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Subsequent Primary Cancers Following Bladder Cancer

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The incidence of a subsequent primary cancer was investigated among 10 014 patients with cancer of the urinary bladder diagnosed in 1953–1989 in Finland. During the follow-up period of 1953–1989, 652 new metachronous cancers were diagnosed. The number equals the expected number based on the national incidence figures. There were 195 second cancers of the lung. The standardised incidence ratio (SIR) for lung cancer was 1.3 among males [95% confidence interval (CI) 1.1–1.4] and 2.6 among females (95% CI 1.4–4.5). An increased SIR for larynx cancer in males (SIR=1.7, 95% CI 0.91–2.8) and for kidney cancer in females (SIR=3.6, 95% CI 1.8–6.2) was observed. The risk of a second cancer was greater among patients less than 60 years of age at the time of first diagnosis than among older patients. No consistent differences were observed in the risk of new cancer between bladder cancer patients treated with or without radiotherapy.

Key words: urinary bladder cancer, second primary cancer, standardised incidence ratio, radiotherapy
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INTRODUCTION

WITH THE increase in the incidence of cancer and improvement in both early diagnosis and treatment, the number of surviving cancer patients is increasing [1]. Therefore, knowledge of the risk of new primary cancers is important. Second primary cancer is defined as an independent new primary malignant tumour arising after the diagnosis of the first neoplasm [2]. Each tumour must be distinct and must present a definite pattern of malignant disease. Metastases from other organs must also be excluded. In multiple cancer studies both aetiological aspects and treatment-related factors can be investigated. The purpose of the present study was to estimate the risk of a subsequent new cancer among urinary bladder cancer patients, especially after radiation therapy.

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MATERIALS AND METHODS

The files of the Finnish Cancer Registry (founded in 1952) cover all cancer cases diagnosed in the country. They include cancers diagnosed and/or treated in hospitals or by medical practitioners, those verified in pathological and cytological laboratories and those mentioned in death certificates. The percentage of microscopic verification (i.e. histology or cytology) increased from about 50% in the mid-1950s to over 90% in the early 1970s [3]. The records for the period from 1953 to 1989 were analysed to assess the risk of patients with cancer of the urinary bladder of developing a new malignant tumour. Papillomas of the bladder were excluded from the patient material. One should notice, however, that in the 1950s and 1960s the diagnosis of papilloma was more widely used than today when these tumours are often designated as carcinomas grade I. Thus, the more recent part of the urinary bladder carcinoma material includes tumours that in the past would have been called papillomas.

The follow-up started 5.5 months after the diagnosis of bladder cancer, and ended at the date of death, emigration or on December 31 1989, whichever came first. Subsequent cancers diagnosed during the follow-up time were tabulated according to sex, primary site, age at the time of diagnosis of the new cancer and time since the date of diagnosis of the first primary.

Table 1. Characteristics of patients reported to the Finnish Cancer Registry with cancer of the urinary bladder in 1953–1989 and with at least 5.5 months of follow-up after the diagnosis

	Males	Females	Total
Number of patients	7643	2371	10014
Histological verification	95.6%	95.3%	95.5%
Per cent given radiotherapy	26.5%	26.3%	26.4%
Average age at diagnosis (years)	66.2	68.3	66.7
Person-years of follow-up	33702	11955	45657
Average follow-up (years)	4.4	5.0	4.6

The expected numbers for each stratum were calculated by multiplying the stratum-specific numbers of person-years by the corresponding national incidence rates. The analyses were run separately for patients aged less than 60 years and 60 years or more at the time of diagnosis of bladder cancer, and separately for patients who received radiotherapy for bladder cancer and for those who did not.

The risk of contracting a new primary cancer was expressed as a standardised incidence ratio (SIR), defined as the ratio of the observed and expected numbers of cases. The 95% confidence interval (CI) for the SIR was estimated under the assumption that the observed numbers followed a Poisson distribution.

RESULTS

During the study period 10 014 patients with bladder cancer and with a follow-up time of more than 5.5 months were identified. Patients' characteristics are given in Table 1.

The observed number of subsequent cancers at any site (except bladder) was 517 versus 532 expected in men and 135 observed versus 120 expected in women (Table 2). In addition, there were six new bladder cancers versus 31.3 expected among males and two versus 2.55 expected among females. In both sexes the SIR for a new cancer was significantly increased in age group 45–59 years, and it decreased with increasing age (Table 2). Eighty-four per cent of the subsequent cancers had histological and/or cytological verification (Table 3).

The only significantly increased risk was found for lung cancer (SIR=1.31, 95% CI 1.13–1.50). Among males, 182 lung cancers were observed versus 145 expected (SIR = 1.26, 95% CI 1.08–1.44). Among females the corresponding figures were 13 observed versus 4.95 expected (SIR=2.63, 95% Cl 1.40–4.50).

Table 2. Observed numbers (Obs) of new cancers (bladder cancers excluded), standardised incidence ratios (SIR) and their 95% confidence intervals (95% CI) among 10 014 patients with urinary bladder cancer in Finland 1953–1989, by age at diagnosis of the new cancer and sex

Age (years)	Males			Females		
	Obs	SIR	95% CI	Obs	SIR	95% CI
30–44	1	1.20	0.03–6.71	1	2.38	0.06–13.3
45–59	41	1.44	1.03–1.95	16	2.34	1.34–3.80
60–74	265	1.06	0.93–1.19	54	1.17	0.88–1.53
75+	210	0.83	0.72–0.95	64	0.96	0.74–1.23
Total	517	0.97	0.89–1.05	135	1.13	0.94–1.32

Table 3. Observed numbers (Obs), percentages of microscopical verification (Micr) and standardised incidence ratios (SIR) with their 95% confidence intervals (95% CI) of new cancers among 10 014 patients with urinary bladder cancer in Finland in 1953–1989, males and females combined, by site

Site of new cancer (ICD-7)*	Obs	Micr (%)	SIR	95% CI
Any site (excluding bladder)	652	84	1.00	0.93–1.08
Lip (141)	9	100	0.83	0.38–1.57
Oesophagus (150)	10	70	0.78	0.38–1.44
Stomach (151)	63	86	0.84	0.65–1.07
Colon (153)	34	94	1.02	0.71–1.42
Rectum (154)	28	100	0.96	0.64–1.39
Pancreas (157)	24	63	0.84	0.54–1.24
Larynx (161)	14	100	1.63	0.89–2.74
Lung (162)	195	70	1.31	1.13–1.50
Breast (170)	22	95	0.98	0.61–1.48
Cervix uteri (171)	2	100	0.71	0.09–2.57
Corpus uteri (172)	7	100	1.15	0.46–2.37
Ovary (175)	2	100	0.38	0.05–1.37
Prostate (177)	95	89	0.91	0.74–1.11
Kidney (180)	26	92	1.40	0.91–2.05
Thyroid (194)	4	100	1.08	0.29–2.75
Soft tissue (197)	3	100	0.94	0.19–2.75
Non-Hodgkin's lymphoma (200 202)	6	83	0.55	0.20–1.19
Leukaemia (204)	17	94	1.07	0.63–1.71

**International Statistical Classification of Diseases, Injuries, and Causes of Death.* 7th revision, World Health Organisation, Geneva, 1955.

The SIR for larynx cancer among males was 1.7 (14 observed versus 8.39 expected, 95% CI 0.91–2.79). The SIR for kidney cancer among females was 3.55 (12 observed versus 3.39 expected, 95% CI 1.84–6.20), while among males it was 0.92 (14 observed versus 15.2 expected, 95% CI 0.50–1.54). The risks of ovarian cancer (SIR=0.38, 95% CI 0.05–1.37) and non-Hodgkin's lymphoma (SIR=0.55, 95% CI 0.20–1.19) were lower than expected but did not reach statistical significance (Table 3).

Among the 2428 patients less than 60 years of age at the time of diagnosis of bladder cancer, 157 new cancers were observed versus 124 expected (SIR=1.27, 95% CI 1.08–1.48), whereas the SIR for older parents was below unity (Table 4). Among the younger patients, significantly elevated risks were obtained for cancers of the larynx (SIR=3.12, 95% CI 1.35–6.15), lung (SIR=1.53, 95% CI 1.14–1.99) kidney (SIR=2.24, 95% CI 1.22–4.38) and for leukaemia (SIR=2.48, 95% CI 1.00–5.11).

The risk of lung cancer was similarly increased among male and female patients in both age groups. The risk of kidney cancer among females was increased among both the younger patients (< 60 years: SIR=6.89, 95% CI 2.24–16.1) and the older ones (≥ 60 years: SIR=2.62, 95% CI 1.05–5.39). Among males it was not significantly increased in either group.

The risk of a second cancer did not change systematically by follow-up time. For lung cancer in females the risk was significantly increased during the first 10 years of follow-up (0–4 years: SIR=2.64, 95% CI 1.06–5.43; 5–9 years: SIR=3.95, 95% CI 1.28–9.22), whereas in males the SIR was greatest 10 to 19 years after diagnosis of bladder cancer (SIR=1.68, 95% CI 1.13–2.40). The SIR of larynx cancer among males was highest at 5–9 years (SIR=3.1, 95% CI 1.12–6.65) and that of kidney cancer among females at 5–9 years (SIR=5.80, 95% CI 1.88–13.5).

Table 4. Observed numbers (Obs) and standardised incidence ratios (SIR) with their 95% confidence intervals (95% CI) of new cancers among 10014 patients with urinary bladder cancer in Finland in 1953–1989, males and females combined, by site and by age at diagnosis of bladder cancer. Sites with less than two cases in any age-group excluded

	Age < 60 years			Age ≥ 60 years		
Site of new cancer (ICD-7)	Obs	SIR	95% CI	Obs	SIR	95% CI
Any site (excluding bladder)	157	1.27	1.08–1.48	495	0.93	0.85–1.02
Oesophagus (150)	2	1.06	0.13–3.83	8	0.74	0.32–1.44
Stomach (151)	12	0.99	0.51–1.73	51	0.81	0.60–1.06
Colon (153)	6	1.12	0.41–2.43	28	1.00	0.66–1.44
Rectum (154)	7	1.45	0.58–2.97	21	0.87	0.54–1.32
Pancreas (157)	3	0.58	0.12–1.69	21	0.89	0.55–1.36
Larynx (161)	8	3.12	1.35–6.15	6	1.00	0.37–2.16
Lung (162)	53	1.53	1.14–1.99	142	1.24	1.05–1.45
Breast (170)	4	0.68	0.18–1.72	18	1.09	0.64–1.71
Corpus uteri (172)	3	1.69	0.35–4.94	4	0.93	0.25–2.37
Prostate (177)	16	1.39	0.79–2.25	79	0.85	0.67–1.06
Kidney (180)	11	2.45	1.22–4.38	15	1.06	0.59–1.75
Leukaemia (204)	7	2.48	1.00–5.11	10	0.75	0.36–1.38

Twenty-six per cent of the urinary bladder cancer patients were treated with radiotherapy. Only 16 second cancers were observed among these patients. The risks of cancer of the uterus and leukaemia among patients treated with radiotherapy were non-significantly higher than among those not treated with radiotherapy (Table 5). The combined SIR of all cancers in the radiotherapy field (cervix and corpus uteri, colon, rectum and leukaemia) was close to unity among both irradiated and non-irradiated bladder cancer patients.

DISCUSSION

The observed number of new cancers among patients with cancer of the urinary bladder was close to that expected both in males and in females. Cancers of the lung, larynx and kidney were found in excess. This finding is in accordance with earlier observations [4] and indicates the importance of a common aetiological risk factor, i.e. smoking, in the pathogenesis of both the first cancer and subsequent cancers.

The results of an earlier study from the Finnish Cancer Registry showed a positive association between many cancers with similar aetiologies but no increase in the risk of second cancer for cancer patients in general [5]. The possibility of coding errors due to metastatic findings of organs of frequent sites of metastasis was also investigated. The results suggest that the registration of metastases as new primaries has been successfully avoided.

The clustering of two or more primaries in the same individuals may be due to common aetiology or due to a genetic predisposition to develop cancer [6]. In this series, in line with earlier studies [7, 8], younger patients had a higher standardised incidence ratio for a new cancer than the older ones. One explanation for this could be that those who get bladder cancer earlier in their life have a predisposition to get cancer in general.

It has been estimated that over 60% of bladder cancer cases could have been avoided if people did not smoke [9]. Cartwright and coworkers [10] have estimated that genetically determined metabolism of smoking-related carcinogens may affect the individual cancer risks. The effects of carcinogens differ between individuals, the enzymes of carcinogen metabolism being genetically regulated. Whether multiple malignancies are related to genetic sensitivity or to continuing exposure to strong carcinogenic factors cannot be answered in this study. Chemical carcinogens may initiate the proliferation of many clones of cells of the urothelium, and subsequent promotion of growth by carcinogens or inflammatory factors may lead to the formation of multifocal tumours in the bladder [11]. The pathway of genetic changes in the presence of a strong common aetiological factor warrants further studies.

The results of a Danish cohort study suggested that smoking women are less susceptible to bladder cancer development than smoking men [12]. If this means that in order to contract bladder cancer women must smoke, on average, more than men, it is well in accordance with our observation that the SIR for lung cancer among females (2.6) was double that among males. This may also be one explanation for the female–male SIR difference (3.6 versus 0.9) in kidney cancer.

Arai and coworkers [13] observed a significant excess of rectum cancer, urinary bladder cancer and leukaemia among cervix cancer patients who were treated with radiotherapy compared to patients treated with surgery only. In agreement with this and with the results of Boice [8], a slightly increased risk of leukaemia and cancer of the uterus following radiotherapy was observed in our series. However, the magnitude of the excess risk was not of clinical importance and should not influence the choice of treatment. The SIR for colorectal cancer was even reduced among our irradiated patients.

The results suggest that a common aetiological factor, i.e. smoking, is the main cause of clustering of several cancers in patients with bladder cancer. A general sensitivity to develop cancer may also play a role in the causation of the observed multiple cancer pattern. Smoking is the strongest common aetiological factor for cancers of the urinary bladder, lung, larynx and kidney. The majority of urinary bladder cancer patients are diagnosed at early stage and are effectively treated with surgery. Life prolonging treatment is available for all stages of urinary bladder cancer. Therefore, it is important to inform urinary bladder cancer patients of the risk of smoking-related new cancers.

Table 5. Observed numbers (Obs) of cases, and standardised incidence ratios (SIR) with their 95% confidence intervals (95% CI) of cancers in the radiotherapy field and leukaemia among bladder cancer patients treated with (R+) or without (R−) radiotherapy, males and females combined, by follow-up time starting 5.5 months after the diagnosis of bladder cancer

Site of the new cancer / Treatment	Follow-up time (years) 0–4 Obs	SIR	95% CI	5–9 Obs	SIR	95% CI	10+ Obs	SIR	95% CI	Total Obs	SIR	95% CI
Colon and rectum												
R+	5	0.73	0.24–1.71	1	0.46	0.01–2.56	2	1.03	0.13–3.72	8	0.73	0.31–1.43
R−	32	1.07	0.73–1.50	17	1.31	0.77–2.10	5	0.60	0.19–1.39	54	1.05	0.79–1.37
Cervix uteri												
R+	—	(exp 0.36)	0–10.2	1	8.35	0.21–46.5	—	(exp 0.12)	0–30.7	1	1.64	0.04–9.16
R−	1	0.79	0.02– 4.40	—	(exp 0.57)	0–6.47	—	(exp 0.37)	0–9.97	1	0.45	0.01–2.52
Corpus uteri												
R+	—	—	0–5.89	1	4.75	0.12–26.5	1	3.70	0.09–20.6	2	1.80	0.22–6.49
R−	2	0.73	0.09–2.64	2	1.50	0.18–5.40	1	1.10	0.03–6.12	5	1.00	0.33–2.34
Leukaemia												
R+	4	2.15	0.59–5.50	—	(exp 0.60)	0–6.18	1	1.96	0.05–10.9	5	1.68	0.55–3.92
R−	7	0.89	0.36–1.84	3	0.92	0.19–2.70	2	0.98	0.12–3.54	12	0.92	0.47–1.59
Total												
R+	9	0.93	0.43–1.76	3	0.96	0.20–2.82	4	1.41	0.38–3.61	16	1.02	0.58–1.65
R−	42	1.00	0.72–1.36	22	1.22	0.76–1.84	8	0.68	0.30–1.35	72	1.00	0.79–1.26

exp, expected.

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The Prognostic Value of Insulin-like Growth Factor-I in Breast Cancer Patients. Results of a Follow-up Study on 126 Patients

Mikael J. Railo, Karl v. Smitten and Fredrika Pekonen

The insulin-like growth factor-I is an important mitogen and has a growth promoting property, especially in breast cancer. This work analyses the prognostic value of the insulin-like growth factor receptor-I (IGFR-I), which belongs to the group of membrane receptors for growth factors. The study included 126 patients. 49 patients (39%) were IGFR positive (≥4.0%). There was a significant correlation between IGFR and oestrogen receptor (ER) status ($P = 0.001$), but not between IGFR and progesterone receptor status (PR; $P = 0.07$). There was no correlation between node status and IGFR. The expression of IGFR had a strong significance in the disease-free analysis ($P = 0.0108$). The IGFR status was not of predictive value in the node-negative subgroup (64 patients). Within the ER-negative group, the disease-free analysis further stratified with IGFR revealed that patients with IGFR-positive and ER-negative cancers are in a worse situation than IGFR-negative ER-negative cancer patients ($P = 0.01$).

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INTRODUCTION

THE INCREASING number of options for the treatment of breast cancer will make the prognostic evaluation of the disease even more important. The histological criteria for grading of the cancer into poorly differentiated and well differentiated, established by Bloom and Richardson [1], correlated a shorter relapse-free survival of patients with poorly differentiated tumours, and a better prognosis for patients with well differentiated tumours. Node positivity has also been found to shorten the disease-free survival rate [2, 3]. The measurement of S phase cells by indirect [^{3}H]thymidine incorporation [4, 5], and the measurement of the DNA content by flow cytometry [6], are well established but complex procedures. The mouse monoclonal antibody, KI-67, introduced by Gerdes and colleagues [7], simplified the measurement of proliferating activity in breast cancer tissue. The ability to grow breast cancer cells *in vitro* has lead to the identification of polypeptide hormones that regulate their growth.

The insulin-like growth factor-I (IGF-I) is an important mitogen, and has growth promoting property in many tumour types, especially breast cancer [8]. The primary role of IGF-I is to act on the skeletal development via the endocrine pathway