LUND UNIVERSITY
Faculty of Medicine

LUP

Lund University Publications

Institutional Repository of Lund University

This is an author produced version of a paper published in Annals of Oncology : official journal of the European Society for Medical Oncology / ESMO. This paper has been peer-reviewed but does not include the final publisher proof-corrections or journal pagination.

Citation for the published paper:
Xiaochen Shu, Jianguang Ji, Kristina Sundquist, Jan Sundquist, Kari Hemminki

"Survival in cancer patients with previous hospitalization for sarcoidosis: a Swedish population-based cohort study during 1964-2006."

Annals of Oncology : official journal of the European Society for Medical Oncology / ESMO
2010 Dec 24

http://dx.doi.org/10.1093/annonc/mdq614

Access to the published version may require journal subscription.
Published with permission from: Oxford University Press

Original article

Survival in cancer patients with previous hospitalization for sarcoidosis: a Swedish population-based cohort study during 1964 to 2006

Xiaochen Shu, MD[1], Jianguang Ji, MD, PhD[1], Kristina Sundquist, MD, PhD [1], Jan Sundquist, MD, PhD[1,3], and Kari Hemminki MD, PhD [1,2]

[1] Center for Primary Health Care Research, Lund University, Malmö, Sweden,
[2] Division of Molecular Genetic Epidemiology, German Cancer Research Center, Heidelberg, Germany,
[3] Stanford Prevention Research Center, Stanford University School of Medicine, California, USA.

Corresponding Author:
X. Shu
Center for Primary Health Care Research
CRC, building 28, floor 11, entrance 72
Malmö University Hospital
S-205 02 Malmö
Sweden
Tel: +46-40-391334
Fax: +46-40-391370
E-mail: xiaochen.shu@med.lu.se

Running title: Cancer survival after sarcoidosis

Words: 2771 (text), 196 (abstract).

Abstract

Background: Sarcoidosis has been reported to be associated with an increased risk of cancer; however, little information is available about the prognosis for sarcoidosis patients diagnosed with cancer.

Patients and methods: A population-based cohort of sarcoidosis patients was identified from Swedish registers. Cause-specific and overall hazard ratios (HRs) were estimated by using Cox regression model to show the probability of death in the study group compared with the control population**.**

Results: A total of 1 167 sarcoidosis patients were identified with subsequent cancer compared to 1 023 725 cancer patients without sarcoidosis from 1964 to 2006, showing a significant survival disparity [overall HR 1.21, 95% confidence interval (CI) 1.13-1.30 and cause-specific HR 1.16, 95%CI 1.08-1.27). Site-specific analyses revealed that an overall mortality excess in sarcoidosis patients was observed for six cancers in comparison with a cancer-specific mortality excess for four cancers. Notably, stratified analyses showed that the prognosis was worse for cancer patients diagnosed below age 65 yrs. Cancer sites with significant mortality excess after sarcoidosis were mutually exclusive for men and women.

Conclusions: A previously diagnosed sarcoidosis worsens the prognosis of cancer, preferentially for those diagnosed at a relatively younger age. The underlying mechanisms and more prognostic factors warrant further investigation.

Key Words: cancer survival, hazard ratios, mortality, sarcoidosis

introduction

Sarcoidosis is a chronic multisystem granulomatous disease that may occur among people of any racial and

geographic group regardless of age and gender [1, 2]. However, young adults and women are at a somewhat higher risk than others [2]. Incidence and prevalence rates vary widely with the highest annual incidence of 5-40 cases per 100 000 people in northern European countries [3]. A bimodal incidence in women was noted for Scandinavians, with the first peak between 25 and 29 and the second peak between 65 and 69 years of age. In Japan, the annual incidence ranges from 1 to 2 cases per 100 000 people with a peak in the third decade of life [1]. Sarcoidosis is a systemic disease that can affect any organ, with the main involvement of the lung, skin and liver and with additional neurological, ophthalmological, and cardiac manifestations [1]. Despite the advanced understanding of the pathogenesis of sarcoidosis, the etiology remains elusive. The roles of immunological response, genetic susceptibility, and environmental agents had been reported [1-4]. Immune response is widely believed to start with the presentation of unknown antigens to T lymphocytes, leading to the formation of sarcoidosis granulomas [1]. Familial cluster of sarcoidosis had been reported. There are also various lines of evidence that would support the genetic predisposition of sarcoidosis. The most prominent findings are the association of sarcoidosis with specific human leukocyte antigen haplotypes [2-4]. At present, two major categories of environmental agents are considered as potential cause of sarcoidosis: microbial organisms and noninfectious agents [2].

Increased cancer risk in patients with sarcoidosis has been reported in previous studies [5-8]. However, a population-based prognosis for sarcoidosis patient diagnosed with cancer has never been reported to the best of our knowledge. It could be hypothesized that prognosis of cancer may be impacted by previously diagnosed sarcoidosis. In the present study, we focused on the impact of sarcoidosis on the prognosis of subsequent cancers by quantifying the cancer-specific and overall mortality and trying to explore the prognostic factors influencing the survival using Swedish national registers. The full coverage of the Swedish national registers and the clinically verified diagnosis ensured a high diagnostic accuracy and statistical power to examine survival. The follow-up on cancer survival after sarcoidosis (1964-2006) is longer than in any previous study.

patients and methods

Study population, design, and follow-ups

The sarcoidosis cohort comprising 10 668 patients was constructed by identifying all sarcoidosis patients diagnosed during 1964-2006 in Swedish Hospital Discharge Registry (HDR) according to the seventh (1964-1968 code 138.00-138.10), eighth (1969-86 code 135), ninth (1987-96 code 135) and 10th (1997-2006 code D86) International Classification of Disease (ICD) codes. A four-digit diagnosis code according to the seventh revision of the International Classification of Diseases (ICD-7) has been used to classify cancer groups: "upper aerodigestive tract cancer" codes 161 (larynx) and 140-148 (lip, mouth, pharynx), except for code 142 (salivary glands), "nasal cancer" code 160, "lung cancer" code 162-163, "melanoma" code 190, "skin cancer" code 191 (squamous cell carcinoma as basal cell carcinoma of the skin is not registered in the Swedish Cancer Registry), "eye cancer" code 192. Lung cancer could be subdivided into small-cell lung cancer ("small-cell lung cancer" code 8041/3) and non-small-cell lung cancer only after 1993 when the related histopathological types were available. HDR was founded in 1964-65 and a complete nationwide coverage was achieved since1987 [9, 10]. The sarcoidosis cohort was further linked to the Swedish Cancer Registry (2006) where tumors were ascertained with a four-digit ICD-7 code [9, 10]. The Cancer Registry records all new cases of cancer and nearly all of them are histologically or cytologically confirmed at a full national coverage [11]. Only cases classified as primary neoplasms were considered in the present study.

Cancer patients diagnosed after last hospitalization of sarcoidosis were retrieved as the study population. Other cancer patients without hospitalization for sarcoidosis were used as the control population. Follow-ups for survival in cancer patients were started from the diagnosis date of cancer both in the study population and in the control population. The primary study ending points were death, emigration or closing date on 31 December, 2006, whichever came first. Additional information including date of death and causes of death was identified from the Death Register. Information retrieved from the various registers was linked at the individual level via the national 10-digit civic registration number assigned to each person

in Sweden for his or her lifetime. Before inclusion in the database, civic registration numbers were replaced by using a serial number for each person to ensure anonymity for all individuals.

statistical adjustment and analysis

Co-variables adjusted for in the present study included gender, age at diagnosis of the primary neoplasm, calendar year at diagnosis of the primary neoplasm, and chronic obstructive pulmonary disease (COPD). Patients' previous hospitalization for COPD, which was suspected to be one important prognostic factor for cancer, was identified in HDR accordingly. As a surrogate of smoking, 287 999 COPD cases were retrieved in HDR according to seventh (1964-68, code 500-502), eighth (1969-86, code 490-493), ninth (1987-96, code 490-496) and tenth (since 1997 code J40-J49) revisions. Patients' COPD status in HDR was individually linked to their cancer status using a serial number.

The Cox regression and Kaplan-Meier analyses were used to estimate hazard ratios (HRs), which could be interpreted as mortality rate ratio [12], after adjustment for aforementioned co-variables. Regarding the analysis of cause-specific HRs, deaths from cause-specific cancers were the primary end points while deaths due to other causes were censored. With respect to the analysis of overall HRs, deaths due to any cause were the end point. The proportional hazard assumption for the covariates was tested by Schoenfeld residuals and by plotting the log of the negative log of the survival function versus the log of time; covariates were stratified in the models if they did not meet the assumption [13, 14]. The 95% confidence interval (CI) for HRs was calculated and rounded to the nearest two decimals.

The Swedish Cancer Registry provided data on cancer TNM staging only from 2002 onwards; therefore the cancer TNM staging information was not adjusted in the analysis. We analyzed cancer TNM staging distribution by sarcoidosis status, using chi-square test or Fisher's exact test whichever is appropriate (as a rule of thumb, Fisher's exact test was only used when the expected value in any cell in a contingency table was $<$ 5). Cause-specific survival curves were plotted using the life-table method and the difference was analyzed using log-rank tests [15]. Moreover, stratified analyses were carried out with respect to gender and

age at diagnosis of cancers (≤ 65 yr *versus* > 65 yrs) regarding the overall mortality to test whether the effects of different levels of these variables on subsequent survival were different.

All the analyses were carried out using the SAS statistical package v 9.2 (SAS Institute Inc., Cary, NC. USA).

ethical approval and consent

The study was approved by the ethics committee at Lund University and recommendations of Declaration of Helsinki had been followed.

results

A total of 1 167 cancer patients with prior hospitalization for sarcoidosis were retrieved from 1964 to 2006 and they were compared with 1 023 725 cancer patients without hospitalization for sarcoidosis. The distribution of cancers in sarcoidosis patients was listed in Table 1. The most common cancers were breast, prostate, lung and colon cancers and non-Hodgkin's lymphoma (NHL). On average, cancer patients in the control experienced longer survival times in comparison with cancer patients in the study group. Totally, the study group had a similar diagnosis age of primary neoplasms with the control. The largest difference was noted for other female genital cancer, testicular cancer, bone cancer, and cervical cancer.

We primarily analyzed the relative mortality rates for cancer patients with precedent hospitalization for sarcoidosis compared with the control. For all cancers, significant survival disparity was observed between two group during the entire follow-up (overall HR 1.21, 95%CI 1.13-1.30 versus cause-specific HR 1.16, 95%CI 1.08-1.27) (Table 2). A wide spectrum of cancer sites with significant excess of overall HRs, ranging from 1.35 to 4.50, were observed including lung, NHL, leukemia, thyroid gland, salivary gland, and skin (squamous cell carcinoma). Significant excess of cancer-specific HRs was observed for lung cancer, NHL, Hodgkin's disease, and anus cancer. As for skin (squamous cell carcinoma) cancer, other causes of death except for the cancer-specific ones were further dissected. Over 60% of deaths were

explained by deaths of cardiovascular disease or discordant cancers. Other causes of deaths were heterogeneous. Survival curves for lung cancer and NHL, where most of the worse survival after sarcoidosis were observed and sufficient cases were available, were plotted according to the life-table analysis in Figure 1 and Figure 2 [15]. Survival was worse for cancer patients with sarcoidosis. The log-rank test showed a significantly different prognosis for these two cancer sites between two groups ($P<0.05$).

Age at diagnosis of cancer might be associated with the prognosis for patients. Stratified analysis by diagnosis age of cancer with respect to overall mortality was thus carried out, and results were presented in Table 3. We observed that the prognosis was worse in cancer patients diagnosed at an earlier age (n=327; HR 1.31, 95%CI 1.18-1.45 for ≤ 65 yrs versus n=432, HR 1.08, 95%CI 0.99-1.19 for >65 yrs). As for cancer patients with sarcoidosis diagnosed <65 yrs, excess death was additionally observed for nasal cancer, kidney cancer, and connective tissue cancer. For those >65 yrs, increased mortality was only observed among patients with squamous cell skin carcinoma and Hodgkin's disease.

The death excess in cancer patients with sarcoidosis is suspected to be different between women and men considering the higher incidence of sarcoidosis among women and the different manifestations of sarcoidosis according to gender. We examined separated mortality by gender, and results were showed in Table 4. No overlapped cancer sites with significantly increased mortality risk were observed between men and women. Regarding the site-specific cancer, previously observed mortality excess of lung cancer and thyroid cancer in Table 2 was only observed among female patients, whereas worse prognosis of NHL and squamous cell skin cancer were observed only among male patients. In addition, significant mortality excess of liver cancer, nervous system cancer, and ophthalmologic cancer was observed in men. For all cancers, similar excess of cancer mortality was noted for men and women in the study group.

Cancer TNM staging, which describes the extent or severity of an individual's cancer based on the extent of the primary tumor and the extent of spread in the body, is by far the most commonly used system to estimate cancer prognosis. We compared the case numbers for main cancers between two groups (data not shown). No significant difference in TNM stage distribution by sarcoidosis status was observed for the

main cancer sites (P>0.05).

Cancer patients with previous hospitalization for sarcoidosis may be at risk to be diagnosed at an earlier stage or at a younger age compared with the control group due to more frequent medical surveillance after sarcoidosis hospitalization. We therefore examined the distribution of prostate cancer (one of the most common cancer types in the present study) in the T1c stage (an established indicator of prostate specific antigen (PSA) screening [16]) according to different age groups (≤65 yrs, 66-75, ≥76). No difference was observed between the study group and the reference (P=0.73).

discussion

This population-based cohort study was carried out to compare survival difference between cancer patients with previous hospitalization for sarcoidosis and those without sarcoidosis. The significant mortality excess for a wide spectrum of cancer sites observed in the current study confirmed our previous hypothesis that sarcoidosis, as an immune-mediated disease, worsened the prognosis of subsequent cancers. The worse prognosis in the study group was even more pronounced in cancer patients diagnosed at an earlier age (≤65 yrs). Cancer sites with significant mortality excess were mutually exclusive for men and women, which may indicate different underlying mechanisms for the worse survival according to genders. The increased mortality seemed unlikely to be related to tumor stage, given that the TNM staging distribution was not different comparing study group with the reference for the main cancer sites. It is important to emphasize, however, an underestimation of the sarcoidosis patients may have occurred in the present study and our results should not be directly extrapolated to all sarcoidosis patients since hospitalized sarcoidosis is associated with more comorbidities and represents more severe symptoms.

The current study design confers both strengths and limitations. The major strength is the full coverage of Swedish national registries and the longest follow-up duration (1964-2006) so far. The use of health-related database at national level excludes the selection bias at its maximum, ensuring high statistic power

even for rare cancers. The Swedish Cancer Registry is based on the compulsory clinical reports provided by physicians and pathology report by pathologists or cytologists, ensuring a high diagnostic accuracy and a complete coverage at the national level [14]. Although the unavailability of TNM staging information before 2002 raised analytical concerns, analysis of cancer TNM stage distribution showed the similar TNM staging distribution for main cancers, suggesting TNM effect could be minimal. Absence of information of lifestyle is also a shortcoming of the current study, whereas the possible confounding impact of COPD (a surrogate of smoking) was adjusted for in the analyses. Increased medical surveillance after sarcoidosis hospitalization may shift the diagnosis of cancer earlier, which might bias our findings. In the present study, however, the possible effect of surveillance bias was minimized considering the distribution of prostate cancer with T1c by age was not different across patient's diagnosis of sarcoidosis. Some findings in the present study may be due to chance considering the insufficient number of cases.

To the best of our knowledge, data reporting the influence of sarcoidosis on survival of subsequent cancers has been very limited so far and the available data showed conflicting results. An earlier Danish study observed no excess number of deaths from lung cancer or lymphoma based on a small sample of 254 pulmonary sarcoidosis patients [17]. By contrast, a Japanese study reported increased mortality of lung cancer among sarcoidosis patients on the basis of 1 411 sarcoidosis patients with a short follow-up duration of 3 years [18]. Conclusions about the prognosis of other cancers diagnosed after sarcoidosis were, however, not drawn owing to the very small number of observed cases [17, 18]. In this population-based cohort study, we, for the first time, observed worse prognosis in the study group for a wide spectrum of cancers, mainly including lung, thyroid gland, salivary gland, anus, and squamous cell skin carcinoma as well as NHL, Hodgkin's disease, and leukemia. Mutually exclusive cancer sites with death excess after sarcoidosis were observed between male and female patients, possibly suggesting different underlying mechanisms for the increased mortality by gender. Death excess observed among younger kidney cancer patients and in male patients with nervous system cancer and liver cancer after sarcoidosis may represent more severe symptoms and altered functions, which deserves much more awareness for clinicians and patients. The underlying mechanisms for the worse survival may be complex. Given that both sarcoidosis and cancers are immune-mediated diseases, the increased cancer mortality after sarcoidosis may be partially attributable to the

dysregulation of immune system. We observed that NHL and Hodgkin's disease that originate from the immune system had a high ratio with and without sarcoidosis (respectively over 2/1000 and over 3/1000 for NHL and Hodgkin's disease in comparison with 1/1000 for most other cancers). The excess could partly be explained by sarcoidosis-lymphoma syndrome [19]. In particular, the immunosuppressants inevitably complicated the situation, impacting the tumor prognosis as believed [20]. Unfortunately, treatment information was not available in the present study, which is a shortcoming of the present study. The possible impact of smoking on the prognosis for cancer patients with sarcoidosis was not observed in the present study.

TNM stage distribution by sarcoidosis status was not different between the study population and the control population for the main cancer sites. The worse survival observed in the present study seemed unlikely to be caused by the advanced metastasis of cancers although chance findings may exist because of the limited cases with TNM stage.

In summary, previously diagnosed sarcoidosis worsen the prognosis of a wide spectrum of cancers. Worse survival in the study group was more pronounced in cancer patients diagnosed at a younger age (≤65 yrs). Different mechanisms may be underlying the worse prognosis between men and women. The current findings provided patients and clinicians with novel information about risk assessment and prognostic factors. The mechanisms underlying this disparity warrant further studies.

Disclosure

The authors have declared no conflicts of interest.

Acknowledgements

This work was supported by Swedish Cancer Society, Swedish Council for Working Life and Social Research, and the Deutsche Krebshilfe. The registers used in the current study are maintained by National Board of Health and Welfare and Statistics Sweden.

REFERENCES

1. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. N Engl J Med 2007; 357: 2153-2165.
2. Lazarus A. Sarcoidosis: epidemiology, etiology, pathogenesis, and genetics. Dis Mon 2009; 55: 649-660.
3. Dempsey OJ, Paterson EW, Kerr KM, Denison AR. Sarcoidosis. BMJ 2009; 339: b3206.
4. Baughman RP, Lower EE, du Bois RM. Sarcoidosis. Lancet 2003; 361: 1111-1118.
5. Ji J, Shu X, Li X et al. Cancer risk in hospitalized sarcoidosis patients: a follow-up study in Sweden. Ann Oncol 2009; 20: 1121-1126.
6. Boffetta P, Rabkin CS, Gridley G. A cohort study of cancer among sarcoidosis patients. Int J Cancer 2009; 124: 2697-2700.
7. Reich JM. Concurrent sarcoidosis and lung cancer. Chest 2009; 136: 943; author reply 944.
8. Sato Y, Sasano S, Oyama K et al. Lung cancer associated with sarcoidosis. Jpn J Thorac Cardiovasc Surg 2003; 51: 21-24.
9. Hemminki K, Li X, Sundquist J, Sundquist K. Cancer risks in ulcerative colitis patients. Int J Cancer 2008; 123: 1417-1421.
10. Hemminki K, Li X, Sundquist J, Sundquist K. Cancer risks in Crohn disease patients. Ann Oncol 2009; 20: 574-580.
11. Epidemiology Cf. Cancer Incidence in Sweden 2005. Stockholm, Sweden: The National Board of Health and Welfare 2007.
12. Larsen M, Mose H, Gislum M et al. Survival after colorectal cancer in patients with Crohn's disease: A nationwide population-based Danish follow-up study. Am J Gastroenterol 2007; 102: 163-167.
13. Ji J, Forsti A, Sundquist J et al. Survival in ovarian cancer patients by histology and family history. Acta Oncol 2008; 47: 1133-1139.
14. Hemminki K, Ji J, Forsti A et al. Survival in breast cancer is familial. Breast Cancer Res Treat 2008; 110: 177-182.
15. Pocock SJ, Clayton TC, Altman DG. Survival plots of time-to-event outcomes in clinical trials: good practice and pitfalls. Lancet 2002; 359: 1686-1689.
16. Lerner SE, Seay TM, Blute ML et al. Prostate specific antigen detected prostate cancer (clinical stage T1c): an interim analysis. J Urol 1996; 155: 821-826.
17. Viskum K, Vestbo J. Vital prognosis in intrathoracic sarcoidosis with special reference to pulmonary function and radiological stage. Eur Respir J 1993; 6: 349-353.
18. Yamaguchi M, Odaka M, Hosoda Y et al. Excess death of lung cancer among sarcoidosis patients. Sarcoidosis 1991; 8: 51-55.
19. Brincker H. The sarcoidosis-lymphoma syndrome. Br J Cancer 1986; 54: 467-473.
20. White ES, Lynch JP, 3rd. Current and emerging strategies for the management of sarcoidosis. Expert Opin Pharmacother 2007; 8: 1293-1311.

Table 1 Case number, median age of diagnosis, and median follow-up duration among cancer patients diagnosed after sarcoidosis and cancer patients without hospitalization for sarcoidosis

Cancer	After sarcoidosis			Without sarcoidosis		
	n	Median age of diagnosis	Median follow-up (months)	n	Median age of diagnosis	Median follow-up (months)
Upper aerodigestive tract	25	65	26	23,183	64	52
Salivary gland	4	59	17	2,705	60	88
Oesophagus	7	60	6	8,087	68	6
Stomach	37	69	8	38,970	69	6
Small intestine	10	67	9	4,525	66	23
Colon	90	70	29	72,548	70	30
Rectum	37	71	31	41,456	69	34
Anus	5	55	42	2,066	65	44
Liver	34	70	2	26,495	70	2
Pancreas	26	70	1	26,761	69	2
Nose	5	61	13	1,794	64	40
Lung	96	65	4	74,592	67	6
Breast	137	64	73	144,493	59	81
Cervix	14	60	101	22,797	48	123
Endometrium	35	70	70	29,275	63	101
Uterus	0	0	0	220	29	221
Ovary	33	68	30	27,066	59	31
Other female genital	7	51	67	4,283	69	43
Prostate	135	68	44	143,213	72	42
Testis	4	49	57	7,588	34	137
Other male genital	3	59	74	1,918	64	64
Kidney	44	65	20	30,340	65	24
Urinary bladder	24	65	73	46,740	69	58
Melanoma	37	64	103	38,449	56	90
Skin, squamous cell	66	73	45	35,875	75	63
Eye	3	63	161	3,540	58	82
Nervous system	36	61	16	39,078	54	27
Thyroid gland	12	51	157	10,087	52	128
Endocrine glands	36	64	99	18,951	59	121
Bone	2	49	62	2,858	36	56
Connective tissue	5	68	10	7,871	59	43

Non-Hodgkin's lymphoma	78	61	18	32,229	65	33
Hodgkin's disease	25	44	60	7,399	40	74
Myeloma	17	70	19	13,806	69	27
Leukemia	38	66	12	32,467	63	27
All	1,167	66	30	1,023,725	66	37

Table 2 Overall and cause-specific HRs in cancer patients diagnosed after sarcoidosis in comparison with cancer patients without hospitalization for sarcoidosis

Cancer		Cause-specific mortality				Overall mortality			
	Cases	Deaths	HRs	95%CI		Deaths	HRs	95%CI	
Upper aerodigestive tract	25	9	1.30	0.68	2.50	17	1.07	0.66	1.72
Salivary gland	4	1	1.68	0.24	11.94	4	**4.50**	1.68	12.03
Oesophagus	7	4	0.65	0.24	1.73	6	0.81	0.36	1.81
Stomach	37	29	1.04	0.73	1.50	36	1.09	0.79	1.51
Small intestine	10	2	0.68	0.17	2.72	6	0.87	0.39	1.94
Colon	90	35	0.91	0.65	1.27	60	1.03	0.80	1.33
Rectum	37	10	0.69	0.37	1.28	27	1.04	0.72	1.52
Anus	5	3	**3.09**	1.03	10.04	3	1.15	0.37	3.58
Liver	34	24	1.09	0.73	1.63	34	1.26	0.90	1.76
Pancreas	26	23	1.08	0.72	1.62	24	1.04	0.70	1.55
Nose	5	1	1.18	0.17	8.40	5	2.03	0.84	4.89
Lung	96	80	**1.36**	1.11	1.66	92	**1.35**	1.12	1.63
Small cell	*9*	*7*	*1.44*	*0.74*	*2.92*	*9*	*1.63*	*0.90*	*3.05*
Non-small cell	*41*	*32*	*1.17*	*0.86*	*1.61*	*37*	*1.16*	*0.87*	*1.56*
Breast	137	30	0.89	0.62	1.27	64	1.07	0.84	1.36
Cervix	14	1	0.20	0.03	1.43	8	0.91	0.46	1.82
Endometrium	35	4	1.13	0.42	3.01	14	1.04	0.62	1.75
Uterus	0	0	0.00	0.00	0.00	0	0.00	0.00	0.00
Ovary	33	16	0.88	0.54	1.44	22	0.96	0.63	1.45
Other female genital	7	3	1.48	0.48	4.60	3	0.92	0.30	2.87
Prostate	135	36	0.86	0.62	1.20	65	0.98	0.77	1.25
Testis	4	0	0.00	0.00	0.00	1	1.59	0.22	11.32
Other male genital	3	1	1.98	0.28	14.52	2	2.48	0.62	9.95
Kidney	44	23	1.16	0.77	1.74	35	1.18	0.85	1.64
Urinary bladder	24	2	0.31	0.08	1.22	8	0.55	0.28	1.11
Melanoma	37	5	0.70	0.29	1.69	13	0.81	0.47	1.41
Skin, squamous cell	66	1	0.93	0.13	6.60	40	**1.62**	1.20	2.21
Eye	3	0	0.00	0.00	0.00	1	0.53	0.08	3.78
Nervous system	36	17	1.41	0.87	2.26	25	1.15	0.77	1.70
Thyroid gland	12	2	1.45	0.36	5.82	7	**2.78**	1.33	5.84
Endocrine glands	36	1	1.25	0.18	8.91	15	1.24	0.75	2.05
Bone	2	1	1.49	0.21	10.57	1	0.88	0.12	6.21
Connective tissue	5	2	2.13	0.53	8.54	5	2.22	0.92	5.33
Non-Hodgkin's lymphoma	78	42	**1.60**	1.18	2.17	58	**1.39**	1.07	1.78

Hodgkin's disease	25	12	**1.92**	1.10	3.39	17	1.30	0.81	2.10
Myeloma	17	13	1.26	0.73	2.17	13	1.00	0.58	1.73
Leukemia	38	20	1.56	1.00	2.45	28	**1.51**	1.04	2.19
Acute leukemia	*13*	*11*	*1.42*	*0.83*	*2.40*	*13*	*1.47*	*0.94*	*2.54*
Chronic leukemia	*13*	*6*	*1.32*	*0.65*	*2.81*	*9*	*1.17*	*0.61*	*2.26*
All	1,167	453	**1.16**	1.08	1.27	759	**1.21**	1.13	1.30

HR, hazard ratio; CI, confidence interval.
Bold type, 95% CI does not include 1.00.
Variables adjusted for in the model include gender, age at diagnosis of cancer, calendar year at diagnosis of cancer, and chronic obstructive pulmonary disease (COPD).
Table 3 Overall HRs in cancer patients by diagnosis age of cancer

Cancer	Overall mortality								
	≤ 65					> 65			
	Cases	Deaths	HRs	95%CI		Cases	Deaths	HRs	95%CI	
Upper aerodigestive tract	13	7	0.96	0.46	2.01	12	10	1.12	0.60	2.09
Salivary gland	3	3	**4.92**	1.57	15.37	1	1	2.79	0.39	19.94
Oesophagus	5	4	0.92	0.34	2.45	2	2	0.65	0.16	2.59
Stomach	16	16	1.56	0.95	2.54	21	20	0.87	0.56	1.35
Small intestine	3	3	1.95	0.63	6.07	7	3	0.62	0.20	1.93
Colon	33	18	0.98	0.62	1.56	57	42	1.07	0.79	1.45
Rectum	16	12	1.36	0.77	2.40	21	15	0.89	0.54	1.48
Anus	3	1	0.65	0.09	4.62	2	2	1.84	0.46	7.40
Liver	11	11	1.51	0.84	2.74	23	23	1.19	0.79	1.79
Pancreas	9	8	1.18	0.59	2.36	17	16	1.02	0.63	1.67
Nose	3	3	**3.62**	1.16	11.27	2	2	1.06	0.26	4.26
Lung	55	52	**1.70**	1.32	2.20	41	40	0.96	0.70	1.31
Breast	77	28	1.03	0.71	1.49	60	36	1.17	0.84	1.62
Cervix	8	2	0.46	0.11	1.82	6	6	1.61	0.72	3.58
Endometrium	12	2	0.67	0.17	2.69	23	12	1.12	0.63	1.97
Uterus	0	0	0.00	0.00	0.00	0	0	0.00	0.00	0.00
Ovary	14	8	0.91	0.46	1.82	19	14	1.05	0.62	1.78
Other female genital	6	2	0.71	0.18	2.83	1	1	2.11	0.30	14.96
Prostate	50	16	1.08	0.66	1.77	85	49	0.97	0.73	1.28
Testis	4	1	1.91	0.27	13.56	0	0	0.00	0.00	0.00
Other male genital	3	2	1.94	0.48	7.79	0	0	0.00	0.00	0.00
Kidney	23	18	**1.65**	1.04	2.62	21	17	0.90	0.56	1.45
Urinary bladder	14	3	0.72	0.23	2.25	10	5	0.47	0.20	1.13
Melanoma	21	5	0.63	0.26	1.56	16	8	1.17	0.59	2.35
Skin, squamous cell	12	5	1.58	0.66	3.08	54	35	**1.67**	1.20	2.32
Eye	2	1	1.20	0.17	8.55	1	0	0.00	0.00	0.00
Nervous system	26	17	1.17	0.73	1.88	10	8	1.11	0.56	2.23
Thyroid gland	11	7	**3.74**	1.78	7.85	1	0	0.00	0.00	0.00
Endocrine glands	21	5	1.02	0.42	2.45	15	10	1.47	0.79	2.74
Bone	2	1	1.04	0.15	7.40	0	0	0.00	0.00	0.00
Connective tissue	2	2	**4.93**	1.23	19.77	3	3	1.62	0.52	5.04
Non-Hodgkin's lymphoma	46	32	**1.86**	1.34	2.49	32	26	1.09	0.74	1.60

Hodgkin's disease	21	13	1.03	0.59	1.77	4	4	**6.77**	2.50	18.23
Myeloma	7	5	0.72	0.30	1.72	10	8	1.63	0.81	3.25
Leukemia	19	14	**1.74**	1.03	2.93	19	14	1.31	0.78	2.22
All	571	327	**1.31**	1.18	1.45	596	432	1.08	0.99	1.19

HR, hazard ratio; CI, confidence interval.
Bold type, 95% CI does not include 1.00.
Variables adjusted for in the model include gender, calendar year at diagnosis of cancer, and chronic obstructive pulmonary disease (COPD).

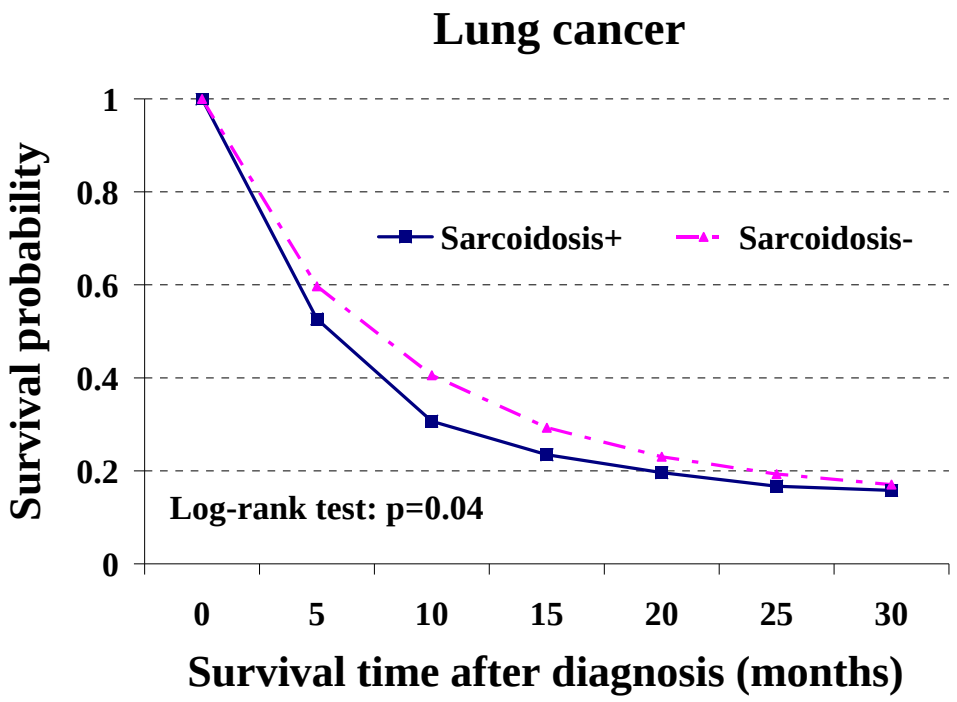
Table 4 Overall HRs in cancer patients by gender

Cancer	Overall mortality									
	Female					Male				
	Cases	Deaths	HRs	95%CI		Cases	Deaths	HRs	95%CI	
Upper aerodigestive tract	6	6	1.52	0.68	3.40	19	11	0.89	0.49	1.61
Salivary gland	2	2	**39.79**	9.78	161.87	2	2	2.37	0.59	9.48
Oesophagus	2	2	0.63	0.16	2.53	5	4	0.89	0.33	2.37
Stomach	16	16	1.07	0.65	1.74	21	20	1.12	0.73	1.74
Small intestine	3	2	1.43	0.36	5.73	7	4	0.74	0.28	1.97
Colon	54	39	1.16	0.85	1.59	36	21	0.84	0.54	1.28
Rectum	16	14	1.20	0.71	2.03	21	13	0.92	0.54	1.59
Anus	3	1	0.44	0.06	3.11	2	2	**4.87**	1.20	19.68
Liver	23	23	1.05	0.70	1.59	11	11	**1.97**	1.09	3.56
Pancreas	14	13	1.20	0.70	2.07	12	11	0.91	0.50	1.64
Nose	1	1	3.67	0.51	26.31	4	4	1.64	0.61	4.37
Lung	41	39	**1.50**	1.14	1.99	55	53	1.13	0.86	1.48
Breast	137	64	1.07	0.84	1.36	0	0	0.00	0.00	0.00
Cervix	14	8	0.91	0.46	1.82	0	0	0.00	0.00	0.00
Endometrium	35	14	1.04	0.62	1.75	0	0	0.00	0.00	0.00
Uterus	0	0	0.00	0.00	0.00	0	0	0.00	0.00	0.00
Ovary	33	22	0.96	0.63	1.45	0	0	0.00	0.00	0.00
Other female genital	7	3	0.89	0.29	2.25	0	0	0.00	0.00	0.00
Prostate	0	0	0.00	0.00	0.00	135	65	0.98	0.77	1.25
Testis	0	0	0.00	0.00	0.00	4	1	1.59	0.22	11.32
Other male genital	0	0	0.00	0.00	0.00	3	2	2.36	0.59	9.48
Kidney	20	16	1.16	0.71	1.89	24	19	1.19	0.76	1.87
Urinary bladder	10	4	0.74	0.28	1.97	14	4	0.43	0.16	1.16
Melanoma	21	8	1.18	0.59	2.35	16	5	0.55	0.23	1.31
Skin, squamous cell	29	17	1.24	0.77	1.99	37	23	**2.00**	1.33	3.01
Eye	2	0	0.00	0.00	0.00	1	1	**9.01**	1.26	64.23
Nervous system	21	13	0.86	0.50	1.49	15	12	**1.84**	1.05	3.24
Thyroid gland	10	6	**3.40**	1.53	7.59	2	1	1.26	0.18	8.93
Endocrine glands	26	12	1.26	0.71	2.22	10	3	1.08	0.35	3.36
Bone	1	0	0.00	0.00	0.00	1	1	1.73	0.24	12.20
Connective tissue	5	5	2.10	0.87	5.06	0	0	0.00	0.00	0.00
Non-Hodgkin's lymphoma	31	25	1.33	0.90	1.98	47	33	**1.45**	1.06	2.01

Hodgkin's disease	10	6	1.03	0.46	2.30	15	11	1.42	0.78	2.57
Myeloma	9	5	1.16	0.52	2.58	8	8	1.67	0.84	3.35
Leukemia	22	16	1.41	0.86	2.30	16	12	1.66	0.94	2.92
All	624	402	**1.22**	1.15	1.34	543	357	**1.19**	1.08	1.31

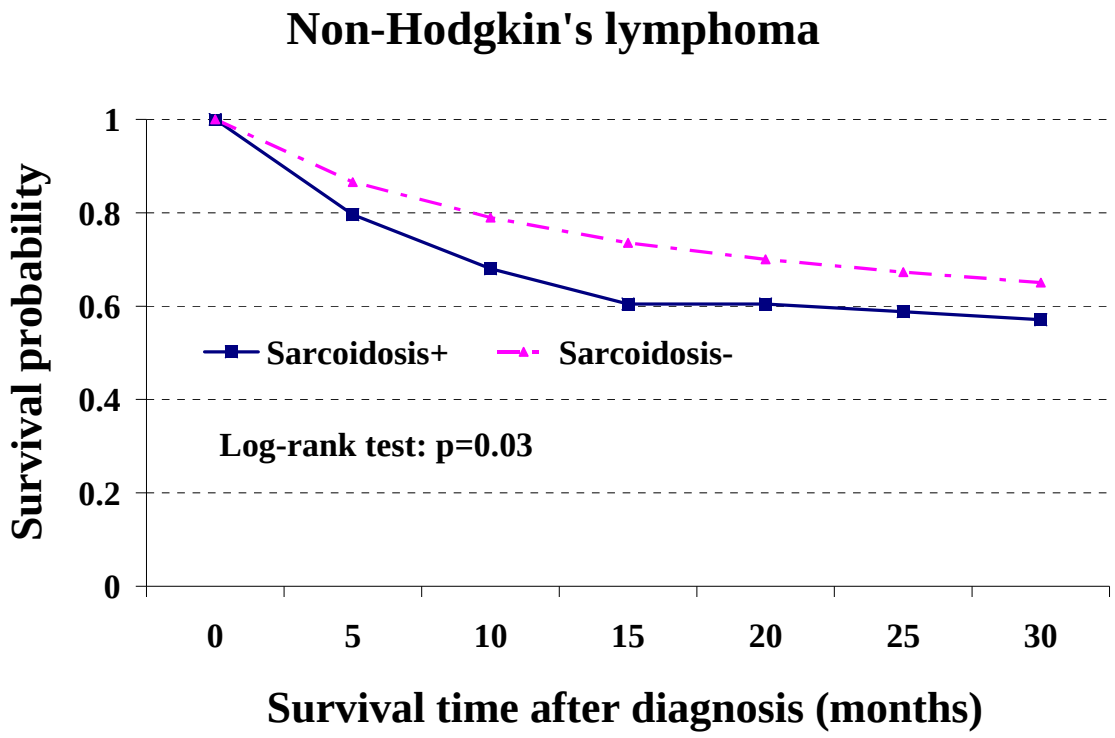
HR, hazard ratio; CI, confidence interval.
Bold type, 95% CI does not include 1.00.
Variables adjusted for in the model include age at diagnosis of cancer, calendar year at diagnosis of cancer, and chronic obstructive pulmonary disease (COPD).

Figure 1 Cause-specific mortality among lung cancer patients diagnosed after sarcoidosis compared with the control



Sarcoidosis+: cancer patients diagnosed after sarcoidosis; sarcoidosis-: cancer patients without hospitalization for sarcoidosis.

Figure 2 Cause-specific mortality among non-Hodgkin's lymphoma patients diagnosed after sarcoidosis compared with the control



Sarcoidosis+: cancer patients diagnosed after sarcoidosis; sarcoidosis-: cancer patients without hospitalization for sarcoidosis.