3
Other skin cancer	68	2.0	1.5–2.5
Leukaemia	18	2.4	1.4–3.7

Table 3. Number of cases (n) and relative risks (RR) for second primary cancer, by type of testicular cancer

	Seminoma		Non-seminoma		Other and unspecified	
	n	RR	*n*	RR	*n*	RR
All sites	337	1.5*	98	1.8*	24	1.6*
Stomach	24	1.9*	7	2.6*	3	3.0
Colon	25	1.7*	2	0.6	1	1.0
Rectum	16	1.3	1	0.4	0	—
Pancreas	15	2.1*	4	2.5	2	4.0
Lung	42	1.0	8	0.8	2	0.7
Prostate	21	1.1	4	1.2	2	1.3
Kidney	16	2.2*	3	1.7	2	4.3
Bladder	37	2.1*	8	2.0	2	1.7
Melanoma	5	1.3	5	3.4*	0	—
Other skin cancer	47	1.8*	17	2.6*	4	2.4
Leukaemia	13	2.3*	3	2.0	2	5.0

*$P < 0.05$.

Table 4. Number of cases (n), and relative risks (RR) for second primary cancer, by period after testicular cancer diagnosis

	0–9 years		10–19 years		20+ years		χ^2 tests	
	n	RR	*n*	RR	*n*	RR	Linear trend	Deviation from linearity
All sites	146	1.5*	146	1.7*	167	1.6*	0.39	0.70
Stomach	10	1.6	16	3.2*	8	1.5	0.01	4.44*
Colon	8	1.3	7	1.2	13	1.8	0.44	0.23
Rectum	4	0.7	9	1.8	4	0.7	0.02	3.98*
Pancreas	3	1.0	9	3.1*	9	2.6*	1.46	1.63
Lung	12	0.7	24	1.4	16	0.7	0.02	5.50*
Prostate	4	0.7	4	0.6	19	1.8*	4.75*	1.34
Kidney	8	2.6*	4	1.4	9	2.7*	0.03	1.44
Bladder	11	1.6	14	2.0*	22	2.5*	1.50	0.00
Melanoma	4	1.6	3	1.8	3	2.2	0.18	0.01
Other skin cancer	17	1.5	19	1.8*	32	2.5*	3.54	0.12
Leukaemia	13	4.6*	3	1.3	2	0.8	8.60*	1.23

*$P < 0.05$.

expected located on the body (29% vs. 9%) and occurred more often at a multitude of sites on the skin (25% vs. 13%).

Cancer of the colon showed a tendency to increase, but the RR did not reach statistical significance: RR = 1.8 (0.9–3.0) 20 years after testicular cancer. Kidney cancer was increased throughout the period of follow-up. Malignant melanoma was not increased significantly overall, but occurred more often than expected after non-seminoma.

Comparison of the occurrence of secondary cancer after seminoma and non-seminoma showed no major differences. Analysis by period of treatment for testicular cancer indicated that the excess of secondary primary cancer may be particularly high in men treated most recently. The combined RR for cancers of the stomach, pancreas, lung, and rectum was higher in men treated after 1973 than in men treated earlier. In the first 15 years of follow-up, the RR of these cancers was 1.8 (1.2–2.6) for men treated after 1973 and 1.1 (0.8–1.5) for those treated earlier. The RR for leukaemia in the first 5 years of follow-up was 7.6 (3.0–17.6) for men treated after 1973 and 5.4 (1.5–13.9) for those treated earlier.

Apart from cases of the 11 cancer diseases described in Tables 2–4, another 116 cancer cases occurred during follow-up, comprising second primary testicular cancers (33 cases), non-Hodgkin lymphomas (9), cancers of the unknown or unspecified origin (8), cancers of the mouth and pharynx (8), larynx (7), oesophagus (6), connective tissue (6), liver (6), gallbladder (5), brain (5), and 12 other cancers (23 cases). Among these only testicular cancer was in statistically significant excess.

Table 5. Subsite distribution of non-melanoma skin cancer cases occurring after testicular cancer and among all Danish men aged 50–69 years

Subsite	After testicular cancer *n* (%)	Danish men aged 50–69 (%)
Face	17 (25)	(45)
Body	20 (29)	(9)
Other specified sites	14 (21)	(33)
Multiple tumours	17 (25)	(13)

DISCUSSION

In the present study, patients with seminoma were the largest group in terms of persons (53%). They contributed the greatest proportion of the person years at risk (64%), and they developed the majority of the observed secondary cancers (73%). The median age of seminoma patients was 10 years higher than patients with non-seminoma. The longer mean duration of follow-up of seminoma patients reflects the better prognosis in seminoma compared with other types of testicular cancer in the relevant period of time.

In order to appreciate the occurrence of secondary tumours in this material, it is necessary to consider the treatment for testicular cancer. In the period from the 1940s to the 1970s the treatment has been surgery plus postoperative radiotherapy [15]. The field of irradiation has most commonly included the paraaortic and pelvic lymph nodes. In the case of stage II seminoma, radiation has also been applied to mediastinal and supraclavicular nodes. From about 1970, chemotherapy has been used for both seminoma and non-seminoma. The RR for

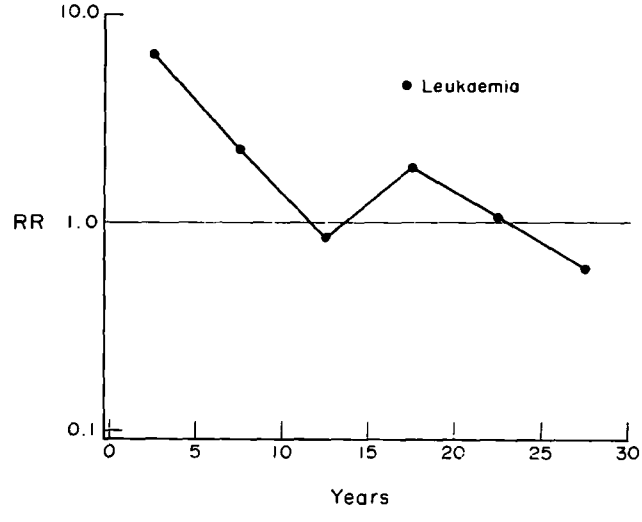

Fig. 1. Relative risk of leukaemia plotted against time after testicular cancer diagnosis.

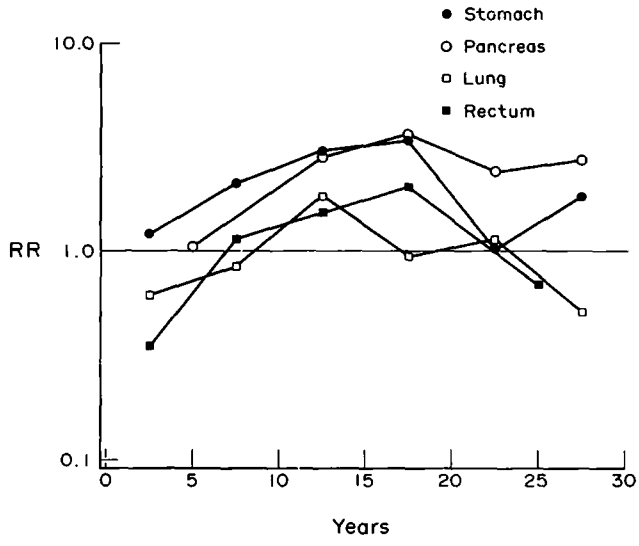

Fig. 2. Relative risk of stomach cancer, pancreatic cancer, lung cancer and rectal cancer plotted against time after testicular cancer diagnosis.

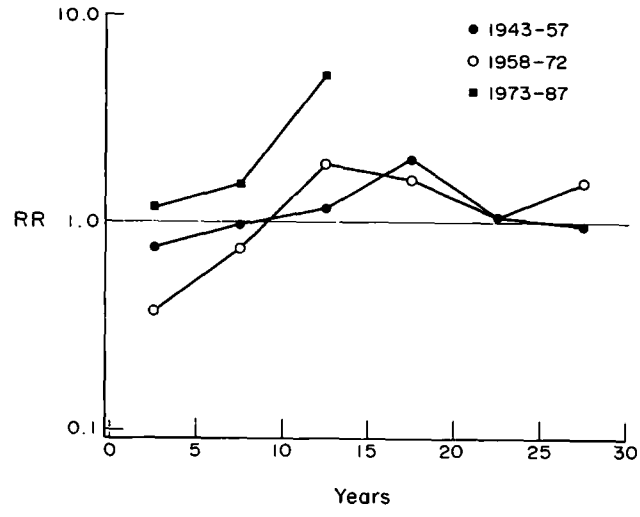

Fig. 4. Relative risk of selected solid tumours (stomach, pancreatic, rectal and lung cancer) plotted against time after testicular cancer diagnosis, by period of testicular cancer treatment.

leukaemia was increased significantly regardless of the period of diagnosis of testicular cancer, but the excess was highest in the more recent period. This additional increase in risk may possibly be caused by chemotherapy.

The pattern of incidence of solid tumours in the cohort is suggestive of radiation induced carcinogenesis. Radiotherapy applied to the field below the diaphragm (the treatment applied to the majority of the patients) will reach directly parts of the bone marrow, stomach, pancreas, colon, rectum, prostate, urinary bladder and part of the skin of the trunk, and a field above the diaphragm, parts of the mediastinum and lungs. The duration of follow-up of men treated for testicular cancer after the introduction of chemotherapy is not yet more than 15 years at maximum, and the increased incidence of solid tumours, which reach its maximum after 15–20 years, are therefore not likely to be influenced by chemotherapy.

The data suggest three different patterns of the excess incidence after testicular cancer. The excess of leukaemia occurs less than 10 years after testicular cancer (Fig. 1). A second wave of excess cancers of the stomach, pancreas, lung and rectum occur mainly 10–19 years after testicular cancer (Fig. 2), and is seen within subgroups of age and of period (Figs 3–4). Finally, the relative risk of non-melanoma skin cancer and of prostate cancer increase throughout the period of follow-up (Fig. 5).

It is tempting to interpret the time patterns of the different tumours as resulting from (a) tumour growth starting at the time of treatment for testicular cancer, and (b) the inherent growth rate of the affected type of cell. The pattern of incidence of leukaemia represents the extremely fast growing neoplasm. Stomach and pancreatic cancer represent neoplasms of intermediate growth rate, and non-melanoma skin cancer and prostate cancer are characterised by a slow growth rate.

The present study is thus in agreement with the findings from the long-term follow-up of patients treated with X-rays for ankylosing spondylitis, which suggested that the excess occurrence of solid tumours levels off just like the excess risk of

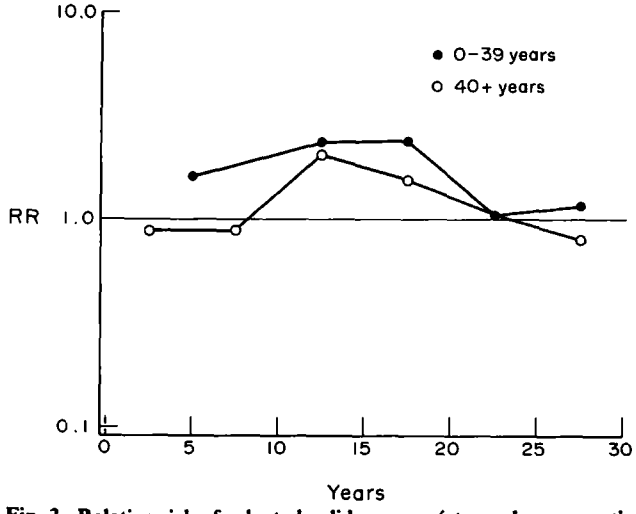

Fig. 3. Relative risk of selected solid cancers (stomach, pancreatic, rectal and lung cancer) plotted against time after testicular cancer diagnosis, by age at treatment for testicular cancer.

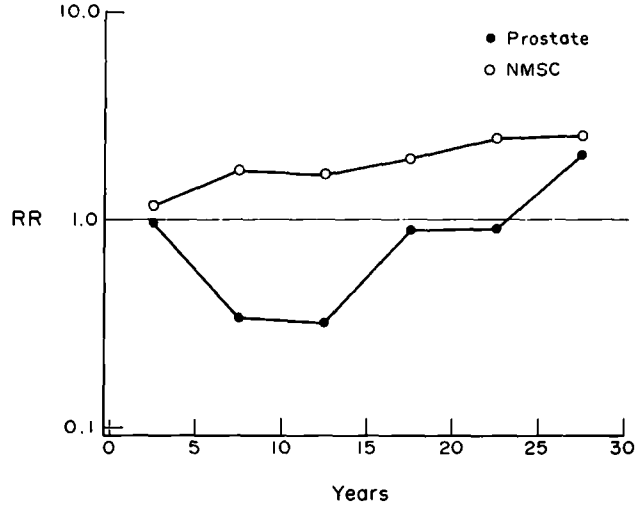

Fig. 5. Relative risk of non-melanoma skin cancer (NMSC) and prostate cancer plotted against time after testicular cancer diagnosis.

leukaemia, only much later [16]. Other studies of cohorts exposed to radiation, mainly women treated with radiotherapy for cervical cancer and the Japanese A-bomb survivors, have not shown this pattern of a wave of excess of solid tumours. Rather, the data from these studies have been interpreted as an excess incidence which continues throughout life [17, 18]. The issue is obviously important for predictions of future mortality and morbidity of irradiated individuals, and has been discussed at length in recent reports on radiation effects [19, 20]. There is some indication in the Japanese data of wave-pattern of solid tumours in persons who were exposed as children [21].

Compared with other follow-up studies of testicular cancer patients, the present study and the collaborative study [6] in which the Danish data contributed, are by far the largest. Although the Danish data contributed 25% of the person years at risk in the collaborative study, the two studies give somewhat different results. Of the main findings from the present investigation, the collaborative study is in agreement regarding leukaemia, but it is not in agreement regarding gastric cancer, pancreatic cancer, bladder cancer and non-melanoma skin cancer. These differences may partly reflect the longer duration of follow-up of the present cohort, or perhaps different routines for registration of multiple primaries in the collaborating cancer registries. The collaborative study showed a statistically significant excess of non-Hodgkin lymphomas which is also observed in the present study, but the excess is not statistically significant (RR = 1.5; 95% CI: 0.7–2.9).

Comparing the present study with the studies from Connecticut [7], Norway [8] and Scotland [9], the agreement between studies is high although results for all cancer sites are not presented in all studies, and the numbers are low for many sites. Gastric cancer is increased in all these studies except the Scottish. Colon cancer, lung cancer and bladder cancer shows increased incidence in all these studies. Pancreatic cancer is also increased in Connecticut, but no data are available from Norway or Scotland. Prostatic cancer is also increased in Connecticut, but not in Scotland. Non-melanoma skin cancer incidence is increased in Denmark and Scotland, but no data are available from Connecticut or Norway.

Regarding leukaemia, only the Connecticut study has sufficient size for comparison with the Danish. In contrast to the situation in Denmark, the excess risk in Connecticut is not confined to the first 10 years, but persists thereafter. Furthermore, the excess is similar in men who received radiotherapy and in those who did not, according to the information in the Connecticut Tumour Registry. This may suggest some predisposition for leukaemia in testicular cancer patients.

A pattern of a peak in the overall cancer incidence some time after testicular cancer is apparent also in the Norwegian and in the Scottish data, with a peak in relative risk at 5–14 years in Norway and at 15–19 years in Scotland. In the Connecticut data, the overall relative risk remains stable at 2.1 in the periods 5–9 years and 10+ years.

In summary, the available data show that the incidence of several solid cancers are increased in persons previously treated for testicular cancer. The excess cancer risk appears to be caused mainly by radiation treatment for testicular cancer. The different incidence patterns over time after testicular cancer diagnosis may reflect differences in the growth rate of neoplasms originating in different tissues.

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