Paper V

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Beisland C, Talleraas O, Bakke A, Norstein J. Multiple primary malignancies in patients with Renal Cell Carcinoma. - A national population-based cohort study.

Multiple primary malignancies in patients with renal cell carcinoma: a national population-based cohort study

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OBJECTIVE

To determine the possibly greater occurrence of multiple malignancies in patients with renal cell carcinoma (RCC).

PATIENTS AND METHODS

In the 7-year period 1987–93, all 1425 patients aged 15–70 years with registered histopathologically verified RCC in Norway were included in the study. All clinical and histopathology reports were checked manually, to verify the registered diagnosis and to ensure that no tumour was a metastasis from another. After this process, 257 patients (287 tumours other than RCC) with multiple primary malignancies were identified. The primary tumours other than RCC were classified as antecedent, synchronous and subsequent. For the subsequently occurring tumours, the expected number of different tumour types was calculated according to age group, gender and observation time.

RESULTS

Of the 1425 patients, 228 (16%) had one, 23 (1.6%) had two, three (0.2%) had three and one (0.07%) had four other primary malignancies. In all, 100 (34.8%) of the other tumours were diagnosed as antecedent, 53 (18.7%) as synchronous and 134 (46.7%) as subsequent to the RCC. Cancer in the prostate, bladder, lung, breast, colon and rectal cancer, malignant melanomas (MM) and non-Hodgkin's lymphomas (NHL) were the most common other malignancies. The observed overall number of subsequent other malignant tumours was 22% higher than the expected number. The observed number of subsequent tumours was significantly higher for bladder cancer, NHL and MM. The estimated 15-year cumulative risk for patients with RCC and no previous or synchronous other malignancy for developing a later second cancer was 26.6% in men, and 15.5% in women (statistically significant, $P = 0.04$). Patients with antecedent or synchronous other cancer had significantly poorer overall survival than those without.

CONCLUSIONS

Patients with RCC seem to have a significantly higher risk of developing other subsequent primary malignancies. This should be considered during the follow-up of patients with RCC.

KEYWORDS

renal cell carcinoma, epidemiology, multiple primary malignancies, mortality

INTRODUCTION

Multiple primary malignant tumours are a well-known phenomenon. In the database at the Cancer Registry of Norway, 5.1% of patients with cancer in the 10-year period 1992–2001 had more than one cancer diagnosis [1]. A much higher percentage of multiple tumours were reported related to cancer of the kidney [2–4]. In Norway, RCC accounts for 2.2% [1] of the annually reported new cancers; it is 1.5–2 times more common in men than in women, and the mean age at diagnosis is 60–65 years.

Earlier reports showed that other primary malignant tumours associated with kidney cancer include cancer of the bladder [3–6], prostate [4,5,7], colorectal cancer [4,5] and lung [5,6]. Malignant melanomas (MM) of the skin [8] and non-Hodgkin's lymphomas (NHL) [5,8,9] are also associated with kidney cancer, but there are contradictory reports for the last [10].

The aetiology of multiple primary malignant tumours is complex, and includes environmental factors (tobacco, occupation, pollution, ultraviolet light), genetic predisposition, previous medical treatment (radio- or chemotherapy), gender-specific factors, hormonal factors, and interactions of these factors.

Most reports on kidney cancer and multiple primary tumours consist of either single-institution studies or purely register-based data. Therefore, in the present study we combined the use of a population-based cancer registry and manually checked histopathology reports, to achieve the best possible basis for the results. The primary aim of the study was to establish the frequency and types of second primary malignant tumours associated with RCC. Another aim was to explore the possibility of previous or synchronous other malignancies having an impact on patient survival after a diagnosis of RCC. In addition, we intended to estimate the risk of developing and the mortality of a second primary tumour after the diagnosis of RCC.

PATIENTS AND METHODS

The Cancer Registry of Norway is a population-based registry of all new cases of cancers in Norway since 1953. Each year >22 500 new cancer cases are reported to the registry, which contains information on >1 100 000 cancer cases. The completeness of the cancer registration is estimated to be close to 100% [1]. In Norway, national law requires both clinicians and pathologists independently to report all new cases of

cancer to the registry, without patient consent [11].

To explore multiple primary malignancies in patients with RCC we established a cohort by selecting all new RCC cases in Norway in the period 1987–93 for the analysis. By using the four-digit diagnosis code (180.0, cancer of the renal parenchyma) according to the 7th revision of the International Classification of Diseases (ICD-7), in all 3119 new cases were found in the registry.

To avoid nephroblastomas (Wilms' tumour) in the sample and because RCC is very rare in those aged 0–15 years, patients aged <15 years were excluded from the study. By excluding patients >70 years old it could be assumed that within the sample the estimated life-expectancy was at least 10–15 years; in Norway the life-expectancy at age 70 years in 1990 was 11.4 years for men and 14.7 years for women [12].

To ensure that all tumours in the material were verified by biopsy and were true RCC, all cases that were not connected with one of the specified histopathological morphology codes, were excluded. The following histopathological morphology codes according to the ICD for Oncology, Second edition (ICD-O-2) were accepted for the study: 8312/3, 8310/3, 8320/3, 8270/3, 8032/3, 7191/3, 8260/3, 7508/3, 7190/3, 8481/3, 8190/3, 8211/3, 8290/3, 8280/3, 7193/3, 7194/3, 8140/3, 8010/3, 8020/3, 8041/3. For the morphological description, the Manual of Tumour Nomenclature and Coding (MoTNaC, 1968) was used at the Registry until 1992. From 1993 the ICD-O-2 codes were used and the MoTNaC codes were re-coded.

All urothelial cancers were thus excluded, leaving only carcinomas derived from renal cells. Two patients were excluded because they were only receiving treatment for RCC in Norway but did not live in the country, and were therefore lost to follow-up. After exclusion according to age (1589), histopathological morphology codes (103) and lost to follow-up (two), 1425 patients with 1432 RCC tumours in all (seven bilateral cancers) remained for further investigation of multiple primary tumours.

The 1425 patients with primary RCC were matched against the Main Database of the Cancer Registry of Norway to identify other reported primary malignancies. In this process, all basal cell carcinomas and premalignant lesions were excluded, but benign tumours of the brain were included. In the database, there were 291 patients (621 primary records) with two or more primary tumours. One author (C.B.) then manually investigated all primary cancer reports for this group. Each tumour had to meet the following criteria by the clinical and histopathological reports (after Warren and Gates [13]): there had to be a definite picture of malignancy on biopsy; and the possibility of one tumour being a metastasis from the other should be excluded. Of 621 primary tumour records, 18 (2.9%) were excluded in this process. Seven patients were excluded, leaving 284 for further analysis of multiple tumours. Of these, 27 patients had a second primary tumour in the opposite kidney only. Three more patients had contralateral tumour reported as their third or fourth primary tumour. In these 27 patients with 57 (27 + 27 + 3) primary tumour records, problems with the second criteria that led to their exclusion. For those with two primary RCC reports within the 7-year period and other primary tumour(s), the date of diagnosis of the first RCC was used in the study. After exclusions, 257 patients with a total of 287 other primary malignancies remained for analyses. The other primary malignancies were divided into antecedent, synchronous or subsequent. Synchronous tumours were defined as other primary malignancies diagnosed <91 days before or after the diagnosis of RCC.

All patients were followed until the date of death, emigration or 31 December 2002, whichever was soonest. Informed consent was not necessary for this study, as it was within the National Cancer Registry

Standardized incidence ratios (SIRs) were used to estimate the risk of later primary cancers, calculated as the ratio of observed numbers (ONo) and expected numbers (ENo) of cases. The ENo of cases were estimated by assuming that the patients in the cohort had the same cancer incidence as prevailed in the general population of Norway. By using the Main Database of the Cancer Registry of Norway, tumour site-, gender-, period- and age-specific rates were combined with the person-years at risk, the last being accumulated for each person starting with date of diagnosis of RCC and ending with date of death, emigration or 31 December 2002, whichever was soonest. SIRs were only calculated for tumours with an ONo of >3, exception for rectal tumours, due to the relationship between this cancer and cancer of the colon.

Statistical significance and CIs were calculated assuming that the ONo of second primary malignancies followed a Poisson distribution. The Kaplan–Meier method was used to calculate the 15-year cumulative risk of an initial second primary cancer after a diagnosis of RCC. All patients with an antecedent or synchronous second primary cancer were excluded in this context. For comparison between groups, the log-rank test was used, and for all statistical analyses $P < 0.05$ was considered to indicate statistical significance.

RESULTS

Of the 1425 patients included, 909 (63.8%) were males and 516 (36.2%) were females (ratio 1.8 : 1); the mean age was 59.1 years, and the median observation time for surviving patients at 31 December 2002 was 12.0 years. Of the 1425 patients, 228 (16.0%) had one biopsy-verified primary malignant tumour other than the RCC; in 23 (1.6%) two other primary tumours were reported, three (0.2%) had three and one (0.07%) had four other primary malignancies. Of the 287 other primaries, 100 (34.8%) were antecedent, 53 (18.7%) appeared synchronously and 134 (46.7%) appeared subsequently. The five most common other primary tumours were those of the prostate, bladder, lung, breast and colon. The location and period of diagnosis of the other malignancies are listed in Table 1.

In Table 2, the SIRs for other primaries are listed; the SIRs for second primary cancer were significantly higher for bladder cancer, MM and NHL. Table 2 also includes the SIRs for each gender separately. The 14 bladder cancers were diagnosed at a median (range) of 4.8 (0.3–12.3) years, with three of the 14 diagnosed >10 years after the diagnosis of RCC. The overall survival rates for patients with antecedent and synchronous other primary cancers at the time of the diagnosis of RCC were significantly lower than for patients with no known other primary cancers (Fig. 1).

The mean (95% CI) 5-, 10- and 15-year cumulative risk of developing a second primary cancer after the primary diagnosis of

TABLE 1 The location of all other primary tumours according to the time (relative to the diagnosis of RCC) that they were diagnosed

Other primary sites	Total	Antecedent	Synchronous	Subsequent
No. of patients				
Prostate	30	6	2	22
Bladder	28	5	9	14
Lung	26	5	8	13
Breast	26	12	6	8
Colon	25	11	4	10
Melanoma of skin	21	10	1	10
Rectum	14	10	1	3
Non-Hodgkin's Lymphomas	12	3	1	8
Thyroid gland	9	5	2	2
Uterine corpus	9	5	1	3
Uterine cervix	8	5	0	3
Ovary	7	4	1	2
Brain	6	1	0	5
Other skin*	6	3	0	3
Stomach	6	0	2	4
Pancreas	6	1	3	2
Renal pelvis/ureter	6	2	3	1
All other tumour sites	42	12	9	21
Total	287	100	53	134

**Not including melanomas of skin and basal cell carcinomas.*

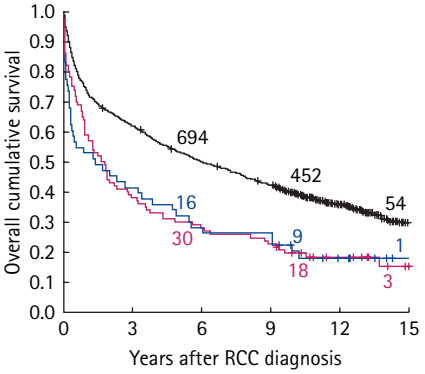
TABLE 2 The ONo, ENo and SIR (95% CI) for the most common secondary primary malignancies after a diagnosis of RCC

			SIR (95% CI)		
Other primary sites	ONo	ENo	All	Males	Females
Prostate	22	18.52	1.19 (0.74–1.80)	1.19	–
Bladder	14	6.69	2.09 (1.14–3.51)*	2.12*	1.97
Lung	13	13.67	0.98 (0.52–1.68)	0.58	2.39
Breast	8	7.98	1.00 (0.43–1.98)	11.33	0.89
Colon	10	11.19	0.89 (0.43–1.64)	1.43	0*
MM of skin	10	4.25	2.35 (1.13–4.33)*	1.48	3.89*
NHL	8	3.24	2.47 (1.07–4.87)*	2.83*	1.79
Brain	5	2.61	1.92 (0.62–4.47)	2.61	0.93
Stomach	4	3.79	1.06 (0.29–2.71)	0.69	2.24
Total	134	109.5	1.22 (1.03–1.45)*	1.25	1.21

**95% CI does not include 1.00, and is thus statistically significant.*

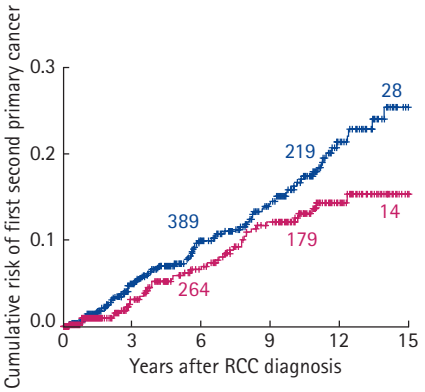
COLOUR FIG.

FIG. 1. Kaplan-Meier plot of overall survival after detection of RCC. The red line represents 100 patients with antecedent second primary tumour, the blue line 53 with synchronous second primary tumour and the black line 1302 with no antecedent or synchronous second primary tumour. The difference is statistically significant (P < 0.001, log-rank test, two degrees of freedom). Numbers represent patients at risk at 5, 10 and 15 years after the diagnosis of RCC.



COLOUR FIG.

FIG. 2. An inverse Kaplan-Meier plot showing the cumulative frequency of patients diagnosed with an initial second malignant tumour after their diagnosis of RCC; males (816, blue line) and females (476, red line). The difference between the genders is statistically significant (P = 0.04). The numbers show persons at risk at 5, 10 and 15 years.



RCC was 7.3 (5.0–9.6)%, 16.0 (12.3–19.6)% and 26.6 (19.5–31.7)% for males, and 5.9 (3.3–8.6)%, 12.2 (8.3–16.1)% and 15.5 (10.4–20.3)% for females, respectively (Fig. 2); this difference was statistically significant ($P = 0.04$). Within the same group, the 5-, 10- and 15-year cumulative risk of death from a second primary cancer after the primary diagnosis of RCC was 1.5 (0.4–2.7)%, 4.7 (2.5–6.9)% and 7.2 (3.9–10.6)% for males, and 1.6 (0.2–3.1)%, 4.9 (2.2–7.6)% and 8.4 (1.9–14.8)% for females, respectively. When omitting patients with primary metastatic RCC from both these analyses, the results were only minor and insignificantly altered (data not shown).

DISCUSSION

In the present study the rate of multiple primary malignancies was 16.1%, and higher than those reported earlier of 4.5–11.9% [2,3], but lower than the 26.9% reported by Rabbani *et al.* [4]. However, all these studies were either single-institution series or smaller groups of patients. Population-based studies like the present have the advantages of larger groups

of unselected patients and a longer follow-up. This allows for more stable estimates of SIRs, and the same population can be used for calculating the ENo of cancers. Biases in geographical factors, local environmental factors or referral patterns are not likely to affect the results. A national registry like the Cancer Registry of Norway also has the advantage of a uniform practice in reporting and coding. Some authors [4] indicated that hospital series may have advantages over population-based series; they are said be more accurate for tumour stage and pathology reports [4], and are also claimed to have better follow-up data, so potential sources of bias may be discovered [4]. However, by manually checking all clinical and histopathology report forms, we tried to eliminate registration errors, and to ensure the quality of the data set so that it resembles the data available at the hospitals. Few registration errors were encountered during this procedure. Data derived from a national cancer registry has the advantage of including all reports on malignancies from all treatment facilities in the country, thus eliminating loss to follow-up or ascertainment of other tumours. In conclusion, we think that the present method gives the best estimate of the occurrence of multiple primary tumours in patients with RCC.

The present SIRs were low estimates; the ONo were checked thoroughly, as described previously (biopsy verified, manually checked forms, etc.), but the ENo were estimated from all the reported cancer cases to the main database at the Registry. The ONo would have been relatively higher than ENo if the same criteria had been applied to this latter group.

The percentage of patients having more than one other primary cancer in the present study is concurrent with earlier reports [4]. By contrast, there are differences in the percentage of other primary tumours detected subsequently. In the present study, almost half were diagnosed subsequently, while earlier studies reported 15–23% [2,4]. The probable cause of this is the longer observation time in the present study. Previous studies [2–7], also supported by the present study, suggest that prostate, breast, colorectal, bladder, NHL and lung cancer seem to be the most common other primary cancers in patients with RCC.

Czene and Hemminki [5] published a large series based on the Swedish Cancer Registry. Their findings of many other significantly elevated SIRs for subsequent primary tumours correspond only partly with the present study. By contrast, the study by Rabbiani *et al.* [4] only identified an elevated SIR for bladder cancer in males. In the study of Czene and Hemminki [5] the higher rate of bladder cancer in males was the only subsequent cancer with a gender difference; this gender difference for bladder cancer was supported by the present study. This higher risk of subsequent bladder cancer after RCC is that most often reported for other primary cancers [3–6].

The high risk of subsequent bladder cancer might be due to surveillance bias because of frequent visits to a urologist during the follow-up. We think that this is unlikely, because bladder cancer seems to appear not only in the early years after the diagnosis of RCC, when follow-up visits are frequent, but also after an interval of >10 years, as shown both by Czene and Hemminki [5] and the present study. In addition, due to the nature of most bladder cancers, during a long follow-up all these cancers will become symptomatic and therefore reveal themselves independently of regular control regimens. Much more intriguing is the possibility of a common environmental or genetic causal agent. Begg *et al.* [6] reported smoking to be among such important factors for the high rate of subsequent bladder tumours. Other carcinogens excreted through the kidneys would probably also influence this disease.

It is well known that cancer therapy may result in other primary cancers [14,15], but these usually appear after 10 years. As the standard treatment of RCC does not include chemotherapy or radiation, this is probably not a major contributory cause to the increased risk of second primaries. In addition, as the usual follow-up regimen in Norway during this period consisted of a physical examination, blood tests and chest X-ray every 6 months, follow-up investigations are unlikely to influence the increased risk. However, if the treatment for RCC results in a patient with worse overall kidney function needing dialysis, and a later renal transplantation, then an increase in second cancers may be due to immunosuppressive medications. NHL was reported to occur at a much greater rate (10–30 times) [16] after renal transplantation. Other primary cancers are also reported to be more common after renal transplantation. After a nephrectomy for RCC, in a group of patients with preoperatively normal kidney function, >20% may develop chronic renal failure over time [17]. End-stage renal disease and renal transplantation related to RCC, may thus be a minor factor influencing the occurrence of other primary tumours, but further investigation is warranted.

The major impact on overall survival by antecedent or synchronous other cancers in this study were discussed by Sato *et al.* [2]. They reported that other primaries at the time of nephrectomy for RCC was an independent prognostic factor for overall survival after the operation. Furthermore, patients with localized RCC (T1–2) and coexistent other cancer had poorer overall survival than those with localized RCC (T1–2) alone. We think that the treatment of RCC in patients with multiple primary tumours should be based not only on the stage and operability of the kidney tumour, but also on an evaluation of the disease status of the other malignant disease.

The cumulative risk of a second primary cancer after a diagnosis of RCC, as shown in the present study, has not been reported previously. The study by Czene and Hemminki [5] clearly indicates that patients with RCC have a greater risk of other cancers not only in the first year after the primary diagnosis, but also after >10 years. For males the cumulative risk of a second cancer reached 26.6% after 15 years; indeed, 7.2% died from the second cancer. This observation may influence how patients with RCC should be followed after the diagnosis. Most current follow-up schedules are discontinued 5 years after surgery [18,19], because further follow-up is not cost-effective for detecting recurrent RCC. In an earlier study [20] we showed that at 5–10 years after nephrectomy for RCC, 100–125 annual routine follow-up visits were necessary to identify one recurrence. However, these studies focus only on the recurrence of RCC, and the follow-up regimens are probably good enough for that. Due to their increased risk of secondary primary malignant tumours, perhaps these patients should be followed with examinations that are more general after the end of the specific follow-up for RCC. Urine analysis, tests for occult blood in the stool and a general physical examination, including skin inspection, a DRE and lymph node palpation every second year by a GP, seems to be an appropriate regimen for such a long follow-

up. To use more invasive screening tools, e.g. cystoscopy or colonoscopy, would probably be less cost-effective, although colonoscopy at 10-year intervals might be considered, as proposed for the general population by some [21]. Such follow-up is probably even more appropriate if the patient is a smoker, despite advice on stopping smoking or having other risk factors for other primary cancers.

CONFLICTS OF INTEREST

None declared.

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REFERENCES

1 **Cancer in Norway 2001.** *Oslo: the Cancer Registry of Norway*. Oslo: Institute of Population-Based Cancer Research, 2004
2 **Sato S, Shinohara N, Suzuki S, Harabayashi T, Koyanagi T.** Multiple primary malignancies in Japanese patients with renal cell carcinoma. *Int J Urol* 2004; **11**: 269–75
3 **Kantor AF, McLaughlin JK, Curtis RE, Flannery JT, Fraumeni JF Jr.** Risk of second malignancy after cancers of the renal parenchyma, renal pelvis, and ureter. *Cancer* 1986; **58**: 1158–61
4 **Rabbani F, Grimaldi G, Russo P.** Multiple primary malignancies in renal cell carcinoma. *J Urol* 1998; **160**: 1255–9
5 **Czene K, Hemminki K.** Kidney cancer in the Swedish Family Cancer Database: familial risks and second primary malignancies. *Kidney Int* 2002; **61**: 1806–13
6 **Begg CB, Zhang ZF, Sun M, Herr HW, Schantz SP.** Methodology for evaluating the incidence of second primary cancers with application to smoking-related cancers from the Surveillance, Epidemiology, and End Results (SEER) program. *Am J Epidemiol* 1995; **142**: 653–65
7 **Wegner HE.** Multiple primary cancers in urologic patients. Audit of 19-year experience in Berlin and review of the literature. *Urology* 1992; **39**: 231–6
8 **Tihan T, Filippa DA.** Coexistence of renal cell carcinoma and malignant lymphoma. A causal relationship or coincidental occurrence? *Cancer* 1996; **77**: 2325–31
9 **Anderson CM, Pusztai L, Palmer JL, Cabanillas F, Ellerhorst JA.** Coincident renal cell carcinoma and nonHodgkin's lymphoma: the M.D. Anderson experience and review of the literature. *J Urol* 1998; **159**: 714–7
10 **Rabbani F, Russo P.** Lack of association between renal cell carcinoma and non-Hodgkin's lymphoma. *Urology* 1999; **54**: 28–33
11 **Cancer Registry of Norway.** http://www.kreftregisteret.no. Accessed September 2005
12 **Statistics Norway.** http://www.ssb.no/emner/02/02/10/dode/tab-2005-04-28-03.html. Accessed September 2005
13 **Warren S, Gates O.** Multiple primary malignant tumors. A survey of the literature and a statistical study. *Am J Cancer* 1933; **16**: 1358
14 **Swerdlow AJ, Barber JA, Hudson GV *et al.*** Risk of second malignancy after Hodgkin's disease in a collaborative British cohort: the relation to age at treatment. *J Clin Oncol* 2000; **18**: 498–509
15 **van Leeuwen FE, Stiggelbout AM, van den Belt-Dusebout AW *et al.*** Second cancer risk following testicular cancer: a follow-up study of 1,909 patients. *J Clin Oncol* 1993; **11**: 415–24
16 **Birkeland SA, Storm HH, Lamm LU *et al.*** Cancer risk after renal transplantation in the Nordic countries, 1964–1986. *Int J Cancer* 1995; **60**: 183–9
17 **Lau WK, Blute ML, Weaver AL, Torres VE, Zincke H.** Matched comparison of radical nephrectomy vs nephron-sparing surgery in patients with unilateral renal cell carcinoma and a normal contralateral kidney. *Mayo Clin Proc* 2000; **75**: 1236–42
18 **Ljungberg B, Alamdari FI, Rasmuson T, Roos G.** Follow-up guidelines for nonmetastatic renal cell carcinoma based on the occurrence of metastases after radical nephrectomy. *BJU Int* 1999; **84**: 405–11
19 **Levy DA, Slaton JW, Swanson DA, Dinney CP.** Stage specific guidelines for surveillance after radical nephrectomy for local renal cell carcinoma. *J Urol* 1998; **159**: 1163–7
20 **Beisland C, Medby PC, Beisland HO.** Presumed radically treated renal cell carcinoma – recurrence of the disease and prognostic factors for subsequent survival. *Scand J Urol Nephrol* 2004; **38**: 299–305
21 **Atkin W.** Options for screening for colorectal cancer. *Scand J Gastroenterol Suppl* 2003; **237**: 13–6

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Abbreviations: **MM**, malignant melanoma; **NHL**, non-Hodgkin's lymphoma; **ICD**, International Classification of Diseases; **MoTNaC**, Manual of Tumour Nomenclature and Coding; **SIR**, standardized incidence ratio; **ONo**, observed number; **ENo**, expected number.