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RISK OF SECOND CANCERS AMONG LUNG CANCER PATIENTS

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The risk of a second cancer among lung cancer patients was investigated using Finnish Cancer Registry data from 1953 to 1989. Among the 36 528 patients with a primary cancer of the lung, 504 new cancers were diagnosed six months or more after the diagnosis of lung cancer, yielding a standardized incidence ratio significantly lower than expected (SIR = 0.81). A significant excess of cancers of the larynx (SIR = 2.10) and urinary bladder (SIR = 1.35) was observed. Among lung cancer patients below 60 years of age, the risks of oesophageal cancer (SIR = 2.47) and kidney cancer (SIR = 2.48) were also significantly elevated. The risk of a second cancer among lung cancer patients increased with the length of follow-up, and there was some indication of an excess risk of oesophageal cancer and leukaemia among lung cancer patients subject to radiotherapy.

Lung cancer is the most common cancer among Finnish men, accounting for 20% of all cancers among males and 4% among females in 1990. Less than 15% of lung cancer patients survive for five years (1). Smoking is the most common etiological factor of lung cancer (2). Lung cancer survivors are at risk of getting second cancers, especially those related to smoking: A previous study from the Finnish Cancer Registry reported a significant excess of larynx cancer among lung cancer patients diagnosed in 1953–1979 (3). In the present study the occurrence of new cancers among lung cancer patients was analyzed for a period ten years longer. The aim was to assess specifically radiation and age related associations between the primary and second cancers among lung cancer patients.

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Material and Methods

The records of the Finnish Cancer Registry (FCR, founded 1952) cover all cancer cases that come to the attention of any hospital, laboratory or medical practitioner in Finland, also including cancers diagnosed at autopsy (4). The study group consisted of all lung cancer patients diagnosed in 1953–1989 and followed up for over 5.5 months by the end of 1989. To minimize the effect of diagnostic delay on the order of two separate cancers in one individual, those lung cancer patients who survived 5.5 months or less were excluded. The limit of the 5.5 months was due to the fact that only the month and year of diagnosis is available in the FCR.

Subsequent new cancers occurring among these patients were identified through the files of the FCR. At the FCR a new cancer is defined as an independent new primary cancer arising after the diagnosis of the first cancer. Each cancer has to present a definite pattern of malignant disease and be anatomically distinct. Metastasis from one organ to another has to be excluded as far as possible. Third cancers were handled as independent cancers. The reference independent numbers used for calculation of expected rates include all cancers of each person. Special attention has always been paid in the FCR to the coding of cases with possibly two or more primary neoplasms. A study about the degree of completeness of FCR has been recently published (5).

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Table 1

Observed numbers (Obs), percentages of microscopical verification (Micr), standardized incidence ratios (SIR) and 95% confidence intervals (95% CI) of new cancers 36 528 lung cancer patients in Finland in 1953–1989, by site of the subsequent cancer and by sex

	All				Males			Females		
Second cancer	Obs	Micr (%)	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI
All (excl lung)	504	82	0.81	0.74–0.88	438	0.79	0.72–0.86	66	1.01	0.78–1.29
Lip	9	89	0.57	0.26–1.07	9	0.58	0.26–1.09	–	–	0–13.1
Oesophagus	22	82	1.48	0.93–2.23	20	1.48	0.90–2.28	2	1.43	0.17–5.15
Stomach	67	88	0.70	0.54–0.88	61	0.68	0.52–0.87	6	0.91	0.33–1.98
Colon	23	91	0.66	0.42–0.98	18	0.59	0.35–0.93	5	1.09	0.35–2.53
Rectum	26	96	0.78	0.51–1.14	25	0.82	0.53–1.21	1	0.33	0.01–1.83
Pancreas	29	80	0.85	0.57–1.22	26	0.85	0.55–1.23	3	0.93	0.19–2.72
Larynx	31	96	2.07	1.43–2.98	28	1.92	1.27–2.76	3	24.7	5.08–72.1
Breast	19	100	1.28	0.77–1.99	1	1.35	0.03–7.61	18	1.27	0.76–2.01
Cervix uteri	3	100	1.55	0.32–4.52	–	–	–	3	1.55	0.32–4.52
Corpus uteri	3	100	0.73	0.15–2.13	–	–	–	3	0.73	0.15–2.13
Ovary	6	67	1.73	0.63–3.75	–	–	–	6	1.73	0.63–3.75
Prostate	85	91	0.71	0.57–0.88	85	0.71	0.57–0.88	–	–	–
Urinary bladder	56	100	1.37	1.02–1.75	54	1.34	1.01–1.75	2	1.58	0.19–5.69
Kidney	30	80	1.25	0.84–1.78	28	1.27	0.85–1.84	2	1.01	0.12–3.63
Thyroid	3	100	0.73	0.15–2.13	2	0.65	0.08–2.36	1	0.96	0.02–5.32
Soft tissues	4	100	1.01	0.27–2.57	3	0.84	0.17–2.44	1	2.53	0.06–14.1
Non-Hodgkin's lymphoma	4	100	0.31	0.08–0.78	4	0.34	0.09–0.87	–	–	0–2.82
Leukaemia	13	100	0.69	0.37–1.18	11	0.64	0.32–1.14	2	1.27	0.15–4.57
Lung	74	64	0.32	0.25–0.40	68	0.30	0.23–0.37	6	2.07	0.76–4.49

The follow-up started 5.5 months after the diagnosis of lung cancer, and ended at the date of death, emigration or on December 31, 1989, whichever came first. Follow-up for emigration was done together with the follow-up for death through the Central Population Registry in Finland. Person-years at risk and new primary cancers during the follow-up time were tabulated according to sex, primary site, age, and follow-up time. The expected numbers were calculated by multiplying the stratum-specific numbers of person-years by the corresponding national incidence rates of the cancer in question.

The analysis was run separately for patients under 60 years and 60 years or more at the time of the diagnosis of lung cancer, and separately for patients who received radiotherapy for lung cancer and who did not. Data on treatment were also obtained from the FCR.

The risk of contracting a new primary cancer was expressed as a standardized incidence ratio (SIR) defined as the ratio of the observed and expected numbers of cases. The statistical significance of the SIR was estimated under the assumption that the observed number of cases followed a Poisson distribution.

Results

The study series consisted of 36 528 lung cancer patients; 87% of them were males. They yielded 66 833 person-years with an average follow-up time of 1.8 years. The mean age of the patients at the diagnosis of lung cancer was 63.4 years. The frequency of microscopical verification (histology or cytology) of the primary lung cancer was 71.8%. The frequencies of microscopical verification for second cancers are shown in Table 1.

A total of 504 new cancers (excluding new lung cancers) were observed in the cohort. The observed number of cases among men was significantly below that expected (SIR = 0.79) whereas among women the SIR was 1.01 (Table 1).

Taking males and females together there were 31 observed cases of larynx cancer as against 15 expected and 56 urinary bladder cancers as against 41 expected (Table 1); both excesses were statistically significant. Reduced risks were observed in males for cancers of the stomach, colon and prostate, and for nodal non-Hodgkin's lymphoma. The number of new lung cancers was less than one-third of the expected level.

The SIR for a new cancer was clearly below unity (0.71) for patients aged 60 years or over at the diagnosis of lung cancer (Table 2). Especially the SIR for cancers of the oesophagus, rectum, larynx, urinary bladder and kidney was higher among younger lung cancer patients than among the older ones, although there was overlapping in the 95% confidence intervals of the SIR values in the two age group (the except for kidney cancer).

Table 2

Observed numbers (Obs), standardized incidence ratios (SIR) and 95% confidence intervals (95% CI) of new cancers among lung cancer patients, in Finland in 1953–1989, by site of the subsequent cancer and age of patients at the date of diagnosis of lung cancer, males and females combined

	Age					
	<60 years			≥60 years		
Second cancer	Obs	SIR	95% CI	Obs	SIR	95% CI
All (excl. lung)	180	1.07	0.92–1.23	324	0.71	0.63–0.79
Lip	5	1.02	0.33–2.37	4	0.37	0.10–0.93
Oesophagus	9	2.47	1.13–4.69	13	1.15	0.61–1.97
Stomach	20	0.81	0.49–1.24	47	0.66	0.49–0.88
Colon	5	0.56	0.18–1.30	18	0.69	0.41–1.09
Rectum	12	1.41	0.73–2.46	14	0.56	0.31–0.94
Pancreas	10	1.06	0.51–1.95	19	0.77	0.46–1.20
Larynx	15	2.62	1.47–4.32	16	1.77	1.01–2.87
Breast	9	1.46	0.67–2.77	10	1.15	0.55–2.10
Cervix uteri	2	2.25	0.27–8.12	1	0.95	0.02–5.31
Corpus uteri	2	1.14	0.14–4.12	1	0.42	0.01–2.35
Ovary	3	2.04	0.42–5.97	3	1.50	0.31–4.39
Prostate	15	0.70	0.39–1.15	70	0.72	0.56–0.90
Urinary bladder	19	1.82	1.09–2.83	37	1.19	0.84–1.63
Kidney	20	2.48	1.51–3.82	10	0.63	0.30–1.15
Thyroid	2	1.37	0.17–4.94	1	0.38	0.01–2.10
Soft tissues	1	0.78	0.02–4.32	3	1.10	0.23–3.22
Non-Hodgkin's lymphoma	1	0.25	0.01–1.37	3	0.33	0.07–0.97
Leukaemia	4	0.77	0.21–1.96	9	0.65	0.30–1.23
Lung	44	0.60	0.44–0.81	30	0.19	0.13–0.27

The SIR for cancers of the kidney and urinary bladder increased by increasing follow-up time, and the SIR for a second lung cancer reached unity ten years after the diagnosis of the first one (Table 3).

The effect of therapeutic radiation on the risk of a second malignant tumour was separately analyzed for locoregional tumours (in the larynx, oesophagus and breast) and leukaemia. The excess risk of oesophageal cancer and leukaemia was attributable only to patients subject to radiotherapy during the initial phase of treatment (4 months) of lung cancer. The SIR for cancers of the larynx and breast in the nonirradiated group were higher than in the irradiated one (Table 4). The SIR for all cancers in the radiotherapy group increased during the first ten years of follow-up.

Discussion

In spite of the development in the diagnostics and early treatment of lung cancer resulting in improved patient survival, the survival times of most lung cancer patients are still relatively short and survival rates thus low. Among lung cancer survivors, the occurrence of second cancers is an important practical issue with regard to differential diagnosis between recurrence and second cancer.

Significantly increased risks of cancers of the larynx and urinary bladder were observed among our lung cancer patients. This finding agrees with earlier studies showing an excess risk of respiratory and urinary tract malignancies among lung cancer survivors (6–9).

Table 3

Observed numbers of cases (Obs), standardized incidence ratios (SIR) and 95% confidence intervals (95% CI) of selected cancers among lung cancer patients, by follow-up time starting 5.5 months after the diagnosis of lung cancer

	Follow-up (years)								
	0–4			5–9			10+		
Second cancer	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI
All sites (excl. lung)	278	0.65	0.58–0.73	116	1.15	0.95–1.37	110	1.20	0.99–1.43
Oesophagus	12	1.13	0.58–1.96	6	2.60	0.95–5.66	4	2.06	0.56–5.28
Stomach	36	0.52	0.36–0.72	18	1.22	0.72–1.93	13	1.10	0.59–1.88
Colon	14	0.59	0.32–0.99	4	0.69	0.19–1.76	5	0.90	0.29–2.10
Rectum	9	0.40	0.18–0.75	9	1.62	0.74–3.07	8	1.58	0.68–3.11
Pancreas	19	0.81	0.49–1.26	8	1.43	0.62–2.81	2	0.41	0.05–1.47
Larynx	20	1.88	1.15–2.9	8	3.32	1.43–6.54	3	1.79	0.37–5.23
Prostate	45	0.57	0.41–0.75	19	0.97	0.59–1.51	21	1.06	0.66–1.63
Urinary bladder	30	1.06	0.72–1.51	10	1.44	0.69–2.65	16	2.50	1.43–4.06
Kidney	17	1.03	0.60–1.65	5	1.23	0.40–2.85	8	2.33	1.01–4.59
Lung	18	0.11	0.07–0.17	18	0.47	0.28–0.74	38	1.29	0.91–1.77

Table 4

Observed (Obs) numbers of cases, and standardized incidence ratios (SIR) with 95% confidence intervals (95% CI) of cancers at radiotherapy area and leukaemia (males and females combined) among lung cancer patients treated with (R+) or without (R−) radiotherapy, by follow-up time starting 5.5 months after the diagnosis of lung cancer

Site of second cancer	Follow-up time (years)											
	0–4			5–9			10+			Total		
	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI
Oesophagus												
R+	7	1.53	0.61–3.14	3	5.29	1.09–15.5	3	7.89	1.63–23.1	13	2.35	1.25–4.01
R−	5	0.82	0.27–1.92	3	1.72	0.35–5.03	1	0.63	0.02–3.55	9	0.96	0.44–1.82
Larynx												
R+	8	1.69	0.73–3.33	1	1.89	0.05–10.6	1	3.33	0.08–18.6	10	1.80	0.87–3.31
R−	12	2.02	1.04–3.53	7	3.71	1.49–7.65	2	1.44	0.17–5.02	21	2.28	1.41–3.48
Breast												
R+	2	0.57	0.08–2.05	1	1.62	0.04–9.02	1	1.85	0.05–10.3	4	0.86	0.23–2.19
R−	5	0.82	0.27–1.91	5	2.58	0.84–6.01	5	2.29	0.75–5.45	15	1.47	0.82–2.42
Leukaemia												
R+	6	1.05	0.38–2.27	1	1.41	0.04–7.87	3	6.00	1.24–17.5	10	1.44	0.69–2.64
R−	2	0.27	0.03–0.96	1	0.42	0.01–2.31	–	–	0–1.64	3	0.25	0.05–0.72

The observed numbers of cancers of the prostate, colorectum and stomach, being the most common cancers in Finnish men after lung cancer, were lower than expected. Lung cancer has typically been a cancer of the lower social classes among men in Finland (10) which can explain the decreased risk of cancers of affluence (colon, rectum and prostate). Another explanation can be that in registry-based cohort studies of cancer risk after an index hospitalization, there is an incidence peak in connection with the first hospital episode, owing to the detection of subclinical cancers during work-up cancers that would otherwise have become clinically manifest within a year or two. This leads to a compensatory drop in incidence in the first years and is likely to explain some of the deficits in cancer risks during first years of follow-up.

We had no smoking data for our patients, but the majority of lung cancer patients are known to be smokers (2). In our series, the risks of cancers of the larynx and urinary bladder were significantly increased among male and female lung cancer patients, clearly suggesting a common aetiology, i.e., smoking. The significantly elevated risks of cancers of the oesophagus and kidney among younger lung cancer patients may also be attributable to smoking. The relationship of smoking to second cancer development is explained by the concept of field carcinogenesis; simultaneous exposure of the lung, oesophagus and urinary tract to smoke carcinogens (9).

The risk of urinary bladder cancer was significantly increased among male lung cancer patients but not among female patients. This finding agrees with the finding of a smaller increase in urinary bladder cancer incidence in a Danish cohort of female lung cancer patients compared to males (11). This suggests that women may be less prone to contract smoking-related urinary bladder tumours than men. Another explanation for the result is that smoking is a more recent habit among women counting with longer latency for cancer of urinary organs than for lung cancer.

A significant excess risk of larynx, kidney and esophageal cancer was observed in lung cancer patients diagnosed before the age of 60 years. As similar age-related pattern has been reported for second malignant tumours among patients with most types of cancer (3, 12). Possible genetic predisposition of young cancer patients for multiple malignancies has been suggested (3, 13). Loss of specific DNA sequences in tumour cells have been shown for several familial and sporadic solid cancers (14). Site-specific allele losses of chromosome 3p have been shown for renal cancer and for lung cancer (all types). Sequences on chromosome 11p are lost in bladder cancer as well as in certain types of lung cancer (15). Whether these changes are caused by the same carcinogenic factor or inherited, is a question requiring further study.

The excess risk related to radiotherapy was so small that it should not at present influence the selection of treatment for an individual patient. Patients treated with or without radiotherapy differ by initial characteristics, tumour extent and histology, and these differences also influence their survival and probably the risk of second malignancies.

The risk of cancer recurrence is greatest during the first five years after treatment, but the risk of cancers of the larynx, urinary bladder and kidney among lung cancer survivors started to increase after five years of follow-up. It seems important, therefore for regular follow-up to be continued over 5 years after diagnosis of lung cancer in

order to avoid delay in diagnosis of the new malignant tumours. Follow-up should include advice and support of quitting smoking.

REFERENCES

1. Pukkala E, Rimpelä A, Läärä E. Cancer in Finland. 6th ed. Finnish Cancer Registry, Helsinki (in Finnish), 1991.
2. Koo LC, Ho JHC. Worldwide epidemiological patterns of lung cancer. Int J Epidemiol 1990; 19: 14–23.
3. Teppo L, Pukkala E, Saxén E. Multiple cancer—an epidemiologic exercise in Finland. JNCI 1985; 75: 207–17.
4. Saxén E, Teppo L. Finnish Cancer Registry 1952–1977. Twenty-five years of a nationwide cancer registry. Finnish Cancer Registry, Helsinki, 1978.
5. Teppo L, Pukkala E, Lehtonen M. Data quality and quality control of a population-based cancer registry. Acta Oncol 1994; 33: 365–9.
6. Reynolds RD, Pajak T, Greenberg B, et al. Lung cancer as second primary. Cancer 1978; 42: 2887–93.
7. Boice JD, Fraumeni Jr JF. Second cancer following cancer of the respiratory system in Connecticut 1953–1982. Natl Cancer Inst Monogr 1985; 68: 83–98.
8. Souhami RL, Law K. Longevity in small cell lung cancer. Br J Cancer 1990; 61: 584–9.
9. Heyne KH, Lippman SM, Lee JJ, Lie JS, Hong W. The incidence of second primary tumors in long-term survivors of small cell lung cancer. J. Clin Oncol 1992; 10: 1519–24.
10. Pukkala E, Teppo L, Hakulinen T, Rimplä M. Occupation and smoking as risk determinants of lung cancer. Int J Epidemiol 1983; 12: 290–6.
11. Skov T, Sprøgel P, Engholm G, Frølund C. Cancer of the lung and urinary bladder in Denmark, 1943–87: a cohort analysis. Cancer Causes Control 1991; 2: 365–9.
12. Day GL, Blot WJ. Second primary tumors in patients with oral cancer. Cancer 1992; 70: 14–9.
13. Fosså SD, Langmark F, Aass N, et al. Second non-germ cell malignancies after radiotherapy of testicular cancer with or without chemotherapy. Br J Cancer 1990; 61: 636–43.
14. Ponder B. Gene losses in human tumours. Nature 1988; 325: 400–2.
15. Willey JC, Weston A, Haugen Å, et al. DNA RFLP-analysis in human bronchogenic carcinoma. In: Barts H, Hemminki K, O'Neill IK, eds. Methods for detection of DNA damaging agents in humans. Lyon: IARC Scientific Publications No. 89, 1988: 439–52.