Co-prevalence of other tumors in patients harboring pituitary tumors

Clinical article

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Objective. The cause of most pituitary tumors remains unknown, although a genetic contribution is recognized for some. The prevalence of pituitary tumors in the general population is high. Analyzing the Utah Population Database (UPDB), the authors investigated the co-prevalence of other independent primary tumors in patients with known pituitary tumors, both benign and malignant, and in the relatives of these patients.

Methods. The authors identified individuals in the Utah Cancer Registry diagnosed with pituitary tumors who also had genealogy data in the UPDB and then calculated relative risks (RRs) of other tumors in these patients and their relatives.

Results. Among the 591 individuals with pituitary tumors, 16 (2.7%) had a malignant pituitary tumor and 77 (13%) had independent primary tumors of other origin. Overall, this is significantly higher than expected (70.6 expected, \( p = 0.009 \)) within the general population (RR = 1.32, 95% CI 1.06–1.61). A significant excess for several different cancer sites was observed among the first-, second-, and third-degree relatives of the cases, including prostate and other cancers. Independent primary tumors at other sites have markedly elevated co-prevalence in patients harboring pituitary tumors and among their close and distant relatives.

Conclusions. This information will prove useful for counseling patients in whom pituitary tumors have been diagnosed and suggests strong genetic or environmental co-risks for the development of other tumors.

Key Words • pituitary neoplasm • co-prevalence • genetics • relative risk • Utah Population Database • pituitary surgery

The Utah Population Database (UPDB) is a dynamic electronic database that includes genealogical and demographic data representing the Utah population. The UPDB was created from computerized genealogical data from Utah pioneers and their descendants, and the data were subsequently record-linked with Utah state vital records. The database receives annual updates from the Utah Cancer Registry (UCR), Utah Department of Health vital records, and driver’s license records, which are incorporated into the existing database and genealogies. Information on more than 7.5 million individuals, often representing multiple generations of families, is now available. The pedigrees span up to 11 generations in some families that were founded by pioneers who emigrated primarily from Northern Europe in the mid-1800s. These pioneers were typically unrelated, with low inbreeding levels, and the Utah population has been shown to be genetically representative of the founding population.

The genealogical records in the UPDB are record-linked to data from the Surveillance, Epidemiology, and End Results (SEER) UCR, which have been collected statewide since 1966, and follow-up rates exceed 95%. All independent malignant primary cancers occurring in the state are required by law to be reported to the UCR, with data including primary site, histology, age at diagnosis, stage, grade, survival, treatment, and follow-up. These data are record-linked to the UPDB genealogy data annually. Data on benign tumors have been reportable by law since 2004. The UPDB records are also linked with the enterprise data warehouse records of the University of Utah Health Sciences Center and the Intermountain Healthcare group, which contain patient data including diagnosis and procedure coding.

Previous studies of the genetic relationships among individuals with a benign or malignant pituitary tumor diagnosis indicate that close and distant relatives of patients with pituitary tumors have a higher incidence of developing a pituitary tumor, indicating evidence for a genetic
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contribution to predisposition to symptomatic pituitary tumors. In the current study, the authors sought to determine the co-prevalence of other tumors in patients and their relatives with a known pituitary tumor diagnosis.

Methods

Data Collection

The UPDB contains identifiable health data; use of the data is overseen by the Resource for Genetic Epidemiology, a regulatory committee that approves all studies using the UPDB. All of the data released for the study were de-identified prior to release. The use of these data resources for this study was also approved by the Institutional Review Board. Data obtained from the UCR include primary cancer site, histology, stage, grade, months of survival, and patient age at diagnosis for each cancer. Only independent primary cancers are included in the UCR.

Relative Risk Method

Relative risks (RRs) in relatives were estimated by comparing the rate of disease in the relatives of affected individuals to the rate of disease in the UPDB population. We used age-, birth year-, and birthplace-specific rates calculated within the UPDB population to estimate RRs for cancer by type in relatives of patients with pituitary tumors as follows. All 2.3 million individuals in the UPDB who belonged to at least 3 generations of genealogy were assigned membership in 1 of 132 birth year (5-year)–, sex–, and birthplace (Utah or not)–specific cohorts. The rate of each cancer type for each cohort was estimated as the total number of individuals with the specific cancer type in each cohort, divided by the total number of UPDB individuals in the cohort.

The expected number of relatives with a cancer of a specific type was estimated by counting all relatives of the probands (by cohort, with no duplication), then multiplying the number of relatives (per cohort) by the cohort-specific rate of the cancer type, and finally summing over all cohorts. The observed numbers of relatives with a specific cancer type were also counted by cohort, without duplication. As an unbiased estimator of RR, we used the number of cancers observed divided by number of cancers expected. We calculated RRs for multiple different relationships. Two-sided probabilities were calculated under the null hypothesis RR = 1.0, under the assumption that the number of observed deaths follows a Poisson distribution with mean equal to the expected number of deaths. Relative risks were calculated for first-, second-, and third-degree relatives.

Individuals from the UPDB who had genealogy data for 12 of their 14 immediate ancestors (parents, grandparents, great-grandparents) were analyzed; this strict genealogical data requirement was used to ensure equivalent quantity and quality genealogy in cases and individuals used for disease rate estimation. Pituitary tumors were diagnosed as being functional (excess hormone secretion) or nonfunctional with symptomatic mass. We did not differentiate between patients with malignant pituitary tumors and those with benign pituitary tumors. We did not have data to determine whether any individuals had multiple endocrine neoplasia.

Results

Among the 1029 individuals with pituitary tumors who were identified from the UPDB, 591 patients had at least 12 of their 14 immediate ancestors included in the database, and these cases were used for analysis. Sixteen of the 591 individuals had a malignant pituitary tumor (16 observed, 0.05 expected; p < 0.000) and 77 had independent primary tumors diagnosed at another cancer site. Overall, this is a significant excess of all cancers (n = 93 observed with 70.6 expected; p = 0.009) within the general population (RR = 1.32, 95% CI 1.06-1.61). When considered by cancer site, in addition to the observed excess of malignant pituitary tumors that was expected, there was a significantly increased prevalence of prostate cancer (28 cases observed, 18.1 cases expected; RR = 1.54, 95% CI 1.03–2.23; p = 0.027; Table 1).

A significant excess of several cancers (p < 0.05) was observed among first-, second-, and third-degree relatives of the 575 patients without a malignant pituitary tumor (Table 1). The 4892 first-degree relatives of the 575 cases had a higher prevalence of cancers of the anus, colon, female genitals, pancreas, and prostate, as well as non-Hodgkin’s lymphoma. A significant excess of cancers at several sites was also observed among the 13,396 second-degree relatives of patients with pituitary tumors, including biliary (non–gall bladder), malignant peripheral nerve sheath tumor, renal, stomach, and prostate tumors. Finally, among the 35,682 third-degree relatives, a significant excess of CNS (excluding brain), lip, and prostate cancers as well as chronic lymphocytic leukemia was observed.

Malignant pituitary tumors did not occur in significant excess in any group of relatives, but 1 case was observed among the first-degree relatives (RR = 2.28, 95% CI 0.06–12.68), 1 case was observed among the second-degree relatives (0.99 expected), and 6 cases were observed among the third-degree relatives (RR = 2.11, 95% CI 0.78–4.60). No correction was made for multiple testing.

Discussion

Prevalence of Pituitary Tumors

Estimates have shown that pituitary tumors occur quite frequently in the general population. Pituitary tumors account for 6.6% of primary brain and CNS tumors by histology, and their prevalence has been estimated at between 14.4% and 22.5%, respectively. Most of these tumors are likely to represent incidental, asymptomatic microadenomas, although with macroadenomas (tumors ≥ 10 mm) occurring at a rate of 1 in 600 persons, there also are likely many persons with unrecognized macroadenomas. The co-prevalence of other tumors with pituitary tumors has not been studied.

Pituitary Tumors and the UPDB

Previous studies have analyzed the genetic relationships among individuals diagnosed with benign or malignant pituitary tumors to investigate whether there was
evidence for a heritable contribution to the disease in non-syndromic cases. The analysis of the genealogical index of familiality, testing the hypothesis of no excess relatedness for all pituitary tumor cases, demonstrated that the pituitary cases had a higher degree of relatedness than expected (p < 0.001). The average relatedness of all pituitary tumor cases was also significantly higher than expected, even when all relationships closer than third-degree relatives were ignored. The RR assessment demonstrated a significantly elevated risk to first- and third-degree relatives of affected individuals.

Using these 2 methods, the authors found strong evidence for a genetic contribution to predisposition to symptomatic pituitary tumors. This evidence for genetic contribution led us to postulate whether a genetic predisposition to one tumor type would affect the likelihood of developing other primary tumors.

**Co-Prevalence of Other Tumors**

Co-prevalence of different cancer types within individuals and pedigrees often forms the basis for syndrome definitions, such as Li-Fraumeni syndrome. We have previously used the UPDB to show patterns of such clustering, which have been observed among some, but not all cancers; pituitary cancer was not analyzed. There have been few studies noting the association of other tumors in patients harboring pituitary tumors (recently reviewed by Furtado et al.18). These reports are supported by data from the current study, which indicate that there is a significantly elevated co-prevalence of other tumors in patients harboring pituitary tumors in the UPDB and their relatives. This observation suggests common genetic or environmental co-mechanisms involved in tumorigenesis among pituitary tumors and the associated primary tumors noted in this study, although common environmental factors cannot explain the significant excesses observed in distant relatives. Whether this is also influenced by increased surveillance in patients with diagnosed pituitary tumors or unrelated cancers is not known from this analysis. Such information will prove useful for counseling of patients with a pituitary tumor diagnosis and their relatives. It also provides an avenue for future investigation of the etiology of the other primary tumors observed in patients with pituitary tumors.

**Conclusions**

Close and distant relatives of patients with pituitary tumors have been shown to have a higher incidence of developing a pituitary tumor, indicating evidence for a genetic contribution to predisposition to symptomatic pituitary tumors. In the current study, we sought to determine the co-prevalence of other tumors in patients and their relatives with a known pituitary tumor diagnosis. The results showed that patients with pituitary tumors were more like-
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ly than expected to have an independent primary tumor in another location. A significant excess of several cancers was also observed among first-, second-, and third-degree relatives of these patients. This observation suggests common genetic or environmental co-mechanisms involved in tumorigenesis. These findings can be used in the counseling of patients with pituitary tumor diagnoses and their relatives.

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