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# Epidemiology of thymoma and associated malignancies

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## Abstract

Thymoma is a rare malignancy of unknown etiology. Based on cancer registry data, the overall incidence of thymoma in the U.S. is 0.13 per 100,000 person-years. Thymoma is exceedingly uncommon in children and young adults, rises in incidence in middle age, and peaks in the seventh decade of life. For unknown reasons, thymoma incidence is especially high among Asians and Pacific Islanders in the U.S. While several studies based at single treatment centers have suggested that thymoma patients have a broadly increased risk for other malignancies, follow up data from U.S. cancer registries support a more limited spectrum of cancer risk. In particular, people with thymoma have a subsequently elevated risk for developing B-cell non-Hodgkin lymphoma, consistent with an effect of immune disturbance arising from the thymoma or its treatment. Based on limited data, thymoma patients may also have an elevated risk for developing soft tissue sarcomas. While these descriptive epidemiologic data may yield clues to the etiology of thymoma, large multi-center case-control studies will be required to formally evaluate environmental and genetic risk factors.

## Introduction

As the site of maturation for T-cells, the thymus plays a central role in adaptive immunity. 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-cell maturation (1). Histologically, thymomas frequently have an accompanying rich infiltrate of T-cells. When released into the circulation (2), these abnormally conditioned T-cells and are likely responsible for the autoimmune conditions that often accompany thymoma, such as myasthenia gravis, blood disorders, and connective tissue diseases (3).

The cause of thymoma is unknown. Due to the rarity of this cancer, most studies of thymoma have been based on small numbers of clinical cases recruited at single treatment centers. In this article, I review the epidemiology of this malignancy using data collected by population-based cancer registries in order to outline some possible clues to its etiology. I also review studies that have examined the associations between thymoma and other malignancies, because such studies can shed light on risk factors that these malignancies share and thus the biology of thymoma.

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## Descriptive epidemiology of thymoma

Information on the demographic characteristics associated with thymoma incidence can yield clues to relevant etiologic factors (4). In the U.S., the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program provides population-based data on cancer incidence for 18 states and metropolitan regions (www.seer.cancer.gov). Together, the SEER cancer registries currently cover approximately 26% of the U.S. general population. Reporting of all malignancies other than basal cell and squamous cell skin cancers is mandated by U.S. state laws, and ascertainment of invasive cancers by SEER is considered essentially complete.

Thymomas have a variable presentation, manifesting either concurrently with myasthenia gravis (one third of cases), with local symptoms (e.g., chest pain, neck mass, superior vena cava syndrome; one third), or asymptomatically as a mediastinal mass on chest radiography (approximately one third of cases) (5-7). Thymomas can be classified as "malignant" or "benign" based on evidence for capsular invasion. Because of the variable presentation and apparent invasiveness, it is likely that not all thymoma cases are captured by cancer registries, because thymomas with a benign behavior or extent limited within the thymic capsule might not be considered malignant by clinicians or diagnosed as such by pathologists. If such cases are not recorded in cancer registries, estimates of thymoma incidence based on registry data would be artifactually low. The frequency of under-ascertainment of thymoma by cancer registries is unknown.

Based on SEER data, the overall incidence of thymoma in the U.S. is 0.13 per 100,000 person-years (Table 1). Although this estimate may be too low for the reasons enumerated above, it is nonetheless apparent that thymoma is a rare cancer. For example, a simple extrapolation to the U.S. population (300 million people) would lead to an estimate of 390 cases per year in the entire country. Thymoma incidence has declined over time (Figure 1A), but this trend could potentially reflect changes in the classification of thymoma or trends in reporting to SEER. Thymoma incidence is similar in males and females (Table 1). Thymoma is exceedingly uncommon in children and young adults, rises in incidence in middle age, and peaks in the seventh decade of life (Figure 1B). This pattern mirrors the age-related rise in incidence for many other cancers and presumably reflects the accumulation of genetic damage with age (8). Nonetheless, the increase in thymoma incidence with age is in striking contrast to the progressive involution of the thymus with age (9), which presumably would reduce the likelihood of malignant transformation of thymic epithelial cells. The decline in thymoma incidence at the oldest ages (Figure 1B) is also unexplained.

Of interest, thymoma incidence in the U.S. is higher in blacks and especially Asians/Pacific Islanders than among whites or Hispanics (Table 1). As shown in Table 1, an elevated risk appears to be present for all major groups of Asians/Pacific Islanders. Furthermore, thymoma arises among blacks at a much younger age than among whites (median age at diagnosis 48 vs. 58 years, SEER data).

Consideration of available epidemiologic data for related medical conditions may also be informative. Like thymoma, myasthenia gravis is extremely rare (incidence 0.4-1.1 per 100,000 person-years) (10-12), and little is known about its epidemiology. In the U.S., myasthenia gravis may be more common in blacks than whites (12), mirroring the pattern for thymoma. Also of interest, Asians have a relatively high risk for developing cancers of the nasopharynx and salivary gland, which (like thymoma) derive from the embryonic foregut (13). The reasons for this clustering of cancer risk among Asians are unclear.

## Secondary malignancies associated with thymoma

Careful evaluation of risk for additional cancers in individuals with thymoma can also be informative with respect to the etiology of thymoma. For example, an increased risk of specific cancers in patients with thymoma could indicate that those cancers share genetic or environmental risk factors with thymoma. Additionally, an elevated risk for specific cancers after thymoma may suggest that the immune dysregulation caused by thymoma predisposes to those cancers. Finally, therapy for thymoma might increase the risk for certain cancers, for example, related to surgery (thymectomy leading to immunosuppression) or radiotherapy (leading to cancers in the radiation field).

Three studies based at single treatment centers have suggested that thymoma patients have a broadly increased risk for cancer, perhaps related to genetic predisposition or immune disturbance (14-16). The secondary malignancies that were described in these patient series included both common cancers (e.g., cancers of the lung, thyroid, and prostate, and lymphomas) and rare malignancies (e.g., brain tumors, sarcomas, and leukemias). Overall cancer risk was estimated to be 3-4 times higher in thymoma patients than in controls (15, 16). Nonetheless, a limitation of these studies is that they were small (100-200 thymoma patients in each study), which precluded a precise estimate of overall cancer risk and made them uninformative for specific cancer types. Thus, it is not possible from these studies to determine whether cancer risk is elevated for a wide spectrum of cancers, or whether any increased risk is restricted to a subset of malignancies. Furthermore, patients were all treated at a single referral center and may not be representative of other thymoma cases. Finally, control groups that served as a basis for comparison with thymoma patients (i.e., patients with parathyroid adenomas, nasopharyngeal carcinoma, or thymectomy) were also not representative of the general population (15,16).

An alternative approach is to use cancer registry data to compare cancer incidence in thymoma patients to the general population. Advantages include the availability of a large and representative sample of thymoma cases from the registry, systematic ascertainment of secondary malignancies through reports to the cancer registry, and availability of cancer rates from the general population to serve as an appropriate comparison. The ratio of cancer incidence observed in thymoma cases to cancer incidence expected based on general population rates (standardized according to sex, age, race, and calendar year) yields a standardized incidence ratio (SIR) that approximates the relative risk for cancer associated with thymoma.

In a 2003 study (4), Engels and Pfeiffer used SEER data to evaluate cancer incidence in 733 U.S. thymoma patients relative to the general population. The study was larger than the three previously mentioned studies combined, and included cases drawn from a large geographic region of the U.S. Results from the study are shown in Table 2. Secondary malignancies arose in 66 (9%) thymoma patients, corresponding to an overall SIR of only 1.5, which was a more modest elevation than seen in the hospital-based series (15,16). Specific malignancies for which thymoma patients had an elevated risk included cancers of the digestive system as a group (SIR 1.8 based on 18 cases), non-Hodgkin lymphoma (NHL, SIR 4.7 based on 7 cases), and soft tissue sarcomas (SIR 11.1 based on 2 cases). The study thus suggests a more limited spectrum of cancers associated with thymoma than reported in the three prior studies (14-16).

The most important association in Table 2 was for NHL (4). Diagnostic confusion of thymic NHLs with thymoma could potentially explain this association. However, among NHLs where immunophenotyping was performed, all were of B-cell origin. Also arguing against an artifactual explanation, NHL risk was elevated for a prolonged period after thymoma diagnosis, with an SIR of 7.1 in the 5-9 year period after thymoma diagnosis. Instead, it is plausible that abnormally functioning T-cells, arising in association with thymoma, either induce or fail to

control B-cell proliferation, which could then lead to NHL. Likewise, much higher NHL risk is present with more severe T-cell dysfunction, as seen in acquired immunodeficiency syndrome (AIDS) or following organ transplantation (17), and in patients with autoimmune conditions (18,19).

In the Engels and Pfeiffer study (4), the modest increase of digestive tract cancers among thymoma patients was difficult to explain, because it was not due to a clear excess at a particular site (Table 2). The increased risk of soft tissue sarcoma was attributable to only two cases. One of these cases was a liposarcoma, and the other was a malignant fibrous histiocytoma in a Japanese person. The occurrence of malignant fibrous histiocytoma is notable because a prior study described three cases of this sarcoma among 102 Japanese thymoma patients (20). The association between thymoma and sarcomas might be due to shared genetic or environmental risk factors.

As noted above, studies that use cancer registry data are limited by inclusion of only malignant neoplasms. Could this limitation have biased the results of the second cancer study by Engels and Pfeiffer? As argued by Welsh (21), under-ascertainment of second cancers could occur if patients with malignant thymoma did not survive long enough to develop a second cancer. However, in the Souadjian study (15), there was an approximately three-fold relative risk for second cancers in the first 5-10 years after thymoma. In the Engels and Pfeiffer study (4), the mean duration of follow-up after thymoma diagnosis was 5.3 years; therefore, the duration of follow-up was likely long enough to detect a strongly increased overall cancer risk. Furthermore, the duration of follow-up of thymoma should not matter if the elevated risk in thymoma patients is due to a shared genetic or environmental etiology with the other cancer, because presumably that etiologic factor has been present for years prior to thymoma diagnosis. Finally, there is no clearly established biological reason why malignant thymomas would be intrinsically less likely to be associated with other cancers than benign thymomas.

A related complementary approach utilizes cancer registry data to examine thymoma risk following other first cancers. One prior report based on SEER data briefly mentioned that there was only a modestly elevated risk of thymoma following other cancer diagnoses (SIR 1.33), and that thymoma risk was not especially increased following any particular cancer (22).

Likewise, Table 3 presents risks for thymus malignancies following specific selected neoplasms, using updated SEER data. As suggested by Travis et al. (22), there is little evidence for an increased risk of thymoma following other cancers. Although wide confidence limits for the SIRs preclude strong conclusions, the null findings argue against strong genetic or environmental risk factors for thymoma that are common with other malignancies. The absence of an increased risk of thymoma following NHL (in distinction to the increased NHL risk following thymoma seen in Table 2) adds support to the hypothesis that the elevated risk of NHL arises due to the thymoma itself, i.e., from immune dysregulation. The association with digestive system cancers seen in Table 2 was not confirmed, and while there was a suggestive increase of thymoma following soft tissue/heart sarcomas, only one thymoma was observed (in a patient with a liposarcoma).

Finally, the absence of increased thymoma risk following lung cancer, breast cancer, and Hodgkin lymphoma, all of which are treated with radiation therapy to the chest, argues against ionizing radiation as a risk factor for thymoma. Further evidence against ionizing radiation as a predisposing factor comes from a study of infants who received thymic radiation to treat a benign enlarged thymus (23,24). Over several decades of follow-up, these individuals had an elevated risk for thyroid cancer, but no thymomas were reported.

## Possible risk factors for thymoma

Although limited, most available evidence regarding risk factors for thymoma derives from descriptive epidemiologic studies of thymoma and associated malignancies (reviewed above). A standard approach to unraveling the etiology of a malignancy, which usually follows on the descriptive epidemiology, is the case-control study, which can directly compare the frequency of potentially relevant environmental exposures, medical conditions, and genetic traits among cancer cases and controls. Unfortunately, no case-control study has been conducted of thymoma, and such a study would be difficult to implement given the rarity of this malignancy.

Table 4 lists the major risk factors considered for most cancers and summarizes the limited evidence for thymoma. The data reviewed above regarding risk of second cancers in association with thymoma do not suggest that tobacco or alcohol use are risk factors (i.e., absence of increased risk for cancers caused by these exposures, such as lung cancer and liver cancer, among thymoma patients), but such considerations can only rule out a very strong effect of these agents. There are no available data concerning the role of occupation, environmental exposures, or diet and nutrition.

The absence of reports regarding family clustering of thymoma would argue against strong genetic risk factors, although the rarity of thymoma and its onset at older ages would make it harder to detect such clustering. In contrast, the elevated risk among diverse Asians and Pacific Islanders suggests a genetic component, as does the association with malignant fibrous histiocytoma among Japanese.

Many cancers, particularly those caused by viruses, occur at increased frequency among immunosuppressed people. However, based on data from a large registry linkage study, the HIV/AIDS Cancer Match Study (25), thymoma risk was not elevated among 516,000 people with AIDS in the U.S. (4 thymoma cases, SIR 0.85) (Engels, unpublished analyses). Similarly, thymoma risk does not appear elevated among immunosuppressed solid organ transplant recipients, as a MEDLINE literature search (conducted by this author in July 2009) revealed no reported cases.

Viruses are implicated in other rare cancers (e.g., human herpesvirus 8 in Kaposi sarcoma), but evidence is limited for thymoma. Two reports described detection of human foamy virus, a retrovirus, in patients with thymoma or myasthenia gravis (26,27), but subsequent larger studies did not confirm the findings (28,29). In 2002, Manca et al. reported finding evidence for human T-cell lymphotropic virus type 1 infection in myasthenia gravis patients, some of whom had thymoma (30), but again these findings were not confirmed (28). Differing results across studies may reflect differences in the patient populations (e.g., geography), but more likely point to difficulties in laboratory methods (e.g., false positive results caused by contamination). Evidence is more convincing that Epstein Barr virus (EBV) is present in a subset of thymic carcinomas, specifically those which display a lymphoepithelial architecture (31-34).

## Conclusion

The available data regarding the descriptive epidemiology of thymoma are limited and yield few clues to the etiology of this malignancy. Thymoma incidence is higher in Asians/Pacific Islanders and blacks than in whites, suggesting that there may be genetic risk factors. This hypothesis is supported by the association between thymoma and sarcomas, particularly malignant fibrous histiocytoma among Japanese individuals. Given the contribution of genetic variation in development of other cancers, it would indeed be surprising if genetic risk factors were not present for thymoma. In the end, large multi-center case-control studies will be required to formally evaluate environmental and genetic risk factors for thymoma.

Research evaluating risk of second cancers among patients with thymoma has been somewhat inconclusive and limited by the rarity of thymoma. Studies based at single treatment centers have suggested a broadly increased risk for diverse malignancies, while another study that utilized data obtained from population-based cancer registries implicated a more limited spectrum of cancers. An elevated risk of NHL following thymoma plausibly arises as a result of disturbed T-cell immune function caused by thymoma or its treatment.

Looking to the future of descriptive epidemiologic studies of thymoma, it would be of interest to evaluate incidence patterns across several countries, to determine whether differences exist that might reflect variation in environmental or genetic risk factors. A key consideration is the under-ascertainment of thymoma by cancer registries, which occurs because clinicians and registrars consider some cases without apparent capsular invasion to be benign. To the extent that there is a consensus concerning the fundamental similarity across thymoma variants, cancer registries should endeavor to collect information on all cases of thymoma regardless of apparent invasiveness. Studies that jointly evaluate the descriptive epidemiology of both thymoma and myasthenia gravis might also provide valuable etiologic information.

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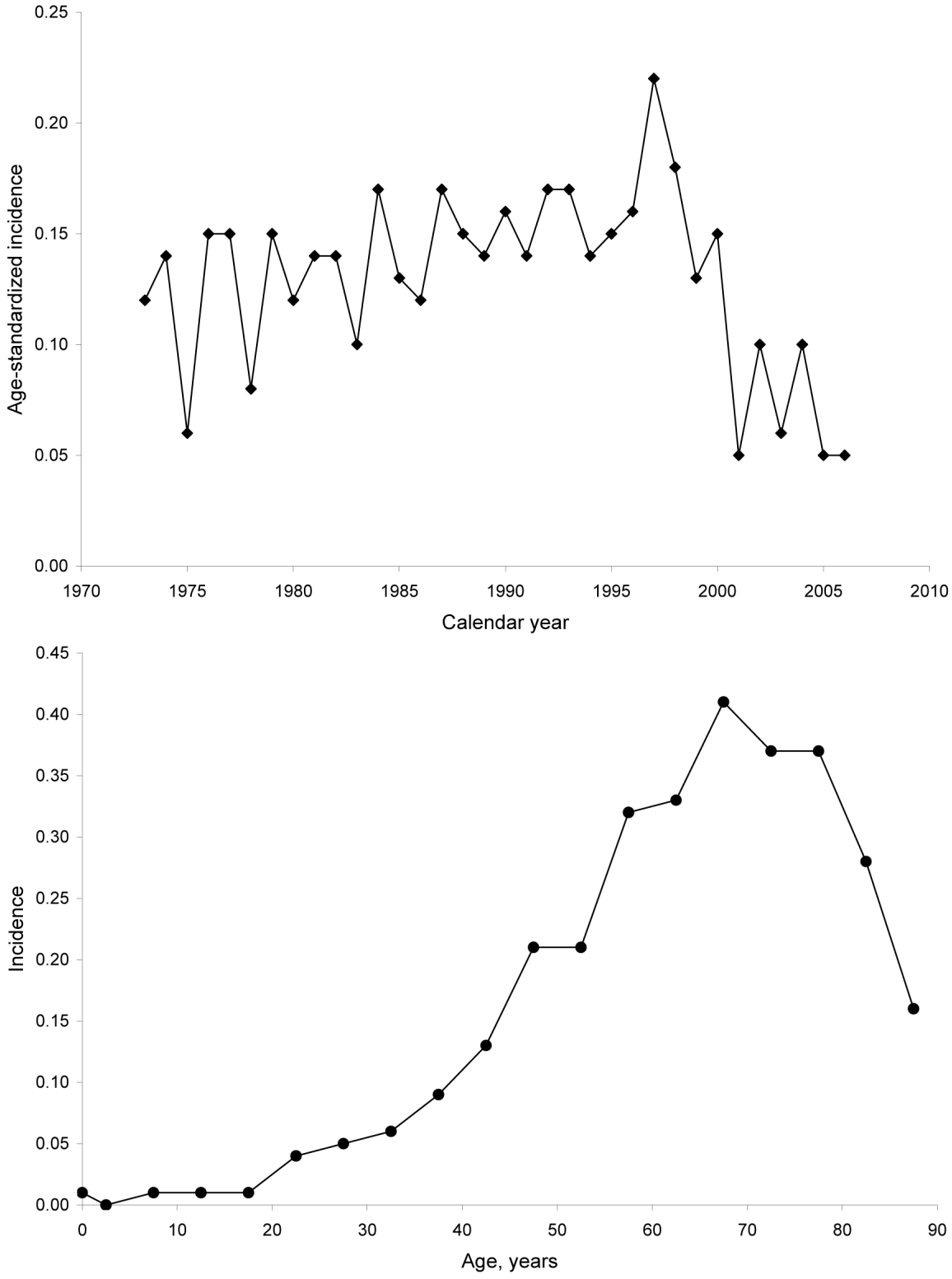


**Figure 1. Thymoma incidence in the U.S, according to calendar year and age at diagnosis**

Panel A shows incidence as a function of calendar year of diagnosis. Incidence is per 100,000 person-years and is standardized to the 2000 U.S. general population. Panel B shows incidence

as a function of age of diagnosis. Crude incidence is per 100,000 person-years. Data are from the SEER9 cancer registries (1973-2006, www.seer.cancer.gov).

## Table 1

Thymoma incidence in the United States (SEER data)

| Category* | Age-standardized incidence, per 100,000 person-years† |
|---|---|
| SEER9 (1973-2006) | |
| Overall | 0.13 |
| By sex | 0.14 |
| Males | 0.12 |
| Females | |
| SEER13 (1992-2006) | |
| By race/ethnicity | |
| Non-Hispanic white | 0.10 |
| Non-Hispanic black | 0.18 |
| Hispanic | 0.08 |
| Asian/Pacific Islander | 0.25 |
| SEER18 (1998-2002) | |
| By Asian/Pacific Islander subgroup | |
| Chinese | 0.17 |
| Japanese | 0.30 |
| Filipino | 0.18 |
| Korean | 0.17 |
| Vietnamese | 0.26 |

*Data are from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program (www.seer.cancer.gov). SEER9, SEER11, and SEER18 refer to the number of cancer registries providing data for the indicated calendar years. Data on Hispanic ethnicity and Asian/Pacific Islander subgroup were available only beginning in 1992 and 1998, respectively.

†Rates are age-standardized to the 2000 U.S. population.

## Table 2

Subsequent malignancies among U.S. patients with thymoma (N=733)

| Site* | Cancers, n (%)† | 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)‡ |
| 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)‡ |
| Bones/joints | - | 0 (0.0-74.9)‡ |
| Soft tissue/heart | 2 (0.3) | 11.1 (1.3-40.1) |
| Non-Hodgkin lymphoma | 7 (1.0) | 4.7 (1.9-9.6) |
| Hodgkin lymphoma | - | 0 (0.0-25.0)‡ |
| 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) |

Table is reproduced with permission from Engels and Pfeiffer (4).

*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.

†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.

‡One-sided confidence interval.

## Table 3

Risk of thymoma following selected other malignancies in the U.S.

| First malignancy | Thymoma cases, n | Standardized incidence ratio (95% CI) |
|---|---|---|
| Digestive system | 8 | 1.0 (0.4-2.0) |
| Lung/bronchus | 4 | 1.8 (0.5-4.7) |
| Female breast | 14 | 1.3 (0.7-2.2) |
| Non-Hodgkin lymphoma | 2 | 1.4 (0.2-5.1) |
| Hodgkin lymphoma | 1 | 3.6 (0.1-20) |
| Soft tissue/heart | 1 | 3.9 (0.1-21) |
| All sites | 68 | 1.3 (1.0-1.7) |

Data are from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program (www.seer.cancer.gov), SEER9 1973-2006. Thymoma risk is evaluated in people who have survived for more than two months after initial cancer diagnosis.

## Table 4

Potential risk factors for thymoma

| Cancer risk factor | Evidence regarding relevance in thymoma* | Comment |
|---|---|---|
| Tobacco/alcohol | - | Absence of increased risk of tobacco and alcohol related cancers. |
| Ionizing radiation | -- | No increased risk following radiation for benign enlarged thymus or other cancers. |
| Occupation | 0 | No data |
| Environmental contaminants | 0 | No data |
| Diet and nutrition | 0 | No data |
| Genetic variants | + | No family clustering. However, increased risk among Asians/Pacific Islanders, and association with sarcomas, are suggestive. |
| Immunosuppression | --- | No increased risk in HIV-infected people or transplant recipients. |
| Infections | - | Unconfirmed reports of associations with viral infections. However, EBV is likely involved in lymphoepithelial carcinoma variant. |

Abbrevitations: EBV Epstein Barr virus, HIV human immunodeficiency virus

*Symbols range from 3 minus signs (strong evidence against relevance), to a zero (no evidence), to 3 plus signs (strong evidence for relevance).