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Risk of Meningioma after CT of the Head[1]

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Purpose: To investigate the association between exposure to head computed tomography (CT) and subsequent risk of meningioma.

Materials and Methods: The study was approved by the local ethics committee. A cohort of 26 370 subjects was retrospectively collected from a radiology archive of CT examinations of the head performed from 1973 through 1992. For comparison, an age- and sex-matched cohort of 96 940 subjects who were not exposed to CT (unexposed cohort) was gathered. The risk of meningioma was assessed by using data from the Swedish Cancer Registry; however, one-third of patients with meningioma had to be excluded because they either had a prevalent meningioma or other brain tumor at the first CT examination or had undergone radiation treatment to the head. Hazard ratios (HRs) were calculated from time of exposure to the occurrence of meningioma or death or until December 31, 2010, with logistic regression.

Results: Comparison of exposed and unexposed cohorts showed that there was no statistically significant increase in the risk of meningioma after exposure to CT of the head (HR: 1.49; 95% confidence interval: 0.97, 2.30; $P = .07$). If incident cases at the time of the first CT examination were not excluded, the risk of meningioma would have been falsely increased (HR: 2.28; 95% confidence interval: 1.56, 3.33; $P = .0001$).

Conclusion: When prevalent cases of meningioma at first exposure to CT of the head are excluded, no statistically significant increase in risk of meningioma was found among exposed subjects compared with unexposed control subjects.

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Computed tomography (CT) has been a great aid in medical care since its introduction in the early 1970s. Owing to the relatively high doses of ionizing radiation delivered during each CT examination compared with conventional radiographic examinations, in combination with the increased use of CT, there are concerns about the long-term risk of cancer (1).

A large part of what is known about the association between exposure to ionizing radiation and risk of cancer comes from studies of atomic bomb survivors from Hiroshima and Nagasaki (2–4). The findings of those studies suggest that exposure to radiation within the range of what is normally received during a CT examination may increase the risk of cancer (5). In more recent studies, exposure from CT examinations has been associated with an increased risk of leukemia and brain cancer (6,7). Studies examining the link between radiation and intracranial tumors have shown meningioma to be more likely to develop than other brain tumors (8). Because meningioma is the most common brain tumor and because CT of the head is one of the most common CT examinations, investigation of meningiomas may be useful to assess tumor risk from CT examinations (1,9).

Advances in Knowledge

- In a cohort of 18 388 subjects exposed to CT of the head and a control cohort of 63 664 unexposed control subjects, no statistically significant difference in risk of meningioma was found (hazard ratio: 1.49 for exposed vs unexposed subjects; 95% confidence interval: 0.97, 2.30; $P = .07$).
- Without knowledge of information in referral notes and radiology reports, the risk of meningioma after exposure to CT of the head would have been overstated because many cases of meningioma prevalent at the first CT examination were included in the cancer registry up to more than 10 years later.

We investigated the association between CT of the head and risk of meningioma in a cohort of more than 123 000 subjects followed up for up to 37 years, 26 370 of whom were exposed during CT of the head in the 1970s and 1980s.

Materials and Methods

Setting

This retrospective study was approved by the local ethics committee. The requirement to obtain informed consent was waived. The first CT scanner in Sweden was installed in the Department of Neuroradiology at Karolinska University Hospital in Stockholm. The machine (EMI Mark I; EMI X-ray Systems Division, Hayes, England) was used from 1973 to 1985. A second CT scanner (GE 8800; GE Medical Systems, Milwaukee, Wis) was installed in 1979 and used until 1992. At that time, all referrals for CT were written by physicians on forms that produced several carbon copies. Although images from the CT examinations have been discarded, the Department of Neuroradiology has saved one of the carbon copies of the report in an archive. From these archived reports, we retrieved the patient's name, surname, personal identity number, date of birth, date of examination, examination type (including anatomic region and use of contrast material), and medical reason for the examination. Data were prepared by A.C.N. (with 7 years of experience).

National Registries

Every Swedish citizen is assigned a personal identity number that is used for all official identification and health care documents. The personal identity number enables linkage of information from hospital-based databases to national health care registries (10). Statistics Sweden, a government organization that collects and organizes census data, provided us with up to four unexposed control subjects for each patient in our exposed cohort; control subjects were matched with regard to sex, age, and residence at time of first examination. The National Board of Health and Welfare in Sweden is responsible for collating data from health care providers into national registries. For this study, we used data from both exposed subjects and their control subjects (unexposed cohort) regarding cancer diagnoses, deaths, and reasons for in-hospital visits in the cancer registry, the causes of death registry, and the patient registry, respectively.

Gamma Knife Registry

A Leksell gamma knife has been in use at the Department of Neurosurgery at Karolinska University Hospital since 1967, and an electronic registry of patients treated with a gamma knife from 1982 and onward exists. In our cohort of CT-exposed patients, 599 were also included in the Gamma Knife Registry and excluded at the time of treatment.

Study Population

The study population consists of patients living in Sweden who were examined at the Department of Neuroradiology at Karolinska University Hospital from 1973 through 1992. The radiology archive included 53 232 reports in 35 095 patients. Of these patients, 6488 (18.5%) were not eligible for the study—3952 (60.9%) because of a faulty personal identity number and 2536 (39.1%) because it was unclear if the patient had undergone a CT examination of the head or another body part—leaving 28 607 patients eligible for the study. We subsequently

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Abbreviation:
HR = hazard ratio

Author contributions:
Guarantors of integrity of entire study, A.C.N., M.K.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, A.C.N., R.B., M.K.; clinical studies, A.C.N.; statistical analysis, A.C.N., M.K.; and manuscript editing, all authors

Conflicts of interest are listed at the end of this article.

Figure 1

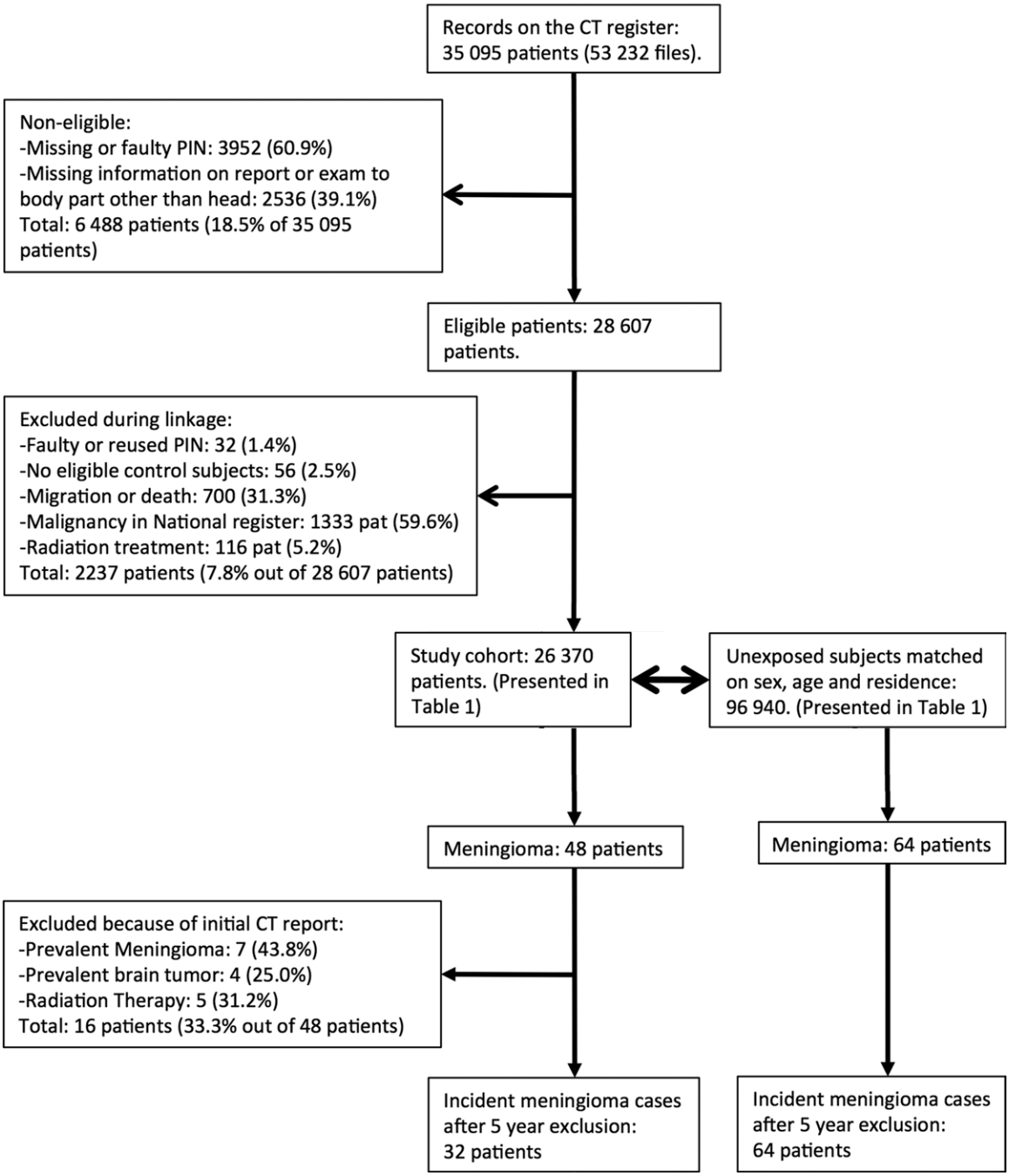

Figure 1: Flowchart of creation of study cohort. Flowchart shows information from initial radiology archives and steps taken until initial study cohort was in place, as well as reasons for exclusion of patients at each step. *pat* = patient.

collected data on migration, vital status, and outcome variables through Statistics Sweden, the National Board of Health and Welfare from the Swedish Cancer Registry, and the Sweden National Patient Register, respectively. After hospital data were linked to national registries, 2237 of the 28 607 patients (7.8%) were excluded—32 of the 2237 patients (1.4%) because of a faulty or reused personal identity number, 56 (2.5%) because of lack of eligible control subjects, 700 (31.3%) because of emigration or death, 1333 (59.6%) because malignancy was

Table 1

Characteristics of the Initial Study Population

Characteristic	Exposed Cohort	Unexposed Cohort
Total population*	26 370 (21.39)	96 940 (78.61)
Sex		
M	13 814 (52.39)	50 346 (51.94)
F	12 556 (47.61)	46 594 (48.06)
Time period for inclusion in cohort		
1973–1975	1005 (3.81)	3964 (4.09)
1976–1980	4228 (16.03)	16 409 (16.93)
1981–1985	8737 (33.13)	32 934 (33.97)
1986–1990	10 219 (38.75)	36 193 (37.34)
1991–1995	2181 (8.27)	7440 (7.37)
Age at time of inclusion in cohort		
0–19 years	2760 (10.47)	10 790 (11.13)
20–39 years	5653 (21.44)	21 516 (22.20)
40–59 years	7906 (29.38)	29 366 (30.29)
60–79 years	9308 (35.30)	32 821 (33.86)
80–99 years	743 (2.82)	2447 (2.52)
Total years of follow-up	380 103	1 268 813
Follow-up time		
0–4 years	7967 (30.21)	32 980 (34.02)
5–9 years	2857 (10.83)	12 143 (12.53)
10–19 years	4964 (18.82)	18 622 (19.21)
20–29 years	8926 (33.85)	28 168 (29.06)
30–39 years	1656 (6.28)	5027 (5.19)

Note.—Unless otherwise stated, data are numbers of subjects, with percentages in parentheses.

* Numbers in parentheses are percentages of exposed or unexposed subjects in the whole study population.

diagnosed and entered into the national registry before the first CT exposure, and 116 (5.2%) because of gamma knife treatment to the head. Thus, 26 370 patients were included in the study. In addition, 16 patients were excluded during the analysis because of information in the referral notes: Seven patients had a prevalent meningioma (43.8%), four (25%) had another brain tumor, and five (31.3%) had previously undergone radiation therapy. The inclusion and exclusion of study subjects and 96 940 unexposed control subjects are further described in Figure 1. Characteristics of the study cohort are given in Table 1.

Censoring events were death, gamma knife treatment, nonmeningioma brain tumors, and emigration from Sweden or December 31, 2010, whichever occurred first. In addition, for the control subjects, censoring occurred at the same date as the index case.

Outcomes

Outcomes were collected from the Swedish Cancer Registry by using a combination of International Classification of Diseases, 7th revision, codes (codes 193.0, 193.1, 193.2, 193.8, 193.9) for collecting all intracranial tumors combined with histopathologic C24 codes (codes 461, 463, 466) that were specific for meningioma.

Radiation Doses

Published data were used as a dose metric, wherein single-scan absorbed doses were measured with thermoluminescent dosimeters on the CT scanners used in this study (11). The thermoluminescent dosimeters were located centrally in an anthropomorphic head phantom, and the technique parameters used during the measurements resembled those of typical head examinations. The absorbed doses to the center of the brain with the EMI Mark I and GE 8800 scanners were 7.3 mGy and 25.7 mGy, respectively. It should be noted that the GE 8800 scanner used a full rotation (360°) for each scan, whereas the EMI scanner used partial rotations (180° or 225°); consequently, the exposure geometry differed between the scanners. Because we included CT scanners that were used clinically between 1973 and 1992 (EMI Mark I, 1973–1985; GE 8800, 1979–1992), details about the exact technique parameters used in the patients, radiation quality, and scanner geometry were difficult to obtain. This made a more comprehensive and patient-specific dose metric (eg, average absorbed dose to the brain) challenging to estimate and validate. Although the dose metric used in this study—the absorbed dose to the center of the brain—is not as comprehensive as the average absorbed dose to the brain, it can be used to gauge the difference in exposure to the patients from the two different scanners.

From the radiology records, it was possible to find the number of series for each examination; we calculated a maximal brain dose for each patient according to the number of series performed, depending on which CT scanner was used. We then divided subjects into groups for every 50 mGy of absorbed dose to the center of the brain.

Data Analysis

We started the follow-up period after exclusion periods of either 5 or 10 years for both cohorts. Exclusion periods were used to minimize the risk of reversed causality—that is, to avoid the risk that a meningioma that led to an examination would be considered to have been caused by that same examination. After a 5-year exclusion period, the cohort contained 18 388 exposed and 63 664 unexposed subjects; after a 10-year exclusion period, the cohort contained 15 534 exposed and 51 398 unexposed subjects (Table 2).

For subjects who initially were recruited to the unexposed cohort but who eventually underwent a CT examination of the head, exposure status was changed after a lag period of 2 years to allow for a meningioma detected from this examination to be registered as

Table 2

Characteristics of the Study Population after 5- or 10-Year Exclusion Period

Characteristic	5-Year Exclusion Period		10-Year Exclusion Period	
	Exposed Cohort	Unexposed Cohort	Exposed Cohort	Unexposed Cohort
Total population*	18 388 (22.34)	63 664 (77.66)	15 534 (23.21)	51 398 (76.79)
Sex				
M	9393 (51.08)	31 944 (50.18)	7748 (49.87)	25 102 (48.84)
F	8995 (48.92)	31 720 (49.82)	7786 (50.13)	26 296 (51.16)
Time period for inclusion in cohort				
1973–1975	698 (3.80)	2576 (4.05)	577 (3.71)	1999 (3.89)
1976–1980	2961 (16.10)	10 786 (16.94)	2511 (16.16)	8718 (16.96)
1981–1985	6162 (33.51)	21 754 (34.17)	5210 (33.54)	17 466 (33.98)
1986–1990	7055 (38.37)	23 638 (37.13)	5975 (38.47)	19 266 (37.48)
1991–1995	1512 (8.22)	4910 (7.71)	1261 (8.12)	3949 (7.68)
Age at time of inclusion in cohort				
0–19 years	2436 (13.25)	9315 (14.64)	2354 (15.15)	8827 (17.17)
20–39 years	4898 (26.64)	17 991 (28.28)	4665 (30.03)	16 653 (32.40)
40–59 years	5889 (32.02)	20 934 (32.90)	5220 (33.60)	17 562 (34.17)
60–79 years	4941 (26.87)	14 955 (23.51)	3241 (20.87)	8294 (16.14)
80–99 years	224 (1.22)	429 (0.67)	54 (0.35)	62 (0.12)
Average age (y)	44.33	42.51	41.27	38.88
Total years of follow-up	278 015	897 178	193 639	611 700
Average follow-up (y)	20.12	19.09	22.47	21.90
Follow-up time				
5–9 years	2854 (15.53)	12 266 (19.27)	0 (0.00)	0 (0.00)
10–19 years	4955 (26.95)	18 457 (28.99)	4955 (31.89)	18 457 (35.91)
20–29 years	8923 (48.52)	27 962 (43.92)	8923 (57.43)	27 962 (54.40)
30–39 years	1656 (9.01)	4979 (7.82)	1656 (10.66)	4979 (9.69)
Meningioma				
Crude	48 (42.86)	64 (57.14)	35 (43.75)	45 (56.25)
After consideration of information in referral notes	32 (33.33)†	64 (66.67)	23 (33.82)‡	45 (66.18)
CT dose				
No CT examination	0	63 664 (100)	0	51 398 (100)
0–50 mGy	12 313 (69.96)	0	10 298 (66.29)	0
50–100 mGy	4894 (27.10)	0	4306 (27.72)	0
≥101 mGy	1091 (5.93)	0	930 (5.99)	0

Note.—Unless otherwise stated, data are numbers of subjects, with percentages in parentheses.

* Numbers in parentheses are percentages of exposed or unexposed subjects within the whole study population.

† Sixteen patients were excluded after examination of referral notes because of radiation therapy ($n = 5$), meningioma ($n = 7$), and other brain tumors ($n = 4$).

‡ Twelve patients were excluded after examination of referral notes because of radiation therapy ($n = 5$), meningioma ($n = 4$), and other brain tumors ($n = 3$).

having occurred in the unexposed cohort rather than in the exposed cohort. In the unexposed cohort, 666 individuals were examined with CT after the 5-year exclusion period. Of these subjects, six were diagnosed with meningioma during either the lag period or the exclusion period. No subjects in the exposed cohort were originally included in the study as unexposed control subjects.

Data categorization and statistical analysis were performed by A.C.N. and M.K.. Total follow-up time was summarized, with average age at time of inclusion as well as average follow-up time calculated for all cohorts. The relative risk of meningioma was calculated as the proportional hazard ratio (HR) by using software (the PHREG procedure in SAS version 9.4 for Windows; SAS Institute, Cary, NC), with meningioma as the dependent variable and CT exposure ("yes" or "no") and radiation dose (continuous and in 50-mGy dose groups) as independent variables. In addition, separate analysis with HRs was performed in 2-year intervals after the initial CT examination. Analyses were stratified on the basis of sex, age, and year of inclusion in 5-year intervals.

Results

The study cohort consisted of 26 370 patients examined with CT of the head

Figure 2

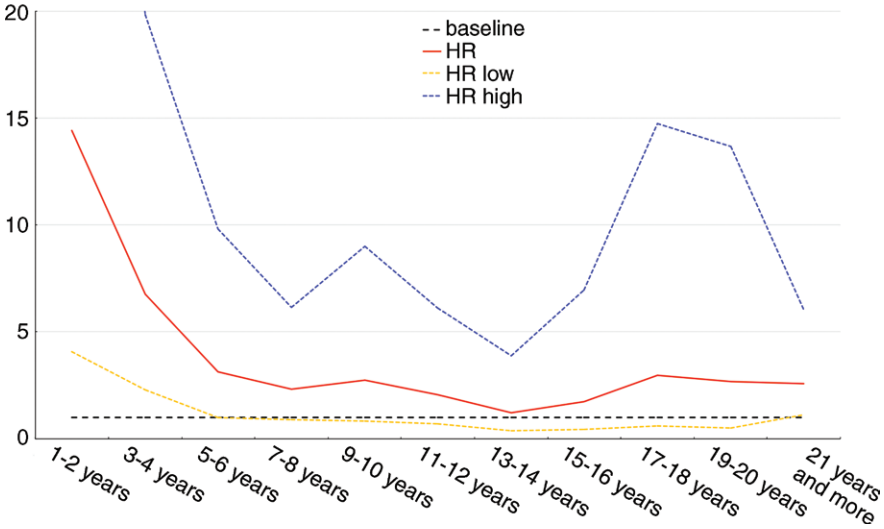

Figure 2: Graph shows HRs without referral check. HRs in 2-year intervals beginning 1st year after initial CT examination of head, without referral notes or radiologic reports taken into account. HR, 95% upper confidence interval (HR high), 95% lower confidence interval (HR low), and baseline risk are shown. HR is highest shortly after CT and then decreases but still stays higher than baseline risk during follow-up period.

Figure 3

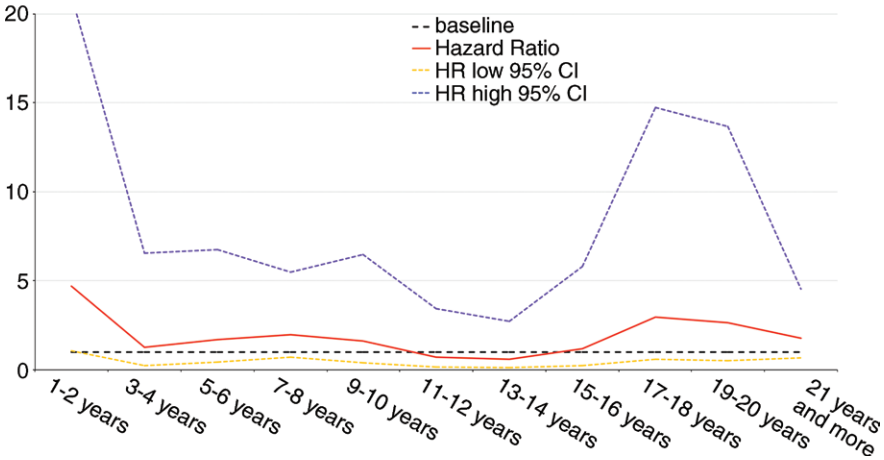

Figure 3: Graph shows HRs with referral check. HRs in 2-year intervals beginning 1st year after initial CT examination of head, after referral notes and radiology reports are taken into account and after exclusion of prevalent meningiomas, intracranial tumors, or CT examination within frames of radiation treatment. HR, 95% upper confidence interval *(CI)*, 95% lower confidence interval, and baseline risk are shown. HR is highest shortly after CT examination and then decreases. After removal of cases, however, HR is lower than that in Figure 1, indicating importance of clinical information at time of initial CT examination.

between 1973 and 1992 and their 96940 matched control subjects. The average age at the start of the study was 48 years for both exposed and unexposed subjects, and the average follow-up time was 13.1 years for unexposed subjects and 14.4 years for exposed subjects. The cohort is presented in further detail in Table 1.

Outcomes

A total of 112 cases of meningioma were detected after an exclusion period of 5 years—48 (42.9%) in the exposed group and 64 (57.1%) in the unexposed control group. Of the 48 patients with meningiomas found in the exposed group, 16 (33.3%) had clinical information on the radiology report that necessitated study exclusion (prevalent meningioma, brain tumor at time of first CT examination, or radiation treatment to the head before or at the time of the first CT examination [Fig 1]). Without exclusion of these subjects, the HR for meningioma among CT-exposed compared with unexposed subjects after a 5-year exclusion period was 2.28 (95% confidence interval [CI]: 1.56, 3.33; $P < .001$), whereas it was 1.49 (95% CI: 0.97, 2.30; $P = .07$) when the 16 subjects were excluded. The HR after a 10-year exclusion period was similar—1.49 (95% CI: 0.89, 2.48; $P = .13$). HRs calculated in 2-year intervals after exclusion of subjects due to information on referral notes changed considerably, particularly in the initial time periods after the first CT scan (Fig 2 compared with Fig 3). Provided that referral notes were taken into account, CT exposure was not a significant risk factor for meningioma. There was a trend toward increasing risk with increased cumulative dose, but this trend was not statistically significant for either the 5-year exclusion period ($P = .07$) or the 10-year exclusion period ($P = .054$). Table 3 shows HRs according to level of exposure for exclusion periods of 5 and 10 years and whether radiologic information was considered or not.

Discussion

In this study, we found no significant increase in risk for meningioma after exposure to CT of the head. Although there was an association between meningioma and CT examination shortly after the first examination, this was likely due to reversed causality and was no longer present when an exclusion period of at least 5 years was used. We also found that long exclusion periods were not enough to minimize reversed causality because we found that additional data from referral notes and radiologic reports were necessary to

Table 3

HRs for Meningioma after CT of the Head

Outcome	5-Year Exclusion Period		10-Year Exclusion Period	
	Without Referral Notes	With Referral Notes*	Without Referral Notes	With Referral Notes†
Meningioma				
Exposed cohort‡	2.28 (1.56, 3.33) [<.0001]	1.49 (0.97, 2.30) [.07]	2.33 (1.49, 3.64) [.0002]	1.49 (0.89, 2.48) [.13]
Unexposed cohort	1	1	1	1
CT dose				
No CT examination	1	1	1	1
0–50 mGy‡	1.58 (0.98, 2.55)	1.46 (0.90, 2.39)	1.37 (0.76, 2.47)	1.30 (0.70, 2.37)
51–100 mGy‡	2.58 (1.37, 4.86)	1.44 (0.65, 3.19)	2.55 (1.18, 5.51)	1.80 (0.75, 4.28)
≥101 mGy‡	11.05 (5.68, 21.52)	2.13 (0.52, 8.82)	15.56 (7.73, 31.31)	3.01 (0.72, 12.70)
P value for trend§	< .0001	.073	< .0001	.054

* Sixteen patients excluded after examination of referral notes because of radiation therapy ($n = 5$), meningioma ($n = 7$), and other brain tumors ($n = 4$).

† Twelve patients were excluded after examination of referral notes because of radiation therapy ($n = 5$), meningioma ($n = 4$), and other brain tumors ($n = 3$).

‡ Data are HRs, with 95% confidence intervals in parentheses. Numbers in brackets are *P* values.

§ *P* values were calculated with dose categories as continuous variable.

exclude cases that were present at the time of the first CT examination exposure or cases in which CT was performed within the frames of radiation treatment to the head. Overall, we did not find any significantly increased risk of meningioma once referral notes and radiologic data had been taken into account.

Other studies, most notably the Life Span Study, have found that low-dose radiation increases the risk of tumors of the central nervous system (2,12). The initial Life Span Study found no increase in risk of nonbrain intracranial tumors but an indication of a dose-response relationship. A follow-up analysis from 2002 (13) showed a slight increased risk of meningioma (excess relative risk, 0.6), although the finding was not statistically significant. There have been other studies considering differing amounts of radiation and the risk of meningioma, and an increased risk of meningioma from high doses of radiation has been well established (8,14). Other studies have shown similar increases in risk at a slightly lower dose range (15). There are still some concerns with regard to increased risks from low doses, in particular from dental radiography, in which an increase in relative risk of 2.0 was found in a case-control study (16). In our study we saw a slight increase to an HR of 1.49 similar to the excess relative risk of 0.6 in the Life Span Study cohort, although neither of the risks were statistically significant (13). It is also important to note that the absolute number of cases seen in studies of meningioma and ionizing radiation are low despite large cohorts and long follow-up times (2,8,13,15). In our study, we found that without access to information from referral notes and radiology reports that allowed for exclusion of subjects who were not eligible, we would have found a significant increase in the risk of meningioma after CT as well as a significant dose-response relationship. This finding may be an important factor to consider when evaluating other studies of CT examinations and risk of slow-growing tumors.

Our study has some limitations. Most important, we lack information on CT examinations of the head performed in other hospitals. During the period in which our study subjects were exposed, however, CT machines were scarce, at least until the later part of the study. We therefore think it is reasonable to assume that the lack of a statistically significant difference in risk of meningioma among exposed and unexposed subjects is a true finding, rather than being the effect of a high number of CT-exposed subjects in the control cohort. Another limitation is that most meningiomas are diagnosed with biopsy at the time of surgery, and asymptomatic meningiomas for which surgery is never performed may not be reported to national registries. This would lead to an underestimation of the risk for meningioma posed by CT. Even if this is true, our results are reassuring because we found no increase in the risk of meningiomas necessitating treatment. In our study, we had more information on the exposed subjects than on the unexposed subjects because the information in the radiology report was confined to exposed subjects. Given that we excluded patients with meningiomas on the basis of this information, this could be a threat to the validity of our study. We think this is unlikely to be of concern, however, because the control subjects most likely would have been followed up at the Karolinska Hospital if they had been subjected to radiation treatment or followed up for meningioma. We also lacked exact individual doses and therefore used an approximation. Because CT examinations of the head during the time period tended to be highly similar, the variability of dose among patients should be fairly low, with the likely exception of children, who have smaller heads and thus also higher doses. Finally, even though this is a large study with a long follow-up time, the low incidence of meningioma in both the

exposed and unexposed cohorts gives the study a lack of statistical power. This does not invalidate the major findings of our study but indicates a need for future follow-up studies in the same cohort.

In conclusion, there was no significant increase in risk of meningioma among more than 15 000 subjects exposed to CT and followed up for 10–37 years after exposure compared with unexposed control subjects.

Disclosures of Conflicts of Interest: A.C.N. disclosed no relevant relationships. **R.B.** disclosed no relevant relationships. **P.A.** disclosed no relevant relationships. **O.F.** disclosed no relevant relationships. **M.K.** disclosed no relevant relationships.

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