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Neoplasms of the central nervous system in Norway

V. Meningioma and cancer of other sites. An analysis of the occurrence of multiple primary neoplasms in meningioma patients in Norway from 1955 through 1986

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The association between meningioma and a primary malignant neoplasm at another site was studied. The data from the population-based Norwegian Cancer Registry were analysed according to whether the meningioma occurred before or after the malignant neoplasm. Male patients with meningioma showed a raised risk for developing a subsequent renal cancer. A significant association was found between meningioma and subsequent breast cancer in females 50-64 years old at time of meningioma diagnosis and between breast cancer and subsequent occurrence of meningioma. Breast cancer patients with symptoms of an intracranial neoplasm may therefore have a potentially curable meningioma and female meningioma patients over 50 years should be considered for breast cancer screening programmes.

Key words: Meningioma; renal cancer; breast cancer; multiple primary cancers.

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All benign and malignant tumours of the central nervous system (CNS) in Norway are reported to the National Cancer Registry. About 21% of all histologically verified CNS tumours are meningiomas (14). The cytogenetics of meningiomas have been extensively studied (1) and interesting karyotype abnormalities on chromosome 22 have been found (1, 5). The association between loss of chromosomal material and tumourigenesis fits the concept of tumour suppressor genes. The chromosomal alterations could imply a genetic predisposition that may be of importance for tumourigenesis in a broader context. An analysis of the occurrence and risk of multiple neoplasms in meningioma patients may contribute to a clarification of the question. An association between meningiomas and breast cancer was first described by *Schoenberg et al.* (22) and confirmed for breast cancer with subsequent meningioma by Emry (8). A total of 67 breast cancer patients with subsequent meningioma have been reported up to 1986 (4, 8). A predisposition to develop breast cancer as the second tumour has not been established in meningioma patients (6, 8). We present the results of an investigation into the occurrence of meningiomas and coincident cancers in the total Norwegian population from 1955 through 1986.

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PATIENTS AND METHODS

In general, meningiomas are treated by surgery alone, whereas irradiation and cytostatics are often part of the treatment of malignant neoplasms. Since a causal relationship between exposure to irradiation/cytostatics and later development of meningioma cannot be excluded, it is necessary to analyse the data according to whether the malignant tumour occurred before or after the meningioma. With meningioma as the second neoplasm, analysis primarily was delimited to breast cancer

for which a significant association had been reported previously (8). A considerable number, up to 35% (12, 18) of all meningiomas are asymptomatic and are found at autopsy.

The number of neoplasms that one would expect to observe in a defined cohort was calculated via a computer program by multiplying the age-, sex- and calendar specific incidence rate by the belonging number of person-years at risk. The end of the follow-up period was determined by death, emigration or end of the study period on December 31, 1986. The ratio of observed to expected tumours was then computed. A Poisson distribution was assumed valid for the observed numbers when presenting confidence intervals (CI) for the relative ratio (RR) between observed and expected numbers. Each primary neoplasm is registered according to month and year of diagnosis in the Cancer Registry and the time lapse between multiple neoplasms was computed.

All patients with a malignant tumour diagnosed one month or more before a meningioma were selected from the data-base and tabulated according to the site of the first tumour. In addition, female breast cancer patients (n = 42,414) were matched with the data-base in order to detect the occurrence of subsequent meningiomas. The observed number was compared with the computed expected value.

Altogether 1632 meningioma patients were registered in the data-base. Patients for whom the diagnosis was first established at autopsy were excluded (n = 271), leaving 454 males and 907 females for further study. These cohorts were matched with the data-base and malignant neoplasms diagnosed subsequently were identified and added to the file. One of the female patients developed bilateral breast cancer, 67 (left side) and 102 months (right side) after the meningioma was diagnosed. Both were adenocarcinomas with metastases to the axillary lymph nodes of the same side.

RESULTS

Malignant tumour first

Ninety-five malignant neoplasms preceded meningioma (Table 1). Except for breast cancer, no marked clustering of tumours was apparent when

TABLE 1. *Number of malignant neoplasms preceding meningiomas according to localisation, sex and clinical status of the meningioma*

	Female		Male	
Cancer localisation	Symptomatic meningioma	Asymptomatic[1] meningioma	Symptomatic meningioma	Asymptomatic[1] meningioma
Lip	0	0	1	0
Pharynx	0	0	1	1
Stomach	0	1	0	1
Intestines	0	1	0	0
Colon	2	0	1	2
Rectum	0	1	0	2
Pancreas	0	1	0	1
Nose, sinuses	1	0	0	0
Lung	1	5	0	4
Breast	12	9	–	–
Cervix uteri	1	3	–	–
Corpus uteri	0	3	–	–
Prostate	–	–	2	7
Testis	–	–	1	1
Kidney	1	2	0	0
Bladder	0	1	1	2
Melanoma	3	1	1	3
Skin[2]	0	0	2	1
Eye	0	1	0	0
Nervous system	1	1	3	0
Thyroid	0	2	0	0
Bone/cartilage	0	1	0	0
Lymphoma	0	0	0	1
Uncertain	1	0	0	0
	23	33	13	26

[1] Found at autopsy ("incidental")
[2] Melanoma not included

TABLE 2. *Observed (obs) and expected (exp) number of meningiomas and breast cancers and relative ratios by order and age, 1955-86*

First tumour	Age	Second tumour	Obs	Exp	Relative ratio (95% CI)	Person-years
Breast cancer	00-49	Meningioma	4	3.61	1.11 (0.30–2.84)	97,398
	50–64		10	4.95	2.02 (0.97–3.72)	112,505
	65 +		7	3.43	2.04 (0.82–4.20)	96,408
	All		21	11.99	1.75 (1.08–2.68)	306,311
Meningioma	00–49	Breast	5	4.05	1.23 (0.40–2.88)	3,550
	50–64	cancer	13	6.76	1.92 (1.02–3.29)	3,932
	65 +		4	3.45	1.16 (0.32–2.97)	1,593
	All		22	14.26	1.54 (0.97–2.34)	9,075

the meningioma was diagnosed as a result of clinical symptoms. The time lapse between the diagnoses of the two neoplasms was shorter than 3 years in 50% of the cases.

Of the 42,414 females registered with breast cancer, 21 later developed a histologically verified meningioma as opposed to the expected number of 11.99 (Table 2). The corresponding relative ratio of 1.75 represents a statistically significant increased risk of meningioma occurrence in breast cancer patients. The mean time lapse was 86.5 months (SD: 86.9) with a range from 4 months to 26 years. Nine of the meningiomas were incidental findings at autopsy. The autopsy frequency according to age for female breast cancer patients that died during the period 1975-1977 (n = 2,807) is given in Table 3. It is evident that there is a lower autopsy rate in these patients than in the general population (9).

Meningioma first

One hundred and nineteen neoplasms occurred subsequently in the cohort of meningioma patients. Table 4 gives the observed and expected numbers according to the site of the second primary. The time lapse between the diagnosis of meningioma and renal cancer in males was 5 months or less in four patients and three and thirteen years in the other two patients. Two of the five thyroid cancers in females were found in one patient. The diagnosis of follicular carcinoma was made after a hemi-thyroidectomy. The other lobe was resected and an occult papillary carcinoma was found. The meningioma and the thyroid cancer were discovered simultaneously in another patient. When these two patients are deducted, the relative ratio is no longer significantly increased.

TABLE 3. *Autopsy rates in all deceased female breast cancer patients (1975–77) according to age at death. The general autopsy rate in Norway is given in brackets*

Age (years)	Autopsy rate
< 50	18% (30%)
50–69	11% (18%)
70–79	9% (13%)
80+	5% (6%)
Total	11% (14%)

Table 2 also shows the coincidence of meningioma and breast cancer. Twenty-two histologically verified breast cancers occurred subsequently in the meningioma patients as opposed to the expected number of 14.26, the relative ratio of 1.54 for the total group approaching statistical significance with regard to an increased risk of developing breast cancer in meningioma patients (p = 6.8%). The relative ratio for the age-group 50-64 years is statistically significant (p = 4.2%). The mean time lapse was 67.7 months (SD: 54.9) with a range from 10 months to 18 years.

Renal cancer and meningioma

The possibility that renal cancer patients develop meningioma was then assessed. For females (n = 4,262) three subsequent meningiomas were registered, compared with an expected number of 0.66 (relative ratio 4.55 with 95% confidence interval 0.94-13.29). No meningiomas occurred in males (n = 6,391; expected 0.57).

TABLE 4. *Observed (obs) and expected (exp) numbers and relative ratios (RR) of subsequent cancers in meningioma patients by site*

Cancer localisation	Female			Male		
	Obs	Exp	RR[1]	Obs	Exp	RR[1]
Lip	0	0.10	–	2	0.53	3.77
Tongue	1	0.19	–	0	0.14	–
Stomach	2	4.59	0.44	3	3.45	0.87
Colon	6	6.76	0.89	4	2.90	1.38
Rectum	4	3.19	1.25	1	2.01	–
Liver	1	0.34	–	0	0.28	–
Gall bladder	0	0.72	–	1	0.20	–
Pancreas	4	2.31	1.73	1	1.42	–
Lung	1	2.32	–	3	4.64	0.65
Pleura	0	0.03	–	1	0.11	–
Breast	22	14.26	1.54	0	0.05	–
Cervix uteri	2	2.99	0.67	–	–	
Corpus uteri	5	3.46	1.45	–	–	
Ovary	3	3.96	0.76	–	–	
Prostate	–	–		11	7.76	1.42
Penis	–	–		1	0.14	–
Kidney	3	1.60	1.88	6	1.26	4.76[2]
Urinary bladder	2	1.84	1.09	3	2.63	1.14
Melanoma	2	1.80	1.11	3	0.70	4.29
Nervous system	3	1.44	2.08	1	0.71	–
Thyroid	5	0.87	5.75[2]	0	0.17	–
Soft tissue	1	0.32	–	0	0.19	–
Lymphoma	3	1.64	1.83	1	0.96	–
Leukemia	1	1.40	–	1	0.90	–
Uncertain	2	3.44	0.58	3	1.59	1.89
Other	0	5.12	–	0	3.74	–
Total	73	64.69	1.13	46	36.48	1.26

[1] RR is not shown if observed number ≤ 1
[2] $p < 0.05$

DISCUSSION

Epidemiological cancer research in Norway profits from having had a National Cancer Registry since 1952 and a defined population in which individuals are identified by a personal number. In addition to a virtually complete registration of all solid malignant neoplasms, benign tumours affecting the nervous system and endocrine organs are also reported. Meningiomas are among the few benign tumours available in the Cancer Registry for epidemiological coincidence studies.

Multiple primary neoplasms

A common determinant may be active in a patient with two or more primary neoplasms. A minority belong to "cancer families", which implies that there is a strong genetic disposition for cancer. Other patients develop more than one primary neoplasm by statistical coincidence. Treated cancer patients have at least the same risk of developing a new primary as others. Additionally, exposure to cancer determinants could for some of the patients have increased their risk of a second primary neoplasm. Also, the number of multiple tumours in a community to a certain extent must reflect the diagnostic opportunities and investigation resources available. The level of patient costs for medical services and the autopsy rate are both factors that are likely to cause variation in the recognition of multiple primary neoplasms.

A causal relationship between the treatment of the first cancer (e.g. cytostatics and irradiation) and the genesis of the second should be considered. This relationship constitutes a source of confusion when the aim of a study is to reveal etiological

factors of importance for both neoplasms. In this series, the coincidence of meningioma, a benign tumour, with malignant tumours is analysed. It was therefore necessary to define the cohorts according to the nature of the first neoplasm.

Coincidence studies of meningiomas demand special attention with regard to: i) differences in autopsy rates between the group of patients under study and the total population, and ii) the diagnostic sensitivity at autopsy to small intracranial tumours. Three neoplasms are known to have a propensity for brain metastasis, bronchogenic carcinoma, breast cancer and malignant melanoma (24). It is possible that the pathologist is more alert when examining the intracranial contents in these patients.

Meningioma and renal cancer

After deduction of two cases with thyroid cancer, significantly increased relative ratios were found for one age-group of female breast cancer patients and for renal cancer in males. A Danish study of 10,723 persones with *all types* of tumours of the nervous system found a significantly increased risk for subsequent cancer of *the kidney*, tumours of connective tissue and melanoma (29). A similar study of 3,744 individuals developing brain cancer in the period 1935-1982 in Connecticut (USA) found an excess of malignant melanoma and acute leukemia as second primary neoplasms (26). In the Connecticut study, however, benign intracranial tumours, e.g. meningiomas, were not included (3). To our knowledge, the present study is the first report of a significantly increased risk of renal cell carcinoma in *meningioma patients*.

Some determinants seem to be common to both meningioma and renal cancer: Meningioma (10) and renal cell carcinoma (23, 19) both express estrogen receptor protein. Monosomy or deletion of parts of chromosome 22 is frequently found in meningiomas and it is proposed that loss of a tumour supressor gene (emerogen) distal to the myoglobin locus on chromosome 22 may be the mechanism involved (7). In renal cell carcinomas loss of alleles on the short arm of chromosome 3 has been demonstrated (17, 25, 28). These deletions are of special interest since an oncogene, c-raf 1, has been located to this region. A structural shift of the c-raf 1 locus to the breakpoint region may alter the expression of the gene (25). Though the genetic sequences involved are dissimilar, both tumours characteristically may have a deletion at a fragile chromosomal site. Data from case-control studies have been compared as regards risk factors. In meningiomas, exposure of the head to therapeutic and diagnostic X-ray, head trauma and nitrites in the food were associated with increased risk in females (20), whereas the former two were revealed in a similar study of male meningioma patients (21). The development of renal cell carcinomas is related to cigarette smoking in case-control and cohort studies conducted on males (27). Obesity, generally, is a significant risk factor (11, 27) and in females diuretics and coffee have been suggested as additional risk factors (27). *Hofman et al.* (15) suggest that the association between smoking and renal cell carcinoma may imply a role of N-nitrosamines in the etiology of the disease. Nitrosamines may emerge as a common risk factor for both meningioma and renal cell carcinoma, although so far only reported for *female* meningioma patients. Renal cell adenomas have also been associated with cigarette smoking (2).

Breast cancer and meningioma

Normal and neoplastic meningeal cells contain receptors for various signal substances including female sex hormones. The biological relevance of the latter in the tumourigenesis of meningiomas is unclear, but they have been linked to the female preponderance of meningiomas. Hormones play an active role in some tumour types, e.g. cancers of the breast, uterine body, ovary and prostate. It is important to note that the meningioma patients in the present study did not show a statistically significant increase or decrease in risk for these cancer types, with one exception, breast cancer patients 50-64 years of age. In a recent study (16), 5 out of 117 female meningioma patients had a combination of intracranial meningioma, breast cancer and genital cancer which the authors propose is a unique combination of neoplasms in women. In this series we found only 2 patients with this combination.

In this study, female meningioma patients 50-64 years of age have a statistically significant increased relative ratio for breast cancer (RR = 1.66) (Table 2). *Emry* (8) did not find an increased risk for breast cancer in meningioma patients. However, the study did not have follow up data at the individual level, in contrast to the situation in Norway. This seems particularly important in the case of benign tumours with good survival prospects.

Patients with breast cancer have a significantly increased risk of developing a meningioma. Our data indicate that the risk is higher for those 50 years and over at the time of breast cancer diagnosis. Nine of 21 of the meningiomas were incidental findings at autopsy. We have documented that breast cancer patients have a reduced autopsy rate (Table 3). Our results then imply either that silent meningiomas are even more common among breast cancer patients than revealed in this study and are therefore of interest for the understanding of tumourigenesis, or that the diagnostic sensitivity for intracranial neoplasms at autopsy is higher for breast cancer patients, or a combination of these factors. The mean time lapse between the breast cancer and the meningioma was 86.5 months (SD = 86.9) in the present study compared to a mean value of 40.4 months (SD = 31.8) reported by *Emry* (8). In terms of a possible causal relationship between the diagnostic procedures and treatment of breast cancer and the development of a subsequent meningioma, the latent period is rather short. It is, however, possible that some of the patients with incidental meningiomas would have developed symptoms if they had lived longer. A causal relationship should therefore not be excluded.

CONCLUSIONS

Our results add to the weight of evidence that there is an association between breast cancer and meningioma. Male meningioma patients have a significantly increased risk of developing renal cancer.

The clinical implications of this are that breast cancer patients with symptoms of an intracranial neoplasm may have a potentially curable meningioma and that female meningioma patients over 50 years should be offered breast cancer screening programmes.

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