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MALIGNANT THYMOMA IN THE UNITED STATES: DEMOGRAPHIC PATTERNS IN INCIDENCE AND ASSOCIATIONS WITH SUBSEQUENT MALIGNANCIES

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The cause of thymoma is unknown. No population-based study has described demographic patterns of thymoma incidence. Previous reports have linked thymoma with diverse subsequent malignancies, but these associations are uncertain. We used Surveillance, Epidemiology and End Results (SEER) data to study the incidence of malignant thymoma by sex, age and race in the United States (1973–1998). Incidence was modeled with joinpoint regression (for age) and Poisson regression. We also used SEER data to compare malignancies following thymoma diagnosis with those expected from general population rates, calculating the standardized incidence ratio (SIR, observed/expected cases) to measure risk. The overall incidence of malignant thymoma was 0.15 per 100,000 person-years (849 cases). Thymoma incidence increased into the 8th decade of age and then decreased. Incidence was higher in males than females ($p=0.007$) and was highest among Asians/Pacific Islanders (0.49 per 100,000 person-years). Following thymoma, there were 66 malignancies (SIR 1.5, 95%CI 1.2–1.9). The most notable excess risk for subsequent malignancy was for non-Hodgkin's lymphoma (B immunophenotype) where the SIR was 4.7 (95%CI 1.9–9.6, 7 cases). There were also excess digestive system cancers (SIR 1.8, 95%CI 1.1–2.9) and soft tissue sarcomas (SIR 11.1, 1.3–40.1). No other cancers were increased after thymoma. In conclusion, malignant thymoma is extremely rare. The peak in late adulthood deserves further study. Variation in incidence by race suggests a role for genetic factors. Our study did not demonstrate broadly increased risk for malignancies following thymoma.

Key words: *thymoma; demography; multiple primary neoplasms; non-Hodgkin's lymphoma*

The thymus plays a central role in adaptive immunity as the site of maturation for T lymphocytes. The thymus is largest during infancy and early childhood, and decreases markedly in size and function with age.[1] Although primary tumors of the thymus are rare, the most common histologic type is thymoma, a neoplasm of the thymic epithelial cells normally responsible for directing T lymphocyte maturation.[2] Thymomas can be classified as "malignant" or "benign" based on evidence for capsular invasion. Histologically, thymomas frequently have an accompanying rich infiltrate of T lymphocytes.[2] These abnormally conditioned T lymphocytes are released into the peripheral circulation[3] and are likely responsible for the autoimmune conditions that often accompany thymoma, such as myasthenia gravis, blood dyscrasias, and connective tissue disorders.[4]

The cause of thymoma is unknown. Thymoma is a neoplasm of middle- or older-aged adults that affects males and females in roughly equal proportions.[5–8] It presents either concurrently with myasthenia gravis (1/3 of cases), with local symptoms (*e.g.*, chest pain, neck mass and superior vena cava syndrome; 1/3) or asymptomatically as a mediastinal mass on chest radiography (approximately 1/3 of cases).[5–8]

Interestingly, several prior studies of thymoma patients reported a frequent occurrence of diverse subsequent malignancies,[9–11] including carcinomas (*e.g.*, breast, colon, lung, prostate and stomach), hematologic malignancies (leukemia and non-Hodgkin's lymphoma) and rarer malignancies (*e.g.*, Kaposi's sarcoma and carcinoid tumors). These observations suggest that T lymphocyte immune surveillance, which may be abnormal in thymoma patients due to their disease and/or its treatment by thymectomy or irradiation, could play a role in protecting against a wide range of neoplasms.

Previous studies of thymoma were based on small numbers of clinical cases. There are no population-based studies that describe demographic patterns of thymoma incidence, which might provide clues regarding etiology. As a step in further understanding the cause of thymoma, we used population-based data to examine demographic patterns in the incidence of malignant thymoma in the U.S. We also documented additional malignancies in persons with thymoma and compared the observed cancers with those expected in the general U.S. population.

METHODS

Thymoma incidence

We used population-based cancer incidence data collected by the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program. For the primary analysis (1973–1998), data were provided by 9 registries (Connecticut, Hawaii, Iowa, New Mexico and Utah, and metropolitan Atlanta, Detroit, Seattle and San Francisco-Oakland). We specified thymoma cases by International Classification of Diseases for Oncology (Revision 2, ICD-O2) codes both for site (379 = thymus) and histology (8580 = thymoma). SEER collects data only on "malignant" thymomas. The distinction between malignant and benign thymoma is based on gross or microscopic evidence of invasion and may not correspond to true biological differences.[5] Cases of malignant thymoma are reported to SEER by cancer registrars, after review of pathology records to identify cases with a description of "malignant" or "invasive" phenotype. The category defined by histology code = 8580 likely also includes some cases of thymic carcinoma, considered under the World Health Organization classification to be a variant of thymoma,[2] since the ICD-O2 codebook lists "thymic carcinoma" as an alternate diagnosis under this code.

Thymoma cases were classified by sex, age (in 18 5-year intervals as 0–4, 5–9,. . ., 80–84, 85+ years), registry and race (categorized as white, black or other; 6 cases of unknown race were

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excluded). In a secondary analysis, we further classified cases in "other" races as either Asian/Pacific Islander or American Indian/Aleutian Islander/Eskimo. This more detailed racial classification was available only for 1992–1998 but included data from Los Angeles and San Jose-Monterey, which joined SEER in 1992.

We fitted a series of Poisson regression models that were piecewise-linear in age (using the midpoint of the age intervals as the independent variable) to identify "joinpoints" where the regression of thymoma incidence on age changes slope.[12] We used an autocorrelated error structure, which resulted in more conservative statistical tests. Also, we restricted the analysis to ages 35 years or older because variance estimates for younger groups were unstable. Under this model, the number of significant joinpoints was found by performing several permutation tests, each of which has correct significance asymptotically.[12] After a joinpoint model was chosen, we assessed the significance of the change in slope across each observed joinpoint.[12] Analyses were conducted using the program Joinpoint (National Cancer Institute, version 2.5, available at http://srab.cancer.gov/joinpoint).

Based on joinpoint analyses, we then used Poisson regression to model thymoma incidence as a function of age and sex, separately for each racial group. For whites and Asians, the 2 racial groups with significant joinpoints, age was modeled as a piecewise linear function, whereas age was modeled using the 18 separate 5-year categories for blacks and "other" races. Poisson regression models were fitted using S-PLUS 2000 (MathSoft, Seattle, WA). All tests and confidence intervals (joinpoint and Poisson regression) were 2-sided.

Malignancies following thymoma

We also used SEER data to identify subsequent malignancies among thymoma cases (patients) for the period from 2 months post-diagnosis until date of last follow-up, death or December 31, 1998, whichever occurred first. We restricted analysis to individuals for whom thymoma was the first cancer diagnosis (among 66 other patients, for whom thymoma was not their first malignancy, there were only 4 subsequent cancers). Subsequent malignancies were classified by site based on ICD-O2 codes. The expected number of cancers at each site was calculated by applying age-, sex-, race- and calendar year-specific rates, derived from SEER, to the person-years of follow-up of thymoma patients. Standardized incidence ratios (SIRs), calculated as the ratio of the number of observed to expected cases, measured relative risk. We computed exact 2-sided confidence intervals and p-values for SIRs.[13]

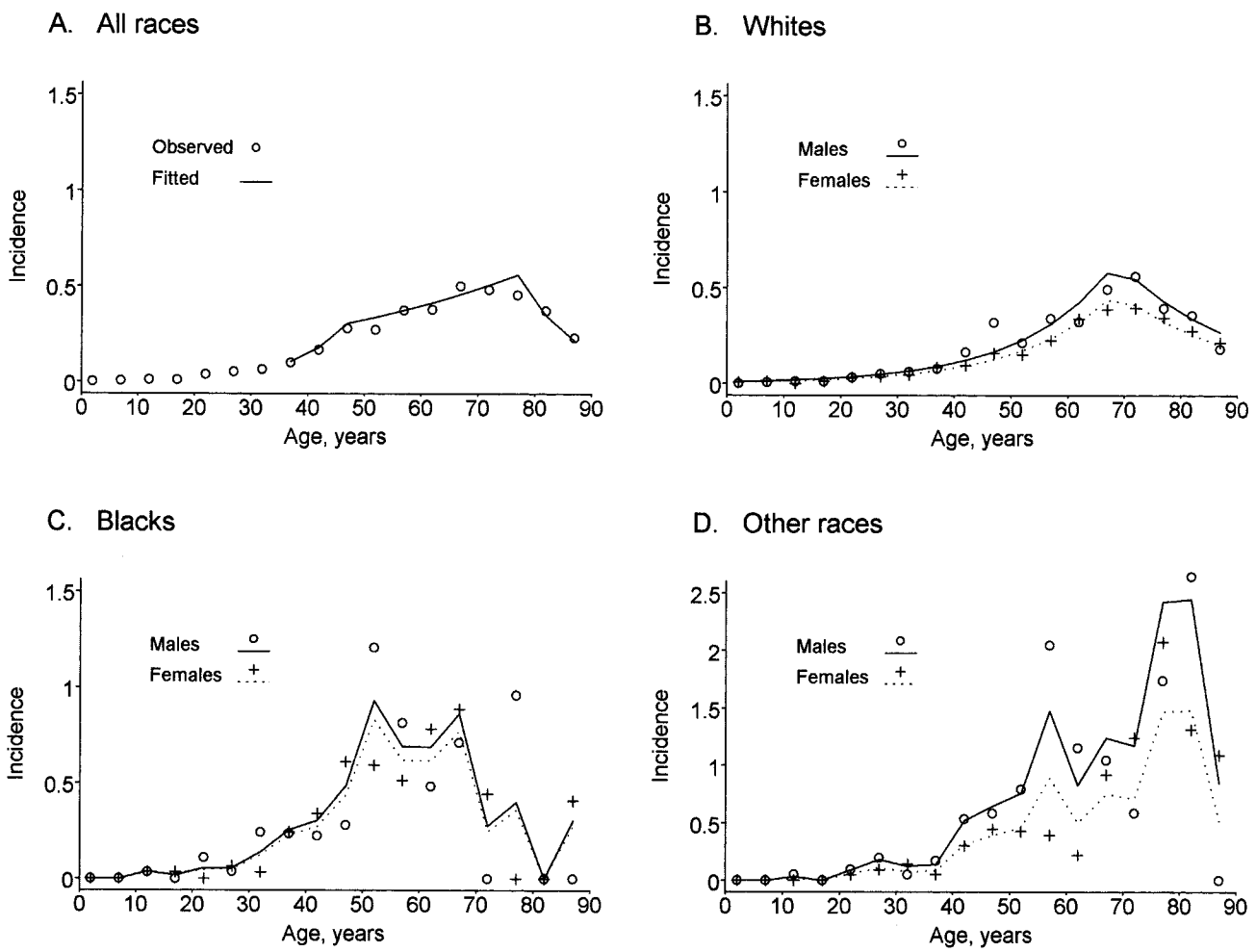

FIGURE 1 – Age-specific incidence of thymoma. Observed and fitted values for thymoma incidence (per 100,000 person-years) are plotted as a function of age, for all races (*a*), whites (*b*), blacks (*c*) and persons of other race (*d*). Observed values are shown as points, while fitted values are shown as lines. In (*a*), fitted values are based on a joinpoint regression model for ages 35 years and older and are shown for both sexes combined. In (*b*), fitted values are based on a Poisson regression model with sex and piecewise linear terms for age ($\leq$ 72 *vs.* $>$ 72 years). In (*c*) and (*d*), fitted values are derived from Poisson models with sex and age (categorized into 18 5-year categories). Note that the vertical scale differs in (*d*) from the other panels. As the regression models were fitted on a logarithmic scale, the linear segments appear curved. Data are from 9 SEER registries, 1973–1998.

RESULTS

Thymoma incidence

During the period 1973–1998, there were 849 cases of malignant thymoma in persons of known race (incidence 0.15 per 100,000 person-years). The mean age of cases was 56 years, and only 11% of cases occurred before age 35 years. Overall, thymoma incidence increased until age 77 years and decreased thereafter (Fig. 1*a*). A change of slope ("shoulder") in age-specific incidence was also seen at age 42 years. In agreement with these observations, a joinpoint model with 2 changes in slope fitted better than models with either 1 change or no change in slope ($p=0.005$ and $p=0.0004$, respectively). The slopes in the 42–77 and >77 year age ranges differed significantly ($p=0.007$), suggesting that the peak at 77 years was not due to chance. In contrast, the difference in slopes between the <42 and 42–77 year age ranges was less significant ($p=0.04$) and was not seen when incidence data were modeled on a linear scale (data not shown). Overall, incidence was higher in males than females (0.16 *vs.* 0.13 per 100,000 person-years, based on 455 *vs.* 394 cases; $p=0.007$). Also, compared to whites (incidence 0.12 per 100,000 person-years, 591 cases), incidence was higher in blacks (0.20 per 100,000, 120 cases; $p<0.0001$) and persons of other race (0.29 per 100,000, 138 cases; $p<0.0001$).

When we considered 5 age categories (0–29, 30–44, 45–64, 65–79 and 80+ years), there was evidence that age-specific patterns in incidence differed by race (age by race interaction, $p=0.03$). We therefore studied each race separately. Among whites, incidence increased until age 72 years and then decreased, for both males and females (Fig. 1*b*). Accordingly, a model with 1 joinpoint fitted better than a model with no joinpoint ($p=0.0002$), and the difference in slope before and after age 72 years was significant ($p<0.0001$). After controlling for age in a piecewise linear model (age ≤ 72 *vs.* > 72 years), males still had higher thymoma incidence than females (relative risk 1.15, 95%CI 1.06–1.25).

Among blacks, incidence peaked at age 52 years, although this peak was not statistically significant (models with 1 joinpoint *vs.* no joinpoint, $p=0.61$). For persons of other race, incidence peaked at age 77 years (models with 1 joinpoint *vs.* no joinpoint, $p=0.10$). After adjustment for age, thymoma incidence was similar for males and females among blacks (relative risk 1.06, 95%CI 0.88–1.26) but higher in males than females among persons of other race (1.29, 1.09–1.52).

During the 1992–1998 period, thymoma incidence was more than twice as high in Hawaii than in other registries ($p<0.0001$; Fig. 2*a*). This was due to high incidence in Asians/Pacific Islanders (0.49 per 100,000 person-years, based on 28 cases), since incidence was not elevated among whites (0.09 per 100,000 person-years, 2 cases), blacks (0 cases) or American Indians/Aleutian Islanders/Eskimos (0 cases). Similarly, thymoma incidence was elevated, though not as high, among Asians/Pacific Islanders in the

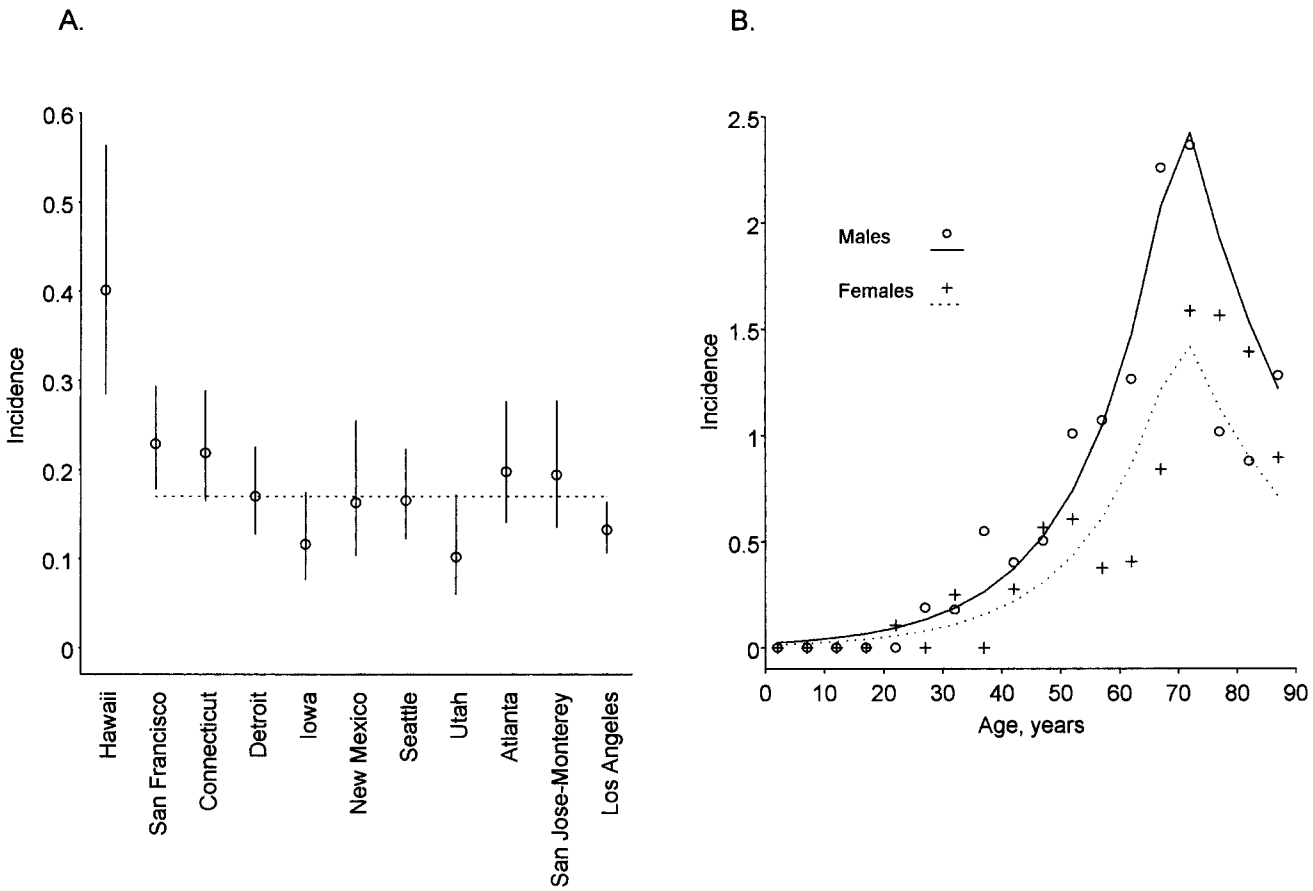

FIGURE 2 – Thymoma incidence by registry and among Asians/Pacific Islanders. (*a*) Thymoma incidence (per 100,000 person-years) by SEER registry is depicted. Point estimates and 95% confidence intervals are shown for each registry. The horizontal dotted line shows the mean incidence across all registries excluding Hawaii. In (*b*), incidence (per 100,000 person-years) is shown as a function of age for Asians/Pacific Islanders in all registries, 1992–1998. Observed values are shown as points, while fitted values are shown as lines. Fitted values are based on a Poisson regression model with sex and piecewise linear terms for age (≤ 72 *vs.* > 72 years). The vertical scale is the same as in Figure 1*d* (as in Fig. 1, the regression model was fitted on a logarithmic scale). Data are from 11 SEER registries, 1992–1998.

other 10 SEER registries (0.31 per 100,000 person-years, 62 cases).

Among all Asians/Pacific Islanders, incidence peaked at age 72 years, the same age as in whites (Fig. 2*b*). A model with 1 joinpoint was preferred over a model with no joinpoint ($p=0.003$), and the change in slope at age 72 years was significant ($p=0.003$). After controlling for age in a piecewise linear model (age $<$ 72 *vs.* $>$ 72 years), males had higher thymoma incidence than females (relative risk 1.71, 95%CI 1.12–.60).

Malignancies following thymoma

At 2 months after diagnosis, 733 patients were alive and were analyzed for subsequent malignancies. Of these, 509 (69.4%) had received cancer-directed surgery and 514 (70.1%) had received radiotherapy. The mean follow-up for subsequent malignancies was 5.3 years.

Overall cancer risk was elevated among surviving thymoma patients (66 cancers, SIR 1.5, 95%CI 1.2–1.9). Table I describes these subsequent malignancies. There was no significant excess for most cancer types, including cancers of the respiratory, urinary and male/female reproductive systems. On the other hand, we found an increase in digestive system cancers (SIR 1.8, 95%CI 1.1–2.9, $p=0.02$). No specific site entirely accounted for this finding, with nonsignificant excesses noted for cancers of the esophagus (SIR 3.8, 95%CI 0.5–13.6), stomach (2.8, 0.6–8.2), colon and rectum (1.7, 0.8–3.1) and liver/biliary tract (3.8, 0.8–11.2).

Notably, non-Hodgkin's lymphoma (NHL) occurred excessively among persons with thymoma (7 cases, SIR 4.7, 95%CI 1.7–9.6, $p=0.002$). NHL risk was elevated up to 10 years after thymoma diagnosis: SIRs were 11.8 (95%CI 1.4–42.5, 2 cases) less than 1 year post-diagnosis, 3.4 (0.4–12.2, 2 cases) in 1–4 years post-diagnosis and 7.1 (1.5–20.9, 3 cases) in 5–9 years post-diagnosis. All NHL cases occurred in irradiated patients. Five NHLs arose in lymph nodes and were classified histologically as diffuse large cell (2 cases), small lymphocytic (1 case), poorly differentiated lymphocytic (1 case) or not specified (1 case). The 2 extranodal NHLs were diffuse large cell NHL of the stomach and NHL originating in the parotid gland (histology not specified). Of the 4 NHLs with immunophenotyping, all were B cell tumors.

We also found an excess of soft tissue sarcomas (SIR 11.1, 95%CI 1.3–40.1, $p=0.03$), due to 2 cases (malignant fibrous histiocytoma and liposarcoma). Although 1 patient had received radiotherapy for thymoma, the sarcomas occurred at sites distant from the thymus. There were no bone/joint sarcomas or cases of Kaposi's sarcoma.

Among patients with subsequent malignancies, the proportions who had received either surgery or irradiation as primary therapy for thymoma (75% and 72%, respectively) was similar to the corresponding proportions among all thymoma patients. Among irradiated patients, we did not see an increased risk for cancers of solid organs potentially in the radiation field (SIRs 0 for thyroid, 1.7 for breast and 1.3 for lung). However, risk for acute nonlymphocytic leukemia (ANLL) was elevated in irradiated patients (SIR 9.1, 95% CI 1.1–32.8, 2 cases).

Five thymoma patients were each diagnosed with 2 subsequent malignancies (Table II). Of interest, 4 of these patients developed lung cancer. The proportion of malignancies that were lung cancer in persons with 2 subsequent malignancies (4/10, 40%) was higher than in persons with only 1 subsequent malignancy (6/56, 11%; $p=0.04$). The fifth patient developed bilateral breast cancer and ANLL.

TABLE I – SUBSEQUENT MALIGNANCIES AMONG PATIENTS WITH THYMOMA (N = 733)

Site[1]	Cancers (%)[2]	Standardized incidence ratio (95% CI)
Oral cavity/pharynx	1 (0.1)	0.8 (0.0–4.5)
Digestive system	18 (2.5)	1.8 (1.1–2.9)
Esophagus	2 (0.3)	3.8 (0.5–13.6)
Stomach	3 (0.4)	2.8 (0.6–8.2)
Colon/rectum	10 (1.4)	1.7 (0.8–3.1)
Liver/biliary tract	3 (0.4)	3.8 (0.8–11.2)
Respiratory system	12 (1.6)	1.5 (0.8–2.7)
Larynx	2 (0.3)	3.8 (0.5–13.9)
Lung/bronchus	10 (1.4)	1.4 (0.7–2.6)
Female breast	6 (0.8)	1.2 (0.4–2.5)
Female reproductive system	1 (0.1)	0.4 (0.0–2.4)
Uterus	1 (0.1)	0.9 (0.0–5.0)
Ovary	—	0 (0.0–4.5)[3]
Male reproductive system	10 (1.4)	1.3 (0.6–2.4)
Prostate	10 (1.4)	1.3 (0.6–2.4)
Urinary system	3 (0.4)	0.9 (0.2–2.8)
Kidney	1 (0.1)	1.1 (0.0–6.3)
Bladder	2 (0.3)	1.0 (0.1–3.5)
Nervous system	1 (0.1)	2.2 (0.1–12.1)
Thyroid	—	0 (0.0–9.4)[3]
Bones/joints	—	0 (0.0–74.9)[3]
Soft tissue/heart	2 (0.3)	11.1 (1.3–40.1)
Non-Hodgkin's lymphoma	7 (1.0)	4.7 (1.9–9.6)
Hodgkin's disease	—	0 (0.0–25.0)[3]
Leukemia	3 (0.4)	2.9 (0.6–8.4)
Multiple myeloma	1 (0.1)	1.8 (0.0–9.8)
Melanoma	1 (0.1)	1.1 (0.0–5.9)
All sites	66 (9.0)	1.5 (1.2–1.9)

[1]Not shown in the table are the following diagnoses with zero observed events: miscellaneous cancers of the digestive system (small intestine, anus, pancreas, retroperitoneum), respiratory system (nasal cavity, trachea), female genital system (cervix, vulva, vagina), and male genital system (testis, penis); adrenal gland; eye and orbit; mesothelioma; Kaposi's sarcoma; and malignancies at ill-defined sites– [2]Number of cancers are expressed as a percentage of patients with thymoma. Five patients, including one patient with two breast cancers, are each counted twice– [3]One-sided confidence interval.

DISCUSSION

Malignant thymoma is exceptionally rare (overall incidence 0.15 per 100,000 person-years). Our study is the first to use population-based data to describe demographic patterns in thymoma incidence and the associations between thymoma and subsequent cancers. It is important to note that we did not study "benign" thymomas. The distinction between "benign" and "malignant" is usually based on apparent invasiveness and may not reflect fundamental biological differences. Because benign thymomas may comprise as much as 67% of thymomas,[14] we underestimated overall thymoma incidence. Nonetheless, our findings provide a useful context for framing hypotheses regarding the pathogenesis of thymoma generally.

Malignant thymoma is primarily a cancer of middle- or older-aged adults. In these U.S. data, few thymoma cases arose before age 35 years, and incidence increased during middle age and into the 7th and 8th decades of life. Of interest, among whites (the largest racial group) and Asians/Pacific Islanders (the highest-risk group), incidence peaked after age 70 years and then declined (Figs. 1 and 2). Age-related changes in the thymus might explain this observation. Thymic function decreases as individuals age, as demonstrated by progressive declines in the number of circulating naive CD4+ and CD8+ T lymphocytes.[1] One may hypothesize that this reflects changes in the number or phenotype of thymic epithelial cells (*e.g.*, decreased activity and increased tendency to enter apoptosis), which could reduce the probability of their neoplastic transformation.

Alternatively, this pattern of increasing and then decreasing incidence for thymoma could be explained by a "birth cohort" effect, as is seen for lung cancer.[15] In the U.S., lung cancer incidence exhibits a similar peak at age 75–79 years (SEER data, not shown). This is thought to arise because cigarettes were first mass produced in the U.S. after World War I, so that individuals born before 1890, as a group, began smoking at an older age than persons born later. No exposure with changing prevalence over time, such as tobacco, has been linked to thymoma, and our data

TABLE II – THYMOMA PATIENTS WITH TWO SUBSEQUENT MALIGNANCIES

Patient	Race, sex	Age at thymoma diagnosis, y	Second malignancy	Age at second malignancy, y	Third malignancy	Age at third malignancy, y
1	White, male	48	Melanoma, lower limb	55	Lung carcinoma	59
2	White, male	53	Non-Hodgkin's lymphoma	59	Lung carcinoma	64
3	Asian (Japanese), male	64	Malignant fibrous histiocytoma, upper limb	70	Lung carcinoma	71
4	White, female	65	Breast carcinoma, bilateral	68	Acute nonlymphocytic leukemia	69
5	Black, female	66	Lung carcinoma	67	Stomach carcinoma (signet-ring cell)	70

were too sparse to separate the effects of age and birth year on incidence. The peak in age-specific incidence could also arise if thymoma is underdiagnosed in the elderly. This would occur, for instance, if symptoms of thymoma (such as weakness from myasthenia gravis) were not pursued. Of relevance in this regard, the presentation of thymoma in the elderly has not been described.

Thymoma incidence also varied by race. Specifically, incidence was higher in Asians/Pacific Islanders and blacks than in whites. These differences could arise from genetic polymorphisms that affect thymoma risk. For example, the distribution of alleles at the human leukocyte antigen (HLA) locus on chromosome 6 varies markedly across racial groups.[16] Both class I and class II HLA proteins are highly expressed on thymic epithelial cells.[17] Further research is needed to understand whether particular genetic variants (at HLA or other loci) predispose to thymoma.

Additionally, males had slightly higher thymoma risk than females. Animal models of thymoma offer conflicting evidence on the importance of sex and reproductive hormones.[18,19] We did not find significantly elevated (or reduced) risk for tumors of reproductive organs among thymoma patients, arguing against a role for hormonal factors. In humans, males have higher risk than females for cancers at many sites, which might be due to a higher prevalence of occupational or other environmental exposures in males.

The second part of our study dealt with subsequent malignancies, which arose in 9% of thymoma patients. Importantly, increased risk was limited specifically to NHL, digestive site cancers and soft tissue sarcoma. Our results thus suggest a more limited spectrum of cancers associated with thymoma than reported in 3 large prior studies,[9–11] 2 of which found additional malignancies in 20–28% of thymoma patients.[10,11]. Differences between these studies are unlikely to arise from differences in patient treatments since we did not find evidence that irradiation or thymic surgery strongly affected cancer risk. Similarly, Vessey *et al.* did not find increased overall cancer risk in myasthenia gravis patients treated with thymectomy.[20] Unlike our study, prior studies included "benign" thymomas,[9–11,20] but it seems improbable that benign thymomas would more frequently be associated with subsequent cancers than malignant thymomas. Indeed, the prior studies of thymoma-associated cancers may have overestimated risk, as they were each based at single tertiary referral centers.[9–11] Furthermore, one study was an autopsy series.[11] Our study is the first to compare incident cancers with those expected based on population rates.

In our analysis, the single most important cancer association with thymoma was for NHL (SIR 4.7). In cases where immunophenotyping was performed, the NHLs were all of B lymphocyte origin. Diagnostic confusion of thymic NHLs with thymoma could explain this association. However, the presence of continued increased risk for a decade following thymoma diagnosis argues against this explanation. It is plausible that abnormally functioning T lymphocytes, arising in association with thymoma or its treatment, either induce or fail to control B lymphocyte proliferation, which could then lead to NHL. Along these lines, much higher NHL risk, particularly for high-grade NHLs, is present with more severe T lymphocyte dysfunction, as seen in acquired immunodeficiency syndrome (AIDS) or following organ transplantation.[21,22] There were no cases of Kaposi's sarcoma, which is extremely common in AIDS, possibly because thymoma-related immune dysfunction is less severe or because infection with Kaposi's sarcoma-associated herpesvirus (the causative viral agent) may be uncommon among thymoma patients.

The modest increase among thymoma patients in digestive tract cancers was not due to a clear excess at a particular site. Based on only 2 cases, we found an increased risk of soft tissue sarcoma (SIR 11.1). Elevated risk for malignant fibrous histiocytoma (1 type that we observed) has previously been described following thymoma.[23] Of interest, our patient with malignant fibrous histiocytoma was Japanese, as were the previously described patients.[23] This association might be due to shared genetic or environmental risk factors and should be explored further.

Radiotherapy could have played a role in the excess risk of hematologic malignancies. All NHLs in our series occurred in irradiated patients. There is some evidence that irradiation of the thymus in infancy increases NHL risk,[24] and radiotherapy for thymoma (given with or instead of surgery) might augment NHL risk by damaging remaining normal thymus tissue. Irradiated patients also had an elevated risk for ANLL, consistent with known radiation effects.[25]

The lack of thymoma cases in young people, and the lack of broadly elevated second cancer risk at a range of sites, together imply that thymoma does not commonly arise as a component of an inherited cancer syndrome, such as Li-Fraumeni syndrome or hereditary retinoblastoma. However, 4 of the 5 thymoma patients with 2 subsequent malignancies had lung cancer (Table II). The association between thymoma, lung cancer and other malignancies needs to be examined further.

The major limitation of our study was the small number of thymoma cases. Nonetheless, our study was larger than the largest 3 previous studies of subsequent cancers combined.[9–11] Furthermore, our study's validity was enhanced by its inclusion of thymoma patients diagnosed and treated in diverse clinical settings across the U.S., and by its use of population rates to establish expected numbers of cancers.

In summary, we identified several areas for additional research. The late-life peak in thymoma incidence suggests that age-related changes in thymic epithelial cell function affect the probability of neoplastic transformation. Other explanations for this peak, including a cohort effect or underdiagnosis in the elderly, deserve consideration. Racial differences in thymoma incidence highlight the possible role of genetic factors (*e.g.*, HLA) in thymoma pathogenesis. Contrary to previous reports,[10,11] we did not find a broad excess of subsequent cancers. The strongest link was between thymoma and NHL, which was possibly due to abnormal regulation of B lymphocyte proliferation by dysfunctional T lymphocytes.

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REFERENCES

1. Douek DC, McFarland RD, Keiser PH, Gage EA, Massey JM, Haynes BF, Polis MA, Haase AT, Feinberg MB, Sullivan JL, Jamieson BD, Zack JA, et al. Changes in thymic function with age and during treatment of HIV infection. Nature 1998;396:690–5.
2. Müller-Hermelink HK, Marx A. Thymoma. Current Opin Oncol 2000;12:426–33.
3. Buckley C, Douek D, Newsom-Davis J, Vincent A, Wilcox N. Mature, long-lived CD4+ and CD8+ T cells are generated by the thymoma in myasthenia gravis. Ann Neurol 2001;50:64–72.
4. Souadjian JV, Enriquez P, Silverstein MN, Pépin J-M. The spectrum of diseases associated with thymoma. Arch Intern Med 1974;134: 374–79.
5. Thomas CR, Wright CD, Loehrer PJ Sr. Thymoma: state of the art. J Clin Oncol 1999;17:2280–9.
6. Bass Wilkins K, Sheikh E, Green R, Patel M, George S, Takano M, Diener-West M, Welsh J, Howard S, Askin F, Bulkley GB. Clinical and pathological predictors of survival in patients with thymoma. Ann Surg 1999;230:562–74.
7. Couture MM, Mountain CF. Thymoma. Sem Surg Oncol 1990;6: 110–4.
8. Salyer WR, Eggleston JC. Thymoma. A clinical and pathological study of 65 cases. Cancer 1976;37:229–49.
9. Pan C, Chen PC, Wang L, Chi K, Chiang H. Thymoma is associated with an increased risk of second malignancy. Cancer 2001;92:2406–11.
10. Welsh JS, Bass Wilkins K, Green R, Bulkley G, Askin F, Diener-West M, Howard SP. Association between thymoma and second neoplasms. JAMA 2000;283:1142–3.
11. Souadjian JV, Silverstein MN, Titus JL. Thymoma and cancer. Cancer 1968;22:1221–5.
12. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. Stat Med 2000; 19:335–51.
13. Breslow NE, Day NE. Statistical methods in cancer research, vol 2. Lyon: IARC, 1987.
14. Verley JM, Hollmann KH. Thymoma. A comparative study of clinical stages, histologic features, and survival in 200 cases. Cancer 1985; 55:1074–86.
15. Changes in cigarette-related disease risks and their implication for prevention and control (97-4213). National Institutes of Health, 1997.
16. Imanishi T, Gojobori T. Diversity in human MHC genes among ethnic groups worldwide. In: Tajima K, Sonoda S, eds. Ethnoepidemiology of cancer. Tokyo: Japan Scientific Societies Press, 1996. 89–96.
17. Vukmanovic S, Bevan MJ, Hogquist KA. The specificity of positive selection: MHC and peptides. Immunol Rev 1993;135:51–66.
18. Seiki K, Sakabe K. Sex hormones and the thymus in relation to thymocyte proliferation and maturation. Arch Histol Cytol 1997;60: 29–38.
19. Nakajima H, Nakajima HO, Soonpaa MH, Jing S, Field LJ. Heritable lympho-epithelial thymoma resulting from a transgene insertional mutation. Oncogene 2000;19:32–8.
20. Vessey MP, Doll R, Norman-Smith B, Hill ID. Thymectomy and cancer: a further report. Br J Cancer 1979;39:193–5.
21. Hoover R, Fraumeni JF Jr. Risk of cancer in renal-transplant recipients. Lancet 1973;2:55–7.
22. Frisch M, Biggar RJ, Engels EA, Goedert JJ. Association of cancer with AIDS-related immunosuppression in adults. JAMA 2001;285: 1736–45.
23. Masaoka A, Yamakawa Y, Niwa H, Fukai I, Saito Y, Tokudome S, Nakahara K, Fujii Y. Thymectomy and malignancy. Eur J Cardiothorac Surg 1994;8:251–3.
24. Hempelmann LH, Hall WJ, Phillips M, Cooper RA, Ames WR. Neoplasms in persons treated with X-rays in infancy: fourth survey in 20 years. J Natl Cancer Inst 1975;55:519–30.
25. Preston DL, Kusumi S, Tomonaga M, Isumi S, Ron E, Kuramoto A, Kamada N, Dohy H, Matsuo T. Cancer incidence in atomic bomb survivors. Part III. Leukemia, lymphoma and multiple myeloma, 1950–1987. Radiat Res 1994;137:S68–97.