INCIDENCE/PREVALENCE & SURVIVAL STUDY TEMPLATE

TITLE: Incidence of thyroid carcinoma in Olmsted County, Minnesota, 1935-1999.

SPECIFIC AIMS

A dramatic increase in the incidence of primary hyperparathyroidism in Rochester, followed by an equally dramatic decline was explained on the basis of a "point source outbreak" resulting from widespread use of therapeutic head and neck irradiation among children and adults in the 1930's and 1940's (Wermers et al., 1997). Additionally, the recent recognition that the Minnesota population was exposed in the 1960's to atmospheric fallout from atomic explosions at the Nevada test-site raises the possibility that the incidence of radiation-associated thyroid cancer may continue to rise (Hundahl, 1998; Gilbert et al., 1998). A previous Rochester Epidemiology Project study examined the incidence of thyroid cancer in Olmsted County, Minnesota from 1935 to 1984. Results from that study indicated a rise in the incidence of thyroid disease from 1935 through 1969, a decrease from 1970-74 through 1975-79, and another rise through 1980-1984 (Hay et al., 1987). Thus, the overall temporal or secular pattern of thyroid cancer incidence in this population is not yet clear.

We propose **to extend the earlier study through 1999 to further examine the trends in thyroid cancer among Olmsted County residents.** We will also determine **whether there are differences in the incidence of the histological subtypes of thyroid cancer** during this time period. Additionally, we will **examine trends in mortality and survival in this population**. These data will assist in generating hypotheses regarding the etiology of thyroid cancer and the histological subtypes. The data are also important for clinical practice, since it is unclear whether conclusions derived from most thyroid cancer outcome studies are relevant to unselected patients from the community, or instead, reflect referral bias.

Our **specific aims** are as follows:

1. To estimate the incidence of thyroid cancer among Olmsted County residents from 1935-1999 and to test the hypothesis that there has been an increase in incidence during the last 15 years.

2. To examine trends in the incidence of sub-types of thyroid cancer (specifically papillary, follicular, and medullary cancer) among Olmsted County residents over the same time period.

3. To determine trends in survival following thyroid cancer by sub-type, and to test the hypothesis there has been an increase in survival in individuals with thyroid cancer over this 65-year time period.

BACKGROUND AND SIGNIFICANCE

Thyroid cancer is a relatively rare form of cancer with wide variations in the degree of malignancy depending on the cell type (Franceschi et al., 1993). The clinical spectrum ranges from rapidly fatal (anaplastic) to relatively benign (papillary). Most primary malignant tumors of the thyroid are derived from follicular cells. The histological types are divided into two groups, differentiated and undifferentiated. The differentiated types, which include papillary and follicular, are by far the most common. Undifferentiated types, also referred to as anaplastic, are seen predominantly in the elderly and have a very rapid growth rate. Another type of thyroid cancer, medullary carcinoma, is derived from the parafollicular C-cells, and is sometimes familial, occurring as a component of the multiple endocrine neoplasia type 2 (MEN 2) syndrome. The gene for MEN 2 has been mapped to chromosome 10 (Franceschi, et al., 1993).

Thyroid cancer has been examined in a number of epidemiological studies in the U.S. (Preston-Martin and Menck, 1979; Hay et al., 1985; Goodman et al., 1988; Franceschi et al., 1993; Zheng et al., 1996). A study in Connecticut examined time trend and age-period-cohort effects on the incidence of thyroid cancer from 1935 through 1992 (Zheng et al., 1996). The overall age-adjusted annual incidence of thyroid cancer increased from 1.30/100,000 in 1935-1939 to 5.78/100,000 in 1990-1992 in females and from 0.30/100,000 in 1935-1939 to 2.77/100,000 in 1990-1992 in males. However, the trends actually decreased for the period 1975-1992, 9.3% in males and 8.3% in females. The authors concluded that the introduction of radiation treatment of benign childhood conditions of the head and neck between 1920 and the 1950's was responsible for the cohort effects. A recent Hawaiian study examined newly diagnosed thyroid cancer cases reported to the Surveillance, Epidemiology, and End Results (SEER) program from 1960 to 1984 and found an overall age-adjusted rate of 8.1 per 100,000 in women and 3.1 per 100,000 in men (Goodman et al., 1988). Lastly, a study in Los Angeles County found an age-adjusted incidence rate of thyroid cancer of 2.4 and 6.1 per 100,000 for males and females, respectively (Preston-Martin and Menck, 1979).

An important issue with thyroid cancer is **the differential epidemiological patterns of histological sub-types**. For instance, multiple studies have found that in iodine-sufficient population, rates of papillary thyroid cancer tend to increase and rates of follicular thyroid cancer tend to decrease relative to iodine-deficient populations (Lind et al, 1998). In the study by Zheng et al (1996), the increase in thyroid cancer from 1935-1939 to 1990-1992 was mostly due to an increase in papillary carcinomas. A study using the Florida Cancer Data System registry also determined that the overall increase in thyroid cancer between 1981 and 1993 was due primarily to the increase in papillary carcinoma (Mulla et al., 2000). **An extension of the previous Mayo study may assist in developing hypotheses regarding the etiology of the different subtypes of thyroid cancer**. It is hypothesized that irradiation has been associated more often with an increase in the incidence of papillary thyroid cancer (Sabbagh et al., 1997)]. An increase in radiation in the 1940's and 1950's would then result in an increase in papillary thyroid cancer, which has been seen in these studies. However, the available data are subject to some reservations due to changes in diagnostic criteria and changes in histopathological description (Franceschi et al., 1993). An advantage to studying thyroid cancer in the Olmsted County population is that the histology slides are available and can be reviewed according to consistent, modern criteria.

Despite the increase in incidence rates, the mortality from thyroid cancer has apparently been declining in countries that formerly showed the highest rates (Franceschi et al., 1993). However, moderately rising mortality rates were seen in France, Greece, Italy, Spain, Yugoslavia, and Japan, mainly or exclusively among males. A study in Denmark found that the mortality among women decreased from 0.87 per 100,000 in 1953-1957 to 0.54 per 100,000 in 1983-1985, but increased in men from 0.35 to 0.57 during the same time period. (Sprogel et al., 1989). Further study is needed to determine changes in the mortality of the histological subtypes of thyroid cancer. In addition, there is **the unanswered question of why the mortality rates are decreasing; is it due to decreasing incidence or increased survival**? We will attempt to address this using the Olmsted County population.

The survival of individuals with thyroid carcinoma has been described in a few studies. A study using the National Cancer Data Base reported on 53,856 cases of thyroid carcinoma treated in the U.S during 1985-95 (Hundahl et al., 1998). The article focused on 10-year survival and found that the survival rates for U.S. patients with papillary, follicular, Hurthle cell, medullary and undifferentiated/anaplastic carcinoma were 93%, 85%, 76%, 75%, and 14%, respectively. In the previous study in Olmsted County, survival for 141 operated cases (median follow-up of 12 years) at 10 and 20 years was 85% and 68%, respectively. **We will determine if the survival is increasing in this population and compare the differing survival rates in the histological subtypes.**

PRELIMINARY STUDIES

A previous study examining thyroid cancer in Olmsted County from 1935 through 1984 identified 164 cases (Hay et al., 1987). Those data will be combined with newly collected thyroid cancer cases occurring after 1984.

RESEARCH DESIGN AND METHODS

Overview

The incidence of thyroid cancer and its sub-types will be estimated from a population-based descriptive study of Olmsted County, Minnesota residents from 1935 through 1999. The trends in survival after thyroid cancer will also be evaluated. We will review the medical records of all Olmsted County residents who had one or more of the following diagnoses: papillary, follicular, Hurthle cell, medullary, anaplastic thyroid carcinoma or thyroid carcinoma, not otherwise specified.

Data Resource

Epidemiologic research in Olmsted County is possible because the county is relatively isolated from other urban centers and nearly all medical care is delivered to patients in the population by a handful of providers. Over the years, the majority of the health care providers in the community have shared their medical records for research purposes under the auspices of the Rochester Epidemiology Project (REP; NIAMS AR 030582). Currently, the participants in the REP include the Mayo Clinic and its two affiliated hospitals, Olmsted Medical Center and its affiliated hospital, and the Rochester Family Medicine Clinic, a private practitioner in the County. Together, these providers provide 90-96% of all health care to Olmsted County residents (Melton, 1996). The result is the linkage of medical records from essentially all sources of medical care available to and utilized by the Olmsted County population. The health care providers who participate in the REP use a unit (or dossier) medical record system whereby all data collected on an individual are assembled in on place (Kurland 1981). These records therefore contain the details of every inpatient hospitalization, every outpatient visit to the offices, clinics, or emergency rooms in the county, every physician visit to nursing homes or private homes, as well as every laboratory results, pathology report (including autopsies), and correspondence concerning each patient. The medical details are collected by physicians for the delivery of subspecialty level medical care and are of high quality.

Case definition

Individuals with a primary diagnosis of thyroid cancer between 1935 and 1999 will be included as cases. Where possible, the histological slides will be reviewed by a pathologist (John Doe, M.D.) with special expertise in endocrine histopathology.

Data collection

The original and complete medical records of each subject will be reviewed by Dr. Smith. All possible cases for inclusion will also be independently reviewed by Dr. Jones, an endocrinologist with a thyroid cancer interest and 30 years of experience in research.

Data will be collected in order to estimate the age- and sex-specific incidence of thyroid cancer; to estimate the age- and sex-specific incidence of histological subtypes of thyroid cancer; and to determine the long-term survival following thyroid cancer.

Pertinent clinical and laboratory date collected will be entered into a pre-coded data form. Collected data will be data entered with independent verification, edited by a range and consistency check program, and a SAS data set will be created for analysis.

Statistical analysis

For the calculation of incidence rates (**Specific Aims 1 and 2**), the entire population of Olmsted County will be considered to be at risk, and the denominator age- and sex-specific person-years (p-y) will be estimated from decennial census data (Bergstralh, 1992). Incidence rates will be calculated separately for all cases of thyroid cancer and for specific histological subtypes. Rates will be directly age- and sex-adjusted to the population structure of the 1990 U.S. Census. Ninety-five percent confidence intervals will be calculated as the adjusted rate ± 1.96 times its standard error (Bergstralh, 1992). The effects of sex, age, and calendar year on the rates will be assessed by using Poisson regression models (Frome et al., 1985) fit with the GENMOD procedure in SAS. The number of observed cases of each sex-age-calendar year category will be modeled as a function of sex, age and calendar year. The log rank function will be used with the $\log_e$ of population used as an offset term.

Long-term survival (**Specific Aim 3**) will be estimated with the Kaplan-Meier method (Kaplan and Meier, 1958). Any death and risk of death due to thyroid cancer will be outcomes of the study and the effects of potential risk factors (sex, age, cell type, stage) will be estimated using Cox Proportional Hazards models (Cox, 1972).

Power

The sample size is essentially fixed due to the fact that we are using all available cases. However, with an anticipated 230 (164 old study + about 70 from 1985-99) incidence cases (**Specific Aims 1 and 2**), using Poisson regression we could detect a rate ratio in incidence rates from 1999 relative to 1935 as small as 1.99 (Signorini, 1991). This translates to being able to detect an average annual increase of about 1%/year over the 65 year period using a two-sided test with alpha of 0.05 and 80% power. Looking at this in another way based on power estimates for comparing two independent proportions, it is estimated that the crude rate in 1935-54 is about 2.6/100,000/yr (879,000 p-y) and that we would have 80% power to detect a rate for the 1980-1999 period (2,100,000 p-y) as small as 4.8/100,000/yr (rate ratio 1.9). Of course, the power would be less for the various sub-types.

For survival analyses (**Specific Aim 3**), we anticipate about 115 total deaths in the 230 cases. Assuming a dichotomous predictor (group variable) with a prevalence of 10%, 25% or 50%, the smallest detectable (80% power, 2-sided, alpha 0.05) hazard ratios are 2.4, 1.9 and 1.7, respectively. The number of deaths due to thyroid cancer is likely in the range of 10 to 20; in which case only extremely large risk ratios would be detectable with reasonable power.

For population-based mortality due to thyroid cancer, the prior incidence study had 6 TC deaths among 141 non-autopsy diagnosed incidence cases from 1935-84. The number of TC deaths in the 23 autopsy diagnosed incidence cases is not known. At any rate, adding 15 more years, and including deaths among residents whose incidence diagnosis was outside of Olmsted County, is not likely to increase the number of deaths beyond 20 (more likely 10), making this endpoint of questionable value.

Timeline:

Approximately one year will be required for complete chart review, including travel to review charts from outside sources. Data editing will be completed 2 months following completion of data abstraction, and analyses will be completed 8 months after editing. A draft manuscript will be completed within two months of completed data analysis.

Strengths and Limitations. The strengths of this study include a well-defined population. Another advantage is that the histology slides are available and can be reviewed to ensure that cases are diagnosed using consistent, modern criteria. This avoids the difficulties of changing diagnostic criteria over time. Limitations of this study include the fact that the population is 96% European-American, and results may not be generalizable to populations of other races or ethnicities. Finally, the total number of subjects is relatively small, and it may not be possible to obtain stable estimates of cancer mortality or detect significant trends over time.

HUMAN SUBJECTS

This project does not involve experimentation on human subjects and is limited only to a retrospective review of medical records. As the study is minimal risk and consists only of a retrospective review of patient medical records, we will request a HIPAA waiver from the IRB. However, since January 1, 1997, Minnesota State law requires a general authorization to review medical records for research from each patient who attended a health care facility after this date. All health care facilities that participate in the REP have implemented systems to comply with this law. No records will be reviewed from patients who have not provided this authorization.

Confidentiality

Privacy of patient medical information will be maintained as follows. Information will be abstracted from medical records and collected and stored electronically. Standard procedures are in place to insure appropriate handling and review of medical records and only persons with appropriate authorization will have access to the study computer files. All staff at Mayo Clinic are trained about the importance of confidentiality and procedures by which this must be maintained. All data will be managed and analyzed anonymously, and all reports will be of a summary nature and no individual will be identified. All results will be reported in aggregate, and no individual patients will be identified. Additionally, no comparisons will be made between data obtained from different institutions.

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