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Association of brain tumours with other neoplasms in families

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Abstract

We used the nationwide Swedish Family-Cancer Database to analyse the association of histology-specific brain tumours with other cancers in family members. Among 0–68-year-old offspring, 9414 patients with brain tumours were identified from 1961 to 2000, of whom, 3387 parents were diagnosed with any primary neoplasm. Astrocytoma, meningioma and neurinoma were the main histological types. Increased standardised incidence ratios (SIRs) were found for brain tumours in association with cancers at sites that are known features in recognised syndromes, such as haemangioblastoma and renal cancer in von Hippel–Lindau disease. In addition, an association between astrocytoma and melanoma was recognised. Among as yet unknown clustering, neurinoma was associated with testicular cancer and myeloma; meningioma was associated with cervical cancer; astrocytoma was associated with prostate cancer; ependymoma was associated with breast cancer. Although some of these may feature a true tumour cluster, they need to be confirmed in another setting.

Keywords: Astrocytoma; Medulloblastoma; Ependymoma; Meningioma; Familial risk

1. Introduction

Cancer syndromes such as Li–Fraumeni or hereditary non-polyposis colorectal cancer (HNPCC) were initially recognised through one index cancer site, but later they were found to encompass a number of other sites [1–3]. Brain cancer is one manifestation in Li–Fraumeni syndrome and HNPCC (Turcot syndrome) and multiple organs are affected even in other syndromes in which nervous system tumours appear, including neurofibromatosis 1, von Hippel–Lindau and Gorlin's syndromes [4–6]. It is thus meaningful to search for associations of tumours at other sites with nervous system tumours. Brain tumours are complex and feature multiple anatomical and histological types, even in the known cancer syndromes. Histologically, the most common brain tumours are (in this order) astrocytomas of different kinds, meningiomas, neurinomas (schwannomas), ependymomas and medulloblastomas [6]. Brain tumours occur at various ages. In Sweden, brain tumours are the most common childhood neoplasia, and they constitute some 7% of all diagnosed brain tumours [7]. Brain tumours of children and young adults are preferentially pilocytic and diffuse astrocytomas, medulloblastomas and ependymomas [6]. Therapeutic irradiation and family history are the only established risk factors of brain tumours [8].

We analysed the co-occurrence of cancers in families with brain tumour patients, covering any age and histological type, using the newest update of the nationwide Swedish Family-Cancer Database [9]. To our knowledge, previous data on the clustering of brain tumours with cancers at other sites are sparse [10–12]. Compared with previous brain cancer studies from this Database, an extended population and more cancer cases were being used, allowing analysis by age of onset through parental and sibling probands. In the Database, family relationships and cancers were obtained from registered sources of practically complete coverage, reducing the chances of bias.

2. Patients and methods

Statistics Sweden maintains a 'Multigeneration Register' where children, offspring, born in Sweden in 1932

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and later are registered with their parents (those stating parenthood at birth) and they are organised as families [9]. Information on the Database is also available at the Nature Genetics website as 'Supplementary information' to reference [13]. The data on families and cancers have a complete coverage, barring some groups of deceased offspring, which affect those born in the 1930s and those who died before 1991. Although this small group of offspring with missing links to parents has a negligible effect on the estimates of familial risk [14], we limited the present study to offspring whose parents were known to eliminate the possibility of bias. This Register was linked by the individually unique national registration number to the Cancer Registry from 1958 to 2000. Cancer registration is currently considered to be close to 100% [7]. Only the first primary nervous system tumours were considered. A four-digit diagnostic code according to the International Classification of Disease (ICD)-7 was used; the code 1930 was used for brain cancer, 1931 for spinal tumours and 1933 for peripheral nerve tumours. The histological classification of brain tumours was used, as present in the Cancer Registry, to define astrocytoma (pathology codes 475–476), medulloblastoma (436), neurinoma (451), ependymoma (481–486), meningioma (461–466), haemangioblastoma (501, 511). These codes have been used since the start of cancer registration in Sweden (World Health Organization (WHO)/HS/CANC/24.1 Histology Code).

Standardised incidence ratios (SIRs) were used to measure the cancer risks for offspring according to the occurrence of cancers in their families. SIRs were calculated and results are shown for offspring brain tumours when the parent or sibling had any cancer, i.e. using parents or sibling as probands. Where there were some interesting findings, we reversed the comparison: SIRs were calculated for parental brain cancer using the offspring as probands. These results afforded an independent confirmation of the findings [15]. The results may not agree for a number of reasons, but if they agree they provide strong evidence for a true effect. Follow-up was started for each offspring at birth, immigration or on 1 January, 1961, whichever was the latest time. Follow-up was terminated at the diagnosis of first cancer, death, emigration or the closing date of the study on 31 December, 2000. When more than two affected offspring were found in any family, they were counted as independent events.

Parents' ages were not limited, but offspring were 0–68 years of age. All tumour incidence rates were based on data in the Family-Cancer Database, and they are essentially similar to rates in the Swedish Cancer Registry. Rates were standardised to the European population. SIRs were calculated as the ratio of observed (O) to expected (E) number of cases. The expected numbers were calculated from 5-year-age-, gender-, tumour type-, period- (5-year bands), socioeconomic status- (six groups) and residential area- (three groups) specific standard incidence rates for all offspring lacking a family history [16]. Confidence intervals (95% CI) were calculated assuming a Poisson distribution, and they were rounded to the nearest two decimals [16]. Risks for siblings were calculated using the cohort method, as described elsewhere in Ref. [17].

3. Results

The Family-Cancer Database covered the years of 1961–2000 from the Swedish Cancer Registry and included 9414 cases of brain tumours in 0–68-year-old offspring. A total of 3387 cases had a parent diagnosed with any primary neoplasm; a total of 612 siblings were diagnosed with cancer in families where one sibling presented with a brain tumour (Table 1). Considering all ages, the SIR for brain tumours was increased when a parent was diagnosed with nervous system (1.71) thyroid gland (1.44) or colorectal (1.11) cancer or melanoma (1.27). Early onset (diagnosed before the age of 50 years) brain tumours were also associated with parental connective tissue tumours; however, all but two, parental connective tissue tumours were diagnosed after the age of 45 years, which is considered an upper age limit for Li–Fraumeni syndrome [18]. In addition to nervous system tumours, prostate cancer (1.45) and melanoma (1.34) were associated with brain tumours among siblings. Early onset cases were also associated with bladder and thyroid cancers.

Association of a specific subtype of brain tumour in the offspring with any parental cancer was then analysed (Table 2). Medulloblastoma in the offspring was increased when a parent was diagnosed with melanoma before the age of 50 years (SIR 3.33, footnote to Table 2). Neurinoma was associated with parental nervous system (1.78) and thyroid (2.53) tumours. Thyroid tumours were of the non-medullary type, diagnosed between ages 62 and 80 years. The seven affected individuals had 13 siblings, two of whom were diagnosed with breast cancer. Meningioma was associated with nervous system tumours (1.61) and early onset bladder cancers (4.00, footnote to Table 2). The risk for astrocytoma was increased in the offspring of parents diagnosed with nervous system tumours (1.85), melanoma (1.43) and endometrial cancers (1.37); the association with colorectal cancers was of borderline significance (1.12, 95% CI 0.98–1.29). Ependymoma was increased to 1.74 when a mother had breast cancer. Haemangioblastoma was particularly linked to renal cancer, SIR 3.21. Among the 8 haemangioblastoma patients, whose parents had a nervous system tumour (5 of them had haemangioblastoma), 1 had an insulinoma and another a renal cancer as a second neoplasm and a third patient

Table 1
SIR for brain tumours in offspring of parents or siblings with cancer

Cancer site in relatives	Parental proband									Sibling proband								
	Offspring age <50 year			Offspring and relatives age <50 year			All ages			Offspring age <50 year			Offspring and relatives age <50 year			All ages		
	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI
Upper aerodigestive tract	55	1.05	0.79–1.37	6	1.05	0.38–2.31	81	1.03	0.82–1.28	6	0.97	0.35–2.13	4	1.16	0.30–3.01	8	0.74	0.31–1.46
Oesophagus	19	1.13	0.68–1.77	2	3.20	0.30–11.76	29	1.10	0.74–1.58	1	0.84	0.00–4.80	1	3.10	0.00–17.76	3	1.31	0.25–3.86
Stomach	111	1.18	0.97–1.42	10	1.20	0.57–2.22	184	1.13	0.97–1.30	5	1.15	0.36–2.70	2	0.94	0.09–3.45	9	1.13	0.51–2.15
Colorectum	282	1.12	0.99–1.26	20	1.02	0.62–1.58	435	**1.11**	**1.01–1.22**	12	0.70	0.36–1.22	7	0.96	0.38–1.99	29	0.90	0.60–1.29
Liver	59	0.93	0.71–1.21	1	0.30	0.00–1.69	105	1.02	0.84–1.24	3	0.85	0.16–2.50	1	0.70	0.00–4.01	7	1.09	0.43–2.25
Pancreas	59	0.91	0.69–1.18	6	1.64	0.59–3.59	96	0.94	0.76–1.14	6	1.75	0.63–3.84				7	1.09	0.43–2.25
Lung	155	0.94	0.80–1.10	10	0.89	0.42–1.65	226	0.93	0.81–1.06	18	1.33	0.70–2.10	6	1.19	0.43–2.62	30	1.18	0.79–1.68
Breast	301	1.07	0.95–1.19	74	1.11	0.87–1.39	414	1.05	0.96–1.16	69	1.06	0.83–1.35	47	1.19	0.98–1.58	118	1.05	0.87–1.25
Cervix	43	0.79	0.57–1.06	26	0.85	0.56–1.25	62	0.81	0.62–1.04	17	1.23	0.72–1.98	16	1.26	0.72–2.05	21	1.02	0.63–1.56
Endometrium	74	1.20	0.94–1.51	5	0.81	0.26–1.91	105	1.18	0.96–1.43	13	1.72	0.91–2.94	5	2.17	0.68–5.10	17	1.12	0.65–1.79
Ovary	61	1.07	0.82–1.37	18	1.44	0.85–2.28	81	0.97	0.77–1.21	12	1.08	0.56–1.90	8	1.10	0.47–2.18	23	1.20	0.76–1.80
Prostate	296	0.98	0.97–1.10	1	0.85	0.00–4.89	485	1.04	0.95–1.14	23	**2.04**	**1.29–3.07**	1	1.77	0.00–10.14	36	**1.45**	**1.02–2.01**
Testis	10	1.27	0.61–2.35	7	1.19	0.47–2.46	11	1.25	0.62–2.24	12	1.32	0.68–2.31	11	1.24	0.61–2.22	15	1.28	0.71–2.11
Kidney	79	1.07	0.84–1.33	14	1.80	0.98–3.02	122	1.08	0.90–1.29	5	0.67	0.21–1.56	2	0.54	0.05–1.97	13	0.96	0.51–1.65
Urinary bladder	121	1.14	0.95–1.36	12	1.79	0.92–3.13	182	1.14	0.98–1.31	17	**1.83**	**1.06–2.94**	8	1.87	0.80–3.71	22	1.26	0.79–1.91
Melanoma	88	**1.25**	**1.00–1.54**	22	1.06	0.66–1.61	114	**1.27**	**1.05–1.53**	31	1.24	0.84–1.76	25	1.31	0.85–1.93	52	**1.34**	**1.00–1.76**
Skin, squamous cell	73	1.05	0.82–1.32	2	0.61	0.06–2.24	107	0.95	0.78–1.15	4	0.70	0.18–1.80				9	0.88	0.40–1.67
Nervous system	127	**1.71**	**1.43–2.04**	44	**2.21**	**1.60–2.97**	173	**1.71**	**1.46–1.99**	62	**2.47**	**1.89–3.16**	54	**2.78**	**2.09–3.63**	82	**2.16**	**1.72–2.68**
Thyroid gland	29	1.40	0.94–2.02	12	1.54	0.79–2.69	41	**1.44**	**1.03–1.96**	12	1.65	0.85–2.89	12	**1.94**	**1.00–3.40**	18	1.61	0.95–2.55
Endocrine glands	42	0.97	0.70–1.31	6	0.72	0.26–1.58	61	1.03	0.79–1.33	13	1.21	0.64–2.08	9	1.19	0.54–2.26	26	1.48	0.96–2.16
Connective tissue	25	**1.62**	**1.05–2.40**	4	1.14	0.30–2.96	31	1.40	0.95–1.98	4	1.03	0.27–2.66	3	0.98	0.18–2.90	8	1.38	0.59–2.73
Non-Hodgkin's lymphoma	69	1.03	0.80–1.31	5	0.60	0.19–1.41	98	1.02	0.83–1.24	13	1.04	0.55–1.78	6	0.79	0.28–1.73	22	1.03	0.65–1.56
Hodgkin's disease	7	0.58	0.23–1.19	3	0.58	0.11–1.72	12	0.69	0.36–1.22	5	0.84	0.27–1.98	5	0.90	0.28–2.11	9	1.13	0.51–2.15
Myeloma	21	0.64	0.40–0.99	2	0.97	0.09–3.56	39	0.76	0.54–1.04	1	0.38	0.00–2.18		0.00	0.91–3.70	4	0.80	0.21–2.07
Leukaemia	64	1.04	0.80–1.33	9	1.06	0.48–2.02	93	0.99	0.80–1.21	17	1.39	0.18–2.23	12	1.34	0.69–2.34	24	1.36	0.87–2.03
All	2269	**1.07**	**1.03–1.12**	321	**1.16**	**1.03–1.29**	3387	**1.07**	**1.03–1.11**	381	**1.29**	**1.16–1.43**	245	**1.35**	**1.18–1.53**	612	**1.22**	**1.13–1.32**

Bold type: 95% CI does not include 1.00. O, observed; SIR, standardised incidence ratio; CI, confidence interval.

Table 2
SIR for histological types of brain tumours in offspring of parents with cancer

	Medulloblastoma			Neurinoma			Meningioma			Astrocytoma			Ependymoma			Haemangioblastoma		
	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI
Upper aerodigestive tract	2	1.59	0.15–5.84	12	1.43	0.74–2.51	14	0.70	0.38–1.18	39	1.07	0.76–1.46	3	1.67	0.31–4.94	6	2.57	0.93–5.63
Oesophagus	0			4	1.41	0.37–3.63	5	0.72	0.23–1.60	14	1.16	0.63–1.94	1	1.74	0.00–9.98	1	1.29	0.00–7.42
Stomach	2	1.19	0.11–4.39	25	1.37	0.89–2.03	47	1.03	0.75–1.36	81	1.10	0.87–1.37	2	0.64	0.06–2.36	7	1.56	0.62–3.23
Colorectum	4	0.75	0.19–1.94	53	1.23	0.92–1.62	119	1.06	0.87–1.27	202	1.12	0.98–1.29	8	0.95	0.41–1.89	9	0.77	0.35–1.47
Liver	0			9	0.80	0.36–1.52	33	1.17	0.81–1.65	52	1.12	0.83–1.46	2	0.96	0.09–3.52	3	0.99	0.19–2.93
Pancreas	1	0.81	0.00–4.66	6	0.53	0.19–1.16	31	1.12	0.76–1.58	40	0.86	0.61–1.17	1	0.48	0.00–2.73	3	1.01	0.19–2.98
Lung	1	0.27	0.00–1.56	19	0.73	0.44–1.15	56	0.91	0.69–1.18	121	1.07	0.89–1.28	3	0.53	0.10–1.57	6	0.80	0.29–1.76
Breast	8	0.90	0.39–1.79	47	1.17	0.86–1.55	98	1.06	0.86–1.30	184	1.01	0.87–1.17	18	**1.74**	**1.03–2.76**	13	0.99	0.52–1.69
Cervix	1	0.63	0.00–3.59	6	0.77	0.28–1.69	17	0.94	0.54–1.50	25	0.71	0.46–1.05	2	1.02	0.10–3.75	0	0.00	0.38–1.55
Endometrium	0			16	1.66	0.95–2.70	20	0.88	0.54–1.36	56	**1.37**	**1.04–1.78**	1	0.50	0.00–2.88	1	0.33	0.00–1.91
Ovary	3	2.06	0.39–6.10	8	0.91	0.39–1.80	25	1.21	0.78–1.78	39	1.02	0.72–1.39	1	0.50	0.00–2.89	1	0.36	0.00–2.08
Prostate	4	0.68	0.18–1.76	47	0.92	0.68–1.22	144	1.16	0.98–1.37	225	1.04	0.91–1.19	13	1.34	0.71–2.29	11	0.83	0.41–1.50
Testis	2	3.77	0.36–13.88	2	3.20	0.30–11.76	0			2	0.46	0.04–1.70	2	4.86	0.46–17.86	0		
Kidney	3	1.80	0.34–5.34	14	1.15	0.63–1.94	25	0.85	0.55–1.26	56	1.08	0.82–1.41	2	0.81	0.08–2.97	11	**3.21**	**1.60–5.77**
Urinary bladder	3	1.30	0.24–3.84	19	1.10	0.66–1.72	43	1.03[a]	0.75–1.39	88	1.19	0.96–1.47	6	1.67	0.60–3.65	4	0.85	0.22–2.19
Melanoma	6	2.12[b]	0.76–4.63	7	0.83	0.33–1.71	19	1.04	0.62–1.62	61	**1.43**	**1.09–1.83**	5	1.78	0.56–4.19	2	0.68	0.06–2.49
Skin, squamous cell	0			12	0.95	0.49–1.67	27	0.88	0.58–1.28	53	1.03	0.77–1.35	1	0.43	0.00–2.48	5	1.56	0.49–3.66
Nervous system	3	1.21	0.23–3.57	18	**1.78**	**1.06–2.83**	37	**1.61**	**1.13–2.22**	88	**1.85**	**1.49–2.28**	4	1.43	0.37–3.60	8	**2.44**	**1.04–4.83**
Thyroid gland	1	1.33	0.00–7.63	7	**2.53**	**1.00–5.23**	5	0.78	0.25–1.84	21	1.58	0.98–2.42	1	1.21	0.00–6.95	0		
Endocrine glands	1	0.76	0.00–4.38	3	0.50	0.09–1.48	16	1.16	0.66–1.89	26	0.94	0.61–1.38	0			2	1.02	0.10–3.75
Connective tissue	1	2.22	0.00–12.75	1	0.43	0.00–2.49	4	0.74	0.19–1.91	13	1.26	0.67–2.17	2	3.59	0.34–13.20	1	1.47	0.00–8.43
Non-Hodgkin's lymphoma	2	1.10	0.10–4.04	9	0.89	0.41–1.71	24	1.02	0.65–1.52	44	0.98	0.71–1.32	3	1.28	0.24–3.80	6	2.01	0.72–4.39
Hodgkin's disease	0			1	0.59	0.00–3.39	0			9	1.12	0.51–2.13	0			1	1.91	0.00–10.95
Myeloma	0			5	0.89	0.28–2.09	18	1.31	0.77–2.07	12	0.51	0.26–0.89	0			1	0.65	0.00–3.75
Leukaemia	1	0.67	0.00–3.85	10	0.99	0.47–1.83	22	0.91	0.57–1.37	38	0.88	0.62–1.20	5	2.34	0.74–5.49	3	1.08	0.20–3.20
All	49	0.94	0.70–1.25	360	1.06	0.96–1.18	840	1.04	0.97–1.11	1589	**1.09**	**1.03–1.14**	86	1.18	0.94–1.45	105	1.09	0.89–1.32

Bold type: 95% CI does not include 1.00. O, observed; SIR, standardised incidence ratio; CI, confidence interval. [a] Parent <50 year, SIR 4.00 ($N=4$, 95% CI 1.04–10.35). [b] Parent <50 year, SIR 3.33 ($N=5$, 95% CI 1.05–7.84).

had a sibling with paraganglioma. The affected offspring were diagnosed between the ages of 12 and 32 years.

We considered all the significant associations from Table 2 in the reverse order, i.e. SIR for parental brain cancer when their offspring were diagnosed with cancer at the sites of interest (data not shown). Ependymoma in parents and breast cancer in offspring was found only for one pair was also found for neurinoma in parents and thyroid cancer in offspring. For the parental medulloblastoma– offspring melanoma combination, no cases were found. SIR for parental meningioma was 1.24 (19, 95% CI 0.74–1.94) when offspring had bladder cancer. SIRs for parental astrocytoma were 0.93 (18, 95% CI 0.55–1.47) and 1.13 (70, 95% CI 0.88–1.42) when the offspring were diagnosed with endometrial cancer and melanoma, respectively.

Risks between siblings are given in Table 3. Only 3 patients with medulloblastoma had a sibling with different cancers and the data are not shown. Neurinoma was associated with sibling testicular (4.34) and endocrine (3.63) tumours and with myeloma (5.28). Among testicular cancers, three were seminomas and two teratomas, diagnosed between the ages of 23 and 58 years; neurinomas were diagnosed between the ages of 22 and 53 years. Among the endocrine tumours, six were parathyroid adenomas and one a thymic carcinoid tumour. Sibling cervical cancer and nervous system tumours were associated with offspring meningioma; early onset meningioma was also increased when a sibling had pancreatic cancer. Astrocytoma associated with prostatic (1.73) and nervous system neoplasms, and early onset cases also with early onset endometrial cancer. Few ependymoma and haemangioblastoma cases were found; however, 5 ependymoma patients had a sibling with breast cancer (2.40, 95% CI 0.76–5.64).

4. Discussion

This type of study is characterised by many comparisons, 25 cancer sites, six histologies, two groups of probands and different age groups. Thus, spurious associations are bound to occur. However, curiously only three SIRs were significantly decreased, compared with 44 significantly increased ones (among those shown in Tables 1–3). Among the recommended ways of sorting out chance findings; repetition, consistency with previous findings and biological plausibility, the options are limited because of a lack of independent data in the literature and understanding of the carcinogenic mechanisms involved. The comparison of the results obtained through parental and sibling probands are helpful, but age differences and the possibility of recessive effects, which would increase risks only among siblings, affect such comparisons. All the tabulated data show offspring brain cancer risks when the parents had any cancer. In cases of positive findings, the comparison was reversed, and parental brain cancer was analysed when the offspring presented with the cancer of interest. This was a completely independent analysis and the results were, in some cases, useful in judging the original findings. Below, we do not discuss the concordant nervous system tumours because a separate publication is currently being prepared. The results for brain cancer in families were in-line with previous publications [10,11,19–24].

The present analysis identified some known cancer syndromes affecting the brain. The association of brain haemangioblastoma with renal cancer is one of the hallmarks of von Hippel–Lindau disease. The diagnosis was further confirmed through pathognomonic second tumours in haemangioblastoma patients and tumours in the siblings [25,26]. Other associations are only suggestive, such as early onset brain cancer and parental connective tissue tumours relating in a small degree to Li–Fraumeni syndrome, neurinoma and parental endocrine gland tumours relating to neurofibromatosis 1, astrocytoma and parental endometrial cancer relating to HNPCC and Turcot syndrome, and neurinoma and parental thyroid cancer in families of breast cancer probably relating to Cowden's syndrome [6]. Association of astrocytoma and melanoma may be related to *p16* mutations, which are also important in sporadic astrocytoma [6,27,28]. The association has also been observed in our previous study and in a Finnish study [11,12].

The increase of ependymoma in offspring of mothers with breast cancer has been observed in our previous analysis and it was supported to some extent by the SIR of 2.40 (95% CI 0.76–5.64) in siblings [11]. The other associations found between offspring and parents, medulloblastoma–melanoma (only early onset melanoma) and meningioma–urinary bladder (early onset urinary bladder) could not be confirmed when the comparison was reversed or when sibling risks were analysed, and they remain tentative. Among siblings, five associations were significant, without considering age-specific findings. Neurinoma was associated with parental testicular cancer and with myeloma. There is no possibility to exclude chance findings in these cases, except that our published analysis of testicular cancer found a significant association between seminoma and nervous system tumours [29]. The associations between meningioma and cervical cancer and astrocytoma and prostate cancer remain tentative. Our data provide no support on the suggested association of meningioma and breast cancer [30].

In summary, the present analysis was based on medically-verified cancers from the Swedish Cancer Registry. Among complex brain tumours several associations to relatively rare known syndromes could be detected.

Table 3
SIR for histological types of brain tumours in offspring whose sibling has cancer

Cancer site in relatives	Neurinoma			Meningioma			Astrocytoma			Ependymoma			Haemangioblastoma		
	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI
Upper aerodigestive tract	0			3	0.96	0.18–2.85	4	0.82	0.21–2.11	0			0		
Oesophagus	0	2.22	0.21–8.16	0			2	1.95	0.18–7.18	0			0		
Stomach	2	1.36	0.43–2.20	1	0.43	0.00–2.45	5	1.39	0.44–3.26	0			0		
Colorectum	5			3	0.31	0.06–0.92	17	1.17	0.68–1.88	2	3.55	0.33–13.0	1	1.21	0.00–6.95
Liver	0			1	0.54	0.00–3.07	4	1.38	0.36–3.57	1	8.33	0.00–47.77	0		
Pancreas	0			5	2.61[a]	0.82–6.15	2	0.69	0.07–2.54	0			0		
Lung	5	1.72	0.54–4.05	12	1.58	0.81–2.76	9	0.79	0.36–1.50	0			2	3.09	0.29–11.35
Breast	15	1.18	0.66–1.95	32	0.98	0.67–1.39	48	0.94	0.69–1.25	5	2.40	0.76–5.64	5	1.65	0.52–3.87
Cervix	1	0.45	0.00–2.59	13	**2.42**	**1.29–4.16**	6	0.63	0.23–1.38	0			0		
Endometrium	3	1.72	0.32–5.08	5	1.07	0.34–2.52	7	1.03[b]	0.41–2.14	0			0		
Ovary	2	0.94	0.09–3.45	6	1.10	0.40–2.41	12	1.38	0.71–2.42	0			1	1.93	0.00–11.04
Prostate	4	1.39	0.36–3.59	9	1.15	0.52–2.19	19	**1.73**	**1.04–2.71**	0			1	1.78	0.00–10.19
Testis	5	**4.34**	**1.37–10.21**	2	0.79	0.07–2.89	5	0.89	0.28–2.10	1	2.95	0.00–16.89	0		
Kidney	2	1.35	0.13–4.95	2	0.52	0.05–1.91	7	1.15	0.46–2.38	0			0		
Urinary bladder	2	1.01	0.10–3.71	6	1.15	0.42–2.53	9	1.15	0.52–2.19	0			1	2.25	0.00–12.90
Melanoma	5	1.19	0.38–2.81	17	1.65	0.96–2.65	22	1.23	0.77–1.87	1	1.18	0.00–6.75	3	2.63	0.50–7.79
Skin, squamous cell	1	0.87	0.00–4.98	2	0.67	0.06–2.48	5	1.08	0.34–2.53	0			0		
Nervous system	7	1.79	0.71–3.72	18	**1.96**	**1.16–3.10**	37	**2.10**	**1.48–2.89**	3	3.02	0.57–8.93	2	1.74	0.16–6.41
Thyroid gland	0			7	2.39	0.95–4.95	8	1.55	0.66–3.08	0			1	3.04	0.00–17.42
Endocrine glands	7	**3.63**	**1.44–7.53**	4	0.83	0.22–2.14	11	1.37	0.68–2.46	1	2.73	0.00–15.67	1	2.03	0.00–11.66
Connective tissue	0			2	1.40	0.13–5.14	5	1.85	0.58–4.36	0			0		
Non-Hodgkin's lymphoma	4	1.73	0.45–4.46	3	0.51	0.10–1.51	9	0.93	0.42–1.77	1	2.26	0.00–12.93	2	3.46	0.33–12.73
Hodgkin's disease	1	1.29	0.00–7.39	0			6	1.59	0.57–3.48	0			0		
Myeloma	3	**5.28**	**1.00–15.63**	1	0.67	0.00–3.84	0			0			0		
Leukaemia	2	1.18	0.11–4.33	4	0.99	0.26–2.56	14	1.70	0.93–2.86	0			1	1.93	0.00–11.06
All	76	**1.38**	**1.09–1.73**	158	1.13	0.96–1.32	273	**1.20**	**1.06–1.35**	15	1.48	2.45	21		0.95–2.35

Bold type: 95% CI does not include 1.00. O, observed; SIR, standardised incidence ratio; CI, confidence interval. [a] Offspring <50 year, SIR 4.21 ($N=4$, 95% CI 1.10–10.90). [b] Both <50 year, SIR 4.15 ($N=4$, 95% CI 1.08–10.73).

These findings indicate the usefulness of the approach. Among as yet unknown associations, clustering of ependymoma and breast cancer and neurinoma and testicular cancer, and other entirely new findings, await confirmation from other sources.

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