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Risk of second primary malignancies among patients with carcinoid of the lung

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ABSTRACT

Objectives: Little is known about the etiology of pulmonary carcinoids (PC). Associations with other types of cancer may identify shared risk factors but results from earlier studies were inconclusive. The aim of the present study was to explore the association between PC and other primary malignancies for identifying risk factors.
Methods: A query of the nationwide Netherlands Cancer Registry generated data about patients diagnosed with PC from 1989 to 2018. The occurrence of second primary malignancies was evaluated separately for year 1 and years 2−30. The expected numbers of second primary malignancies were calculated using incidence reference tables, controlling for age, gender and period. Confidence intervals (95 % CI) for the ratio between observed and expected numbers (SIR: standardized incidence ratio) were calculated using Poisson distributions.
Results: In a total of 2933 patients with PC, 425 consecutive primary malignancies were observed in 376 patients. Concomitant diagnoses in the first year mainly comprised lung (n = 59) and renal cancer (n = 14). Metachronous malignancies beyond the first year were most common for breast (n = 50), colorectal (n = 41), prostate (n = 32), and lung cancer (n = 29). Beyond year 1, the overall risk of second primary cancer in patients with PC was similar to the risk within the general population (n = 256, SIR = 1.12, 95 % CI 0.99–1.27). Increased risks were observed for soft tissue sarcoma (n = 5, SIR = 3.52, 95 % CI 1.14–8.22) and GEPNET (n = 4, SIR = 4.30, 95 % CI 1.17–11.01).
Conclusions: Concomitant diagnosis of PC with other cancers is common, reflecting surveillance diagnostics. Apart from MEN-1 family history, no shared risk factors could be identified.

1. Introduction

Typical and atypical carcinoid tumours of the lung are rare neuroendocrine tumours (NETs), accounting for less than 1 % of all lung cancers. According to data from the US SEER (Surveillance, Epidemiology, and End Results) database, the incidence of pulmonary NETs gradually increased in the previous century and remained stationary in the last decennium at 1.6 per 100.000 persons [1]. This increase can be partially explained by increased recognition of this entity by pathologists and improvement of diagnostics.

Pulmonary carcinoids (PC) are more often diagnosed in women and are generally diagnosed in the fifth decade of life. The pathologic classification of neuroendocrine tumours in the lung is based on the WHO criteria [2]. This system is based on morphologic features and immunohistochemistry; mitotic frequency and necrosis are used to divide tumours into low- and intermediate grade (typical and atypical) carcinoids or into the more aggressive large cell neuroendocrine cancer (LCNEC) and small cell lung cancer (SCLC). In LCNEC and SCLC, smoking is the most important attributable factor, but this does not seem to be the case for PC [3,4]. Overall, very little is known about the

Abbreviations: PC, pulmonary carcinoids; SIR, standardized incidence ratio; NET, neuroendocrine tumour; NCR, Netherlands Cancer Registry; GEPNET, gastro-entero-pancreatic neuroendocrine tumour.

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aetiology of PC.

Associations with other diseases or types of cancer may establish shared risk factors. Previous studies on PC reported contradictory results, suggesting excess risks of prostate cancer and male breast cancer, [5] versus excess risks of renal and thyroid cancer [6], versus excess risks of lung, thyroid, liver and pancreatic cancer [7]. In patients with small-intestinal neuroendocrine tumors, an increased risk of cancers of small bowel, liver, prostate and thyroid cancer has been reported [8]. Furthermore, it was suggested that carcinoid tumors occurred more frequently in patients with gastrointestinal stromal tumors [9].

Previous studies often suffered from small sample size or short follow-up. The aim of the present study was to explore the association between PC and other primary cancers in a sizable population-based cohort with 30 years of follow-up.

2. Methods

Patients data, who were diagnosed with typical or atypical pulmonary carcinoid in the period 1989–2018 were retrieved from the nationwide Netherlands Cancer Registry (NCR), after approval by the Privacy Review Board (application K20.116). In accordance with the regulations of the Central Committee on Research involving Human Subjects (CCMO), this type of study did not require approval from an ethics committee in the Netherlands. The NCR collects data on all cancer patients diagnosed in the Netherlands, based on notification of newly diagnosed malignancies by the national automated pathological archive and of hospital discharge diagnoses. Information in the medical records on demographics, diagnosis, staging, and treatment is extracted routinely by specially trained NCR personnel. The survival status is updated annually using a computerized link with the national civil registry. For the present analysis, information on survival and second primary cancers was analyzed up to the end of 2018.

Synchronous (diagnosed within 12 months from PC diagnosis), and metachronous primary malignancies were identified and tabulated, excluding non-invasive malignancies, non-melanoma skin cancer and secondary PC. For metachronous malignancies, standardized incidence ratios (SIR) were calculated as the ratio of the observed and expected number of cancer cases. In case of multiple metachronous cancers, only the first cancer was included in the analysis. The expected numbers were calculated by matching the follow-up experience with incidence rates for the general population that were specified by age, gender, tumour type and year of diagnosis. Confidence intervals (95 %) were calculated by assuming a Poisson distribution for the observed number of cases. Standardized incidence ratios (SIR) were only calculated for tumour types with 3 or more metachronous cases, to reduce chance findings due to multiple testing.

3. Results

The total series comprised 2933 patients with a median age of 61 years, interquartile range 49–70 years. PC was more common among women (58 %), 17 % of tumours were atypical, 10 % of tumours were located in the main bronchi and 67 % were stage I (Table 1). Median follow-up of censored cases was 8.6 years. Median overall survival was 21.2 years for typical carcinoid versus 8.5 years for atypical carcinoid.

In 2559 patients (87 %) no subsequent cancers were recorded. In 376 patients, 425 subsequent primary malignancies were recorded, and 43 patients had two or more subsequent cancers. Of the 120 cancers diagnosed in year 1, 37 (31 %) were diagnosed on the same day as the PC.

Lung cancer (n = 59) and renal cancer (n = 14) were prominent in year 1 (Table 2). The most common cancers in years 2−30 were breast (n = 50), colorectal (n = 41) and prostate cancer (n = 32). The overall risk of subsequent cancers was not increased (SIR 1.12, 95 % CI 0.99–1.27). With 29 observed cases, the risk of subsequent lung cancer was not increased (SIR 0.86, 95 % CI 0.58–1.23). One metachronous case of male breast cancer was diagnosed.

Table 1
Patient characteristics of 2933 patients with pulmonary carcinoids in the Netherlands from 1989 to 2018.

		n	%
Carcinoid type	Typical	2422	83
	Atypical	511	17
Gender	Men	1175	42
	Women	1760	58
Age (years)	0−59	1378	47
	60−69	775	26
	70+	782	27
Period	1989−1998	704	24
	1999−2008	801	27
	2009−2018	1430	49
Subsite	Main bronchi	303	10
	Upper lobe	872	30
	Middle lobe	474	16
	Lower lobe	1131	39
	NOS	155	5
TNM stage	I	1979	67
	II	266	9
	III	257	9
	IV	285	10
	X	148	5

NOS: Overlapping or not specified.

Table 2
Frequency of synchronous and metachronous second primary malignancies in 376 patients with pulmonary carcinoids compared to the incidence in the general population.

Cancer type	Year 1		Years 2−30		Years 2−30	95 % CI	
	Obs	Exp	Obs	Exp	SIR	Lower	Upper
Breast	3	4.8	50	42.3	1.18	0.88	1.56
Colorectal	7	4.1	41	38.0	1.08	0.77	1.75
Prostate	6	2.8	32	24.4	1.31	0.90	1.85
Lung	59	4	29	33.8	0.86	0.58	1.23
Melanoma	2	1.2	17	11.2	1.52	0.89	2.44
Pancreas	1	0.7	12	6.4	1.87	0.97	3.27
Bladder	3	0.9	10	8.1	1.23	0.59	2.26
Renal	14	0.7	9	5.9	1.52	0.70	2.89
Stomach	1	0.5	8	4.0	2.02	0.87	3.98
NH Lymphoma	1	0.8	6	7.4	0.81	0.30	1.76
Oesophageal	1	0.5	6	5.1	1.17	0.43	2.55
Pharynx	0	0.2	5	2.1	2.39	0.78	5.58
Ovary	2	0.5	5	4.4	1.13	0.37	2.64
Soft tissue sarcoma	1	0.2	5	1.4	3.52	1.14	8.22
GEPNET	3	0.1	4	0.9	4.30	1.17	11.01
Liver	1	0.2	3	1.5	1.99	0.41	5.81
Total	120	26.9	256	228.4	1.12	0.99	1.27

NH: non-Hodgkin, GEPNET: gastro-entero-pancreatic neuroendocrine tumor, Obs: observed, Exp: expected, SIR: standardized incidence ratio, CI: confidence interval.

Increased risks were observed for soft tissue sarcoma (SIR 3.52, 95 % CI 1.14–8.22) and GEPNET (SIR 4.30, 95 % CI 1.17–11.01). Soft tissue sarcoma comprised two cases of fibromyxosarcoma, one synovial sarcoma, one pleomorphic sarcoma and one case of spindle cell sarcoma in a completion pneumonectomy. Of the 4 subsequent GEPNET cases, three lesions were located in the pancreas and one in the small bowel. Two cases were known to be MEN-1 related.

4. Discussion

As far as we know, this is the largest series published in literature, comprising 256 PC patients with metachronous malignancies. As expected, the most frequent metachronous cancers were member of the ‘big four’ ranking: breast (20 %), colorectal (16 %), prostate (13 %) and lung cancer (11 %). There was no excess risk for these cancer types nor

for cancer overall. An increased risk was, however, observed for GEP-NET and soft tissue sarcoma. An association between PC and GEPNET is plausible as patients with a MEN-1 family history may develop neoplastic lesions in pituitary and parathyroid gland, duodenum and pancreas, but may also encounter carcinoids of the lung. The association with soft tissue sarcoma has not been reported before, has no evident biological explanation and should be considered a chance finding until confirmed by others. Although the diagnosis soft tissue sarcoma was made by local pathologists and the cases were not reviewed by an independent pathologist in our study, it is unlikely that metastatic PC was misdiagnosed as soft tissue sarcoma. Fibromyxosarcoma, pleomorphic sarcoma and spindle cell sarcoma are morphologically, immunohistochemically and genetically very different tumors compared to PC. Differential diagnosis between synovial sarcoma and PC could be challenging, especially in pre-molecular diagnostic era, as these tumors share some histological features and positivity for epithelial markers like keratins and positivity for CD56. However, molecular tests to demonstrate specific for synovial sarcoma translocations (*SS18 -SSX1*, *SS18-SSX2* or *SS18 -SSX4*) have been used in the Netherlands for many decades.

Three other large studies reported on second primary malignancies after PC. The first study was based on information from the SEER database and found 118 subsequent malignancies that were not diagnosed in the same calendar year as the PC [5]. Increased risks were reported for prostate cancer and breast cancer in men, the latter based on 2 cases only. The second study analyzed data from the Italian AIRTUM registry and reported 198 metachronous malignancies, without specifying a definition of the boundary between synchronous and metachronous cases [6]. An increased risk was found for cancers of kidney and renal pelvis, but only in men. A recent study evaluated SEER data using a 2-month latency period to exclude synchronous cancers and reported on 79 s primaries after PC. For typical carcinoids, excess risks were suggested for lung, thyroid, liver and pancreatic cancer [7].

Epidemiological studies on secondary cancers can be used to discover shared etiology between primary and secondary cancers. Combining the information from the three previous studies and ours, we may surmise that PC has no relevant association with risk factors known for other types of cancer. PC is more common among women, but association with breast or endometrial cancer is lacking, refuting a hormonal background. Concurrent diagnosis of synchronous tumours frequently occurs, but this can be attributed to surveillance bias. This bias is related to the often indolent nature of PC, and probably reflects incidental findings upon diagnostic procedures for other malignancies. Lung and renal cancer were common synchronous malignancies during the first year, but incidence was not increased thereafter.

The major strength of our study lies in the completeness and size of the database, nation-wide coverage and a 30-year follow-up. Major limitation is that definitions and diagnostic examination of PC may have changed over time. Diagnoses were based on the conclusion of local pathologists and not reviewed by expert panels. Part of the diagnoses were based upon biopsies while surgical specimens are to be preferred.

In conclusion, apart from a high SIR for GEPNET, no relevant associations with other types of cancer were found, leaving the etiology of PC a mystery.

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CRediT authorship contribution statement

Wieneke A. Buikhuisen: Conceptualization, Writing - original draft, Visualization. **Laurie C. Steinbusch:** Writing - review & editing. **Liudmila L. Kodach:** Writing - review & editing. **Margot E.T. Tesselaar:** Writing - review & editing. **Ronald A.M. Damhuis:** Conceptualization, Methodology, Formal analysis, Writing - original draft.

Declaration of Competing Interest

There were no conflicts of interest stated by the authors.

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