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Occurrence of both bladder and prostate cancer in five cancer registries in Belgium, The Netherlands and the United Kingdom

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ABSTRACT

Objective: To assess the occurrence of both bladder and prostate tumours in five well defined cancer registries.

Methods: Anonymous data were provided from each cancer registry on all male bladder and prostate cancers (invasive and non-invasive). Poisson regression was used to model the rate of developing the second primary tumour and generated incidence rate ratios (RRs) with 95% confidence intervals.

Results: For bladder cancer and prostate cancer as first diagnosis, there was an excess risk to develop the second neoplasm. The RR decreased with increasing age of the patients. No effect of the initial treatment of the first neoplasm was found.

Conclusion: This analysis found an excess risk to develop prostate cancer in bladder cancer patients younger than 70 years and the first year of follow-up after the diagnosis of bladder cancer. This may be due to detection bias, although a common aetiology may also be present.

1. Introduction

An estimated 357,000 bladder cancer cases occurred worldwide in 2002, making this the ninth most common cause of cancer for both sexes combined.[1] Approximately half of male urinary tract cancer and one-third of female urinary tract cancer might be attributable to cigarette smoking.[2] Occupational exposure is thought to play an important role in around 10% of bladder cancers.[3]

The world incidence of prostate cancer almost doubles that of bladder cancer, making this the fifth most common cancer in the world and the second most common in men.

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Its prognosis is relatively good. Three-quarters of all cases occur in men aged 65 years or older.[1] The burden of disease shows remarkable variation worldwide. Presently age, area of residence, ethnic background, and family history remain the only established risk factors for prostate cancer. The high prevalence of subclinical cancers among elderly men complicates the interpretation of the importance of environmental factors.[4,5]

During a recently performed case-control study in the Belgian province of Limburg on bladder cancer risk, we noticed that many bladder patients were also diagnosed with prostate cancer.[6] We hypothesised that the occurrence of bladder cancer may be associated with the occurrence of prostate cancer and vice versa. Furthermore, we suggest potential explanations of the coincidence.

A review reports a high frequency of double primary cancers of bladder and prostate. The coincidence varied from 2.5% to 70% for the occurrence of prostate cancers in patients with bladder cancer, and from 1.2% to 3.4% for the occurrence of bladder cancers in patients with prostate cancer.[7] A clinical study reported that patients with prostate cancer have a higher incidence of bladder cancer and those with bladder cancer have a higher incidence of prostate cancer.[8] A disease registry of 9780 patients determined that the incidence of bladder cancer in patients with prostate cancer was 1.5%.[9]

Multiple primary cancers are defined by the International Association of Cancer Registries as the occurrence of two of more primary cancers, where each cancer originates in a separate primary site and is neither an extension, recurrence nor metastasis.[10] Apart from detection bias (due to intensive medical surveillance after the first diagnosis), increased risk of developing a second cancer may be due to either a shared aetiology of the two cancers (both environmental and genetic factors) or as a consequence of treatment of the first tumour.[11] As diagnostic and therapeutic possibilities are increasing for both bladder and prostate cancer, any excess risk of a second primary tumour may have a potentially large public health impact. Furthermore, studying second primary tumours stimulates future molecular research into the origin of both tumours.

2. Methods

2.1. Study population and data collection

Our study incorporated five regional cancer registries. The Belgian Limburg Cancer registry (LIKAR) is a population-based cancer registry, which collects data on cancer in all inhabitants of the province Limburg. Data are provided by all pathological, cytological and haematological laboratories.

The Antwerp Cancer Registry (AKR), also from Belgium, is a hospital-based cancer registry which collects by its own registration team from patient records in all hospitals in the province of Antwerp.

The population-based Eindhoven Cancer Registry (IKZ) collects data on all patients with newly diagnosed cancer in the south-eastern part of the Netherlands. Data on vital status were obtained from the hospital records and the death register of the Central Bureau for Genealogy, which registers all deceased in the Netherlands via the municipal civil registries.

The Maastricht Cancer Registry (IKL) is a population-based registry; its region lies in the south east of the Netherlands. With the aid of the clinical and outpatient medical files, the data are gathered for all new malignancies except basal cell carcinoma of the skin. The registry also receives data on non-microscopically confirmed malignancies.

The West Midlands Cancer Intelligence Unit (WMCIU) is a population-based cancer registry, which collects data on cancers diagnosed and/or treated in the West Midlands health region. The WMCIU regularly receives data from 28 acute hospitals, 17 private hospitals, 9 hospices and some community hospitals.

A list of characteristics of the cancer registries that contributed to the analysis is provided in Appendix A.

Anonymous data were provided by each cancer registry on all male bladder and prostate cancers, including age of the subject, diagnosis, date of the first malignancy, diagnosis and date of the second malignancy, and the treatment provided to the first tumour (categorized as surgery, chemotherapy, hormonal therapy, radiotherapy, immunotherapy, surgery + chemotherapy, surgery + immunotherapy, surgery + radiation therapy and surgery + hormonal therapy). Invasive bladder cancer was defined as: a combination of ICDO organ-code 'C679' with ICDO pathology codes: M-80003, M-80013, M-80103, M-80203, M-80413, M-80423, M-80703, M-80713, M-80723, M-80733, M-81203, M-81403, M-81423, M-82603, M-84803, M-89803. Invasive prostate cancer was defined as: a combination of ICDO organ-code 'C619' with ICDO pathology codes : M-80102, M-80103, M-80203, M-80213, M-80413, M-80733, M-81202, M-81203, M-81403, M-84303, M-84803, M-85003.

Treatment used for the first diagnosed cancer was provided from four cancer registries, as the LIKAR cancer registry does not record information on treatment. Furthermore, it was registered whether the first malignancy was invasive. Invasiveness of bladder cancer was not obtained from the West Midlands cancer registry.

No information on grade and stage of the tumours was recorded.

The time interval between the two tumours was taken as that between the date of the first and second incident diagnosis. Overall, the analysis included 23,535 bladder cancers and 54,460 prostate cancers, whereas 1625 men diagnosed with both malignancies.

2.2. Statistical analysis

Poisson regression modelled the rate of developing the second primary tumour and generated incidence rate ratios (RRs) with 95% confidence intervals. Person years were calculated as the covered population in the age group multiplied by the years of follow up. Per cancer registry and per age group, person years were calculated to take into account the different lengths of follow up between different cancer registries.

Furthermore, the models were stratified for age at first diagnosis (categorized in <60, 60–64, 65–69, 70–74, 75–79, 80–84, 85+) and for the time interval between both tumours (categorized in 0, 1–11, 12–23, 24–35, 36–47, 48–59, 60–71, 72–83, 84–95, 96–108, 108–119, $\geqslant$120 months). A χ^2 test was used to examine independence between the two cancers. All analyses were performed using STATA version 8.0 software.[12]

3. Results

Table 1 shows the variation of first cancer by age, time interval between first and second cancer, and cancer registry. Among the 1625 men diagnosed with both malignancies, 436 were diagnosed within the same month; 317 (27.9%) patients who were first diagnosed with bladder cancers and 160 (17.3%) who were diagnosed with prostate cancer had their second primary tumour diagnosed within 12 months after the diagnosis of the first cancer.

In all age groups bladder and prostate cancer occurrence seemed to be related ($p < 0.001$). Both for bladder cancer and prostate cancer as first diagnosis, there was an excess risk to develop the second neoplasm (2.51(95%CI 2.32–2.70) and 1.85(95%CI 1.69–2.02), respectively). In our analysis, the RR varied with the age of the patients. For bladder cancer as first neoplasm an excess risk to develop prostate cancer was found for men younger than 70 year but for prostate cancer as first neoplasm an excess risk was only found in the youngest age group (see Table 2).

We investigated whether any excess risk remained constant over time or whether it increased with follow-up time, which may indicate a treatment effect. When bladder cancer was the first tumour, an excess risk was found the first year after diagnosis. In none of the strata an excess risk was found, when prostate cancer was the first neoplasm (see Table 3).

Table 4 shows the distribution of treatment of the first malignancy among subjects diagnosed with both tumours, received for their initial malignancy. For each treatment, the median time interval between both tumours is calculated. Surgery was used to treat 79.8% of the bladder cancers. Of the prostate cancers, 35.1% were treated with surgery, 29.4% with hormonal therapy and 13.4% with radiotherapy. The median time interval for all initial treatments for bladder cancer was less than 36 months (3 years); for prostate cancer it was less than 66 months (5.5 years).

Table 1 – Variation with first cancer, age, time interval between first and second cancer, and cancer registry

	First bladder cancers *N* (%)	First prostate cancers *N* (%)
Age at first diagnosis[a]		
Below 60	75 (10.7)	20 (4.1)
60–64	106 (15.1)	35 (7.2)
65–69	142 (20.3)	95 (19.4)
70–74	163 (23.3)	119 (24.3)
75–79	125 (17.9)	110 (22.5)
80–84	61 (8.7)	75 (15.3)
85+	28 (4)	35 (7.2)
Time interval between cancers (months)		
0	436 (35.2)	436 (47.1)
1–11	317 (27.9)	160 (17.3)
12–23	93 (8.2)	102 (11.1)
24–35	62 (5.4)	75 (8.1)
⩾36	228 (20.1)	152 (16.4)
Registry (period)[a]		
LIKAR (1996–2001)	14 (2)	12 (2.4)
Antwerp (1990–2003)	85 (12.1)	78 (15.9)
IKL (1986–2003)	131 (18.7)	72 (14.7)
IKZ (1986–2003)	185 (26.4)	165 (33.7)
West-Midlands (1994–2003)	285 (40.7)	162 (33.1)

a 436 Tumours diagnosed within the same month were excluded.

4. Discussion

In our large study on the occurrence of a subsequent bladder or prostate cancer after bladder or prostate cancer, we found an excess risk to develop prostate cancer in bladder cancer patients younger than 70 during the first year of follow-up after the diagnosis of bladder cancer. For prostate cancer as the first neoplasm an excess risk was only found in men younger than 60.

The frequency of double cancers of the prostate and bladder observed in cancer registry studies varies. An overview of cancer statistics based on data from the Surveillance, Epidemiology, and End Results Program (SEER) found that urinary bladder is the initial primary cancer site with the highest percentage of individuals with multiple primary cancers (16%) and that urinary bladder cancer patients had an elevated risk of subsequent cancers of other urinary organs.[13] Some studies have shown an increased association, others have found no such association. This could be caused by reporting bias associated with cancer registry data.[7] Furthermore, heteroge-

Table 2 – Incidence rate ratio of the second neoplasm, stratified on age group and initial diagnosis

	Either bladder or prostate cancer first		Bladder cancer first[a]		Prostate cancer first[a]	
	Observed number	Incidence rate ratio	Observed number	Incidence rate ratio for prostate cancer	Observed number	Incidence rate ratio for bladder cancer
Age group						
–60	95	12.14 (9.79–3.15.04)	75	11.12 (8.50–13.97)	20	3.10 (2.00–4.82)
60–64	150	3.67 (3.12–4.31)	106	2.99 (2.27–3.63)	35	1.03 (0.73–0.1.43)
65–69	252	2.47 (2.18–2.80)	142	1.50 (1.27–1.78)	95	1.05 (0.86–1.29)
70–74	361	2.14 (1.93–2.38)	163	1.06 (0.91–1.23)	119	0.80 (0.67–0.96)
75–79	386	1.97 (1.78–2.18)	125	0.71 (0.59–0.85)	110	0.66 (0.54–0.79)
80–84	261	1.96 (1.74–2.22)	61	0.51 (0.40–0.66)	75	0.66 (0.53–0.84)
85+	130	1.57 (1.32–1.87)	28	0.37 (0.25–0.54)	35	0.48 (0.35–0.68)
Overall		5.32 (5.06–5.59)		2.51 (2.32–2.70)		1.85 (1.69–2.02)

a 436 Tumours diagnoses within the same month were excluded.

Table 3 – Incidence rate ratio of the second neoplasm, stratified on time interval between both tumours

Time interval (months)	Bladder cancer first		Prostate cancer first	
	Observed number	Incidence rate ratio of prostate cancer	Observed number	Incidence rate ratio of bladder cancer
0	436	2.01 (1.83–2.21)		
1–11	317	1.25 (1.12–1.39)	160	0.51 (0.44–0.59)
12–23	93	0.24 (0.19–0.29)	102	0.49 (0.41–0.58)
24–35	62	0.39 (0.31–0.48)	75	0.36 (0.28–0.45)
36–47	65	0.25 (0.19–0.32)	48	0.13 (0.10–0.18)
48–59	48	0.12 (0.08–0.16)	27	0.11 (0.07–0.16)
60–71	43	0.20 (0.15–0.27)	25	0.13 (0.09–0.19)
72–83	25	0.09 (0.06–0.14)	23	0.06 (0.04–0.09)
84–95	10	0.02 (0.01–0.04)	5	0.02 (0.01–0.05)
96–107	8	0.04 (0.02–0.07)	2	0.01 (0.0–0.02)
108–119	8	0.03 (0.01–0.06)	2	0.01 (0.0–0.02)
⩾120	21	0.05 (0.03–0.08)	20	0.08 (0.05–0.12)

Table 4 – Frequency distribution of the initial treatment of the first neoplasm and median of the time interval

	Number (%)	Median time interval between diagnosis of both malignancies (months)
Initial treatment of bladder cancer		
Missing	45 (6.5)	–
Surgery	553 (79.8)	12
Chemotherapy	18 (2.6)	34.5
Hormonal therapy	3 (0.4)	12.5
Radiotherapy	12 (1.7)	13
Immunotherapy	2 (0.3)	8.5
Surgery + chemotherapy	40 (5.8)	26.5
Surgery + immunotherapy	3 (0.4)	6
Surgery + radiotherapy	17 (2.4)	4
Treatment of prostate cancer		
Missing/none	71 (15.6)	–
Surgery	160 (35.1)	23
Hormonal therapy	134 (29.4)	16
Radiotherapy	61 (13.4)	29
Surgery + radiotherapy	14 (3.1)	61.5
Surgery + hormonal therapy	16 (3.5)	17

Data from LIKAR and the double tumours diagnosed within the same month were excluded.

neity among cancer registry studies may be due to varying incidences of neoplasms, important risk factors, diagnostic and treatment schemes. Cancer registry data may overestimate the true incidence of clinically relevant cancers as the introduction of prostate antigen for screening programs has accounted for a dramatic increase in the incidence of prostate cancer.

4.1. *Detection bias*

In the study population, the overpresentation of the second tumours was significant in the first month after the diagnoses of the primary tumour and even in the first year when considering bladder cancer as the first diagnosis, suggesting a possible detection bias. Diagnostic bias occurs when the presence of one cancer results in the incidental diagnosis of another cancer that would not have been detected without the diagnostic process of the first cancer. Diagnostic bias may lead to treatment of non-clinically relevant tumours. However, by increasing the follow-up period, the independent effect of detection bias decreases. In our analysis, the overall risk of developing a second cancer was significant in the youngest age group for prostate cancer as first tumour and in men younger than 70 for bladder cancer as first tumour. This is probably due to the fact that further investigations of older cancer patients are considered less useful and symptoms due to the second cancer tend to be attributed to the previously diagnosed cancer. For younger patients, more efforts are made to identify and treat a new neoplasm and furthermore these treatments are likely to be more intensive.

Incidental prostate cancer is a quite common finding in cystoprostatectomy specimens of bladder cancer patients, without preoperative prostate cancer.[14]

As information regarding screening procedures was not available, and the reasons why investigations were performed were not known, the magnitude of diagnostic bias cannot be exactly determined. Detection bias may be larger in patients with bladder cancer and subsequent prostate cancer than in

the reverse situation because the bladder cancer cases are younger at diagnosis on average and will have a longer follow-up.

A study based on the cancer registry of one medical institution investigated the effect of diagnostic bias on the excess coincidence of bladder and prostate cancer. The author concluded that after adjusting for diagnostic bias by scrutinizing the clinical records, the incidence of bladder cancer in patients with prostate cancer was still 18 times higher and the incidence of prostate cancer in those with bladder cancer 19 times higher.[15]

4.2. *Treatment effects*

The risk of a second malignancy did not increase with follow-up time. Hence, we assume that our results do not indicate a treatment effect.

Nevertheless, much debate remains on whether or not prostate irradiation leads to an increased risk of second primaries. A large retrospective cohort study, comprising 34,889 prostate cancer patients who had undergone radiotherapy and 106,872 who had not, found an elevated risk (relative risk 1.3; 95% CI 1.0–1.7) of bladder cancer for the radiotherapy group after a relatively long time frame (5–8 years).[16] Another large study in the US compared second malignancy risk in 51,584 men with prostate carcinoma who received radiotherapy and 70,539 men who underwent surgery without radiotherapy. The authors concluded that radiotherapy was associated with a small, statistically significant increase in risk of second solid tumours (cancers of the bladder, rectum and lung), particularly for long-term survivors ($\geqslant$10 years).[17] However, the authors of a retrospective cohort of prostate cancer patients treated with staging pelvic lymphadenectomy and definitive radiotherapy suggested that the increase in second primary malignancies (rectal and bladder) may represent staging bias.[18] A study in the US found that the incidence of developing a secondary bladder cancer five or more years after brachytherapy, with or without supplemental external beam radio therapy, was slightly higher than age-matched SEER data indicates.[19] Two studies found that bladder cancer is diagnosed later, is of higher grade, and has a higher rate of muscle-invasive disease at presentation, in patients who are irradiated for prostate cancer than in those treated with other methods.[20,21] In contrast, a survey of 1743 patients receiving external beam radiation therapy for prostate cancer suggested no increase in bladder cancer risk.[22] Also, a cohort of patients with prostate cancer, of whom 12.5% received radiotherapy, found no increased risk of developing a second primary cancer within a period upto 10 years, as compared to the baseline risk of prostate cancer itself.[23] And a study in British Columbia did not confirm the results of earlier studies of a significant overall association between prostate radiation therapy and subsequent malignancy.[24]

4.3. *Common aetiology*

The increased risk was present during the first year of follow-up when bladder neoplasm was the first cancer and during the first month when it was prostate neoplasm; this may suggest that a common aetiology may be present. Age is an important risk factor of both bladder and prostate cancer. About three-quarters of prostate cancer cases worldwide occur in men aged 65 years or more.[1] Tumours of the bladder rarely occur before the age of 50. The incidence of multiple primary malignancies in general increases with the age of the patient. The increment seemed due to the fact that aging is a risk factor for cancer.[25] Furthermore, the younger one is at the diagnosis of the first cancer, the longer they will be followed-up until they reach the age of greatest natural incidence of the secondary malignancy. If a patient survives the first cancer, he might live long enough to develop a second one. As the therapeutic possibilities of both cancers increase, also survival rates rise. European average 5-year survival rates for both bladder and prostate cancer are in the range 60–79%.[26] Literature suggests a molecular association between bladder and prostate cancer.[26] One study found that the expression of p53 and pRb in both bladder and prostate cancers of the same patient was congruent in 8 of 15 cases (53%) for p53 and 9 of 15 cases (60%) for pRb.[27] *N*-acetyltransferases (NAT) is an enzyme family involved in the detoxification of arylamines which are present in cigarette smoke and many other exogenous carcinogens. A study among 17 patients with both prostate and bladder cancer investigated the association between *N*-acetyltransferase genotypes with smoking history and the risk for developing both cancers. No association was found between *NAT1* genotypes, double cancer and smoking history. However, the rapid *NAT2* genotype significantly correlated with the development of double prostate-bladder cancer.[28] Prostate stem cell antigen (PSCA) is expressed by a majority of human prostate cancers. It has been demonstrated that PSCA is also overexpressed in a majority of human transitional cell carcinomas, particularly carcinoma in situ and superficial tumours of the bladder.[29]

A major strength of the current analysis is the large number of patients obtained by combining five cancer registries. As the five included cancer registries only record histologically tumours, misclassification of diagnosis is excluded. More then 90% of the included bladder cancers were diagnosed transitional cell carcinomas and the majority of the prostate cancers were diagnosed as adenocarcinomas. However, some methodological weaknesses need consideration. Risk may be underestimated as some second cancers may be missed due to patient migration outside the cancer registry's catchments area or when tumours are missed due to incompleteness of a cancer registry. Treatment information may be incomplete, since only the first course of treatment is recorded, without consideration of additional treatment. Misclassification decreases any differences between therapeutic categories. Prescribed treatment is related with clinical information and the speed of tumour progresses; aspects which we were not able to take into account. Follow-up time may not have been sufficiently long for most cases to detect a treatment effect. Also the numbers may be too small to detect such an effect. As both bladder and prostate cancer are neoplasms that occur mainly in an older population, some men may have died before a second tumour manifested itself. Finally, we have no detailed information on the type of surgery that was performed to treat bladder cancer. The rate of prostate cancer on cystoprostatectomy specimens has been

reported as high as 45%.[30] On one hand, some of the reported prostate cancers may have been diagnosed at the moment of surgery. On the other hand, the patients treated in this manner will not develop a second tumour at a later time.

We repeated the main analyses for the different cancer registries separately and found that the results for the West Midlands Cancer registry were significantly lower: an RR of 1.48 (95%CI 1.31–1.66) to develop prostate cancer after bladder cancer for all age groups and an RR of 0.83 (95%CI 0.71–0.97) to develop bladder cancer after prostate cancer for all age groups. This may indicate a difference in the procedure of follow-up of bladder and prostate cancer patients between the UK, Belgium and The Netherlands.

This analysis found an excess risk to develop prostate cancer in bladder cancer patients younger than 70 and the first year of follow up after the diagnosis of bladder cancer. For prostate cancer as first neoplasm an excess risk was only found in men younger than 60. The excess risk in the younger age groups may be due to detection bias, although a common aetiology may also present.

Conflict of interest statement

None declared.

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Appendix A. Characteristics of the cancer registries that contributed to the analysis

Name	Abbreviation	Population	Registry follow-up since	Contact
Belgian Limburg Cancer registry, BE	LIKAR	798,583	1996	http://www.edm.luc.ac.be/likar
Antwerp Cancer Registry, BE	AKR	1,652,450	1990	–
Comprehensive Cancer Centre Limburg, NL	IKL	861,369	1986	http://www.ikcnet.nl/
Eindhoven Cancer Registry, NL	IKZ	4,300,000	1955	http://www.ikcnet.nl/
West-Midlands Cancer Intelligence Unit, UK	WMCIU	5,321,000	1957	http://www.wmpho.org.uk/wmciu

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