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Coupling of Prostate and Thyroid Cancer Diagnoses in the United States

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Abstract

Background—Prostate and thyroid cancers represent two of the most overdiagnosed tumors in the U.S. Hypothesizing that patients diagnosed with one of these malignancies were more likely to be diagnosed with the other, we examined the coupling of diagnoses of prostate and thyroid cancer in a large U.S. administrative dataset.

Methods—The SEER database was used to identify men diagnosed with clinically localized CaP or thyroid cancer between 1995 and 2010. SEER*stat software was used to estimate multivariable adjusted standardized incidence ratios (SIR's) and investigate the rates of subsequent malignancy diagnosis. Additional non-urologic cancer sites were added as control groups.

Results—Patients with thyroid cancer were much more likely to be diagnosed with prostate cancer than patients in the SEER control group (SIR 1.28 [CI 1.1–1.5]; $p<0.05$). Similarly, the

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observed incidence of thyroid cancer was significantly higher in patients with CAP when compared with SEER controls (SIR 1.30 [CI 1.2–1.4]; p<0.05). When stratified by follow-up interval, the observed thyroid cancer diagnosis rate among men with CAP was significantly higher than expected at 2–11 (SIR 1.83 [CI 1.4–2.4]), 12–59 (SIR 1.24 [CI 1.0–1.5]), and 60–119 (SIR 1.25 [CI 1.0–1.5]) months of follow-up. There was no increased risk of CAP or thyroid cancer diagnosis among patients with non-urologic malignancies.

Conclusions—There is a significant association of diagnoses with prostate and thyroid cancer in the U.S. In the absence of a known biological link between these tumors, these data suggest that diagnosis patterns for prostate and thyroid malignancies are linked.

Keywords

prostate cancer; thyroid cancer; overdiagnosis; incidence

Introduction

While prostate cancer (CAP) is the most common noncutaneous cancer in the United States,[1] the merits of widespread PSA-based screening are contested.[2,3] CAP screening has led to a potential reduction in advanced disease and prostate cancer specific mortality,[3] but diagnosis and overtreatment of clinically insignificant malignancy is a tremendous challenge for primary care providers, specialists, and men who undergo PSA-screening.[4] Depending on the method of assessment, estimates of overdiagnosis range from 1.7% to 67%,[4] and overtreatment is associated with a well-documented and significant burden of morbidity that affects quality of life.[5–7] A similar trend exists for thyroid cancer, as diagnosis of small and indolent tumors has steadily risen. [89] Indeed, incidence of thyroid cancer has nearly tripled since 1975, while the mortality rate is largely unchanged.[9]

Second-primary malignancies account for approximately 18% of incident cancers in the United States,[10] and the number of individuals who have undergone cancer treatment at some point in their lives is growing by 2% annually.[11] The development of subsequent cancers can be attributed to a number of potential risk factors, which include receipt of radiation or chemotherapy, genetic predisposition, environmental exposures, endocrinologic alterations, and compromise of immune function.[12,13] Increased long-term surveillance of individuals who have undergone cancer treatments influences subsequent cancer detection – a phenomenon known as surveillance bias.[12–1415–17] The type of care an individual receives may influence the likelihood of future cancer detection. For instance, exposure to urologic care for treatment of non-prostate-related malignancy significantly increases the likelihood of CAP detection, but not prostate cancer death.[18]

Because prostate and thyroid cancer are two of the most over-diagnosed malignancies in the United States, [4,19] it is possible that type, patterns, and intensity of care leading patients to be diagnosed with one of these cancers may result in discovery of the other. Hence we assessed the association of diagnoses of prostate and thyroid cancer in the U.S. using a large administrative dataset.

Material and Methods

The Surveillance Epidemiology and End Results (SEER) database of the National Cancer Institute was used to identify men diagnosed with clinically localized CAP or thyroid cancer between 1995 and 2010.[20] SEER collects data on all individuals diagnosed with cancer residing in several geographically defined regions of the United States.[21] We chose 12 registries based upon those with data available for all years of interest. The SEER registries include a broad spectrum of geographic regions and population densities within the United States, and include Detroit, Connecticut, Hawaii, Iowa, San Francisco-Oakland, Seattle, New Mexico, Utah, Atlanta, San Jose-Monterey, Los Angeles, and rural Georgia.

To measure the relative risk for prostate and thyroid cancer in patients treated for localized prostate or thyroid cancer compared with the general SEER registry population, we calculated standardized incidence ratio's (SIRs) for each type of second and higher primary cancer (i.e. observed/expected) along with its 95% confidence interval (CI). The SEER*Stat Multiple Primary-SIR program (version 8.1.2)[22] was used to calculate the SIRs.[23] The SIR estimates were obtained by using the MP-SIR macro in SEER*Stat. SIRs greater and less than 1 reflect an increase and decrease in tumor incidence compared to what would be expected in the general population (after multivariable adjustment for gender, year of diagnosis, age, and race). Additional cancer diagnoses included as control groups to assess the generalizability of findings included Hodgkin and Non-Hodgkin lymphoma, colon/rectal, pancreas, lung/bronchus, bladder, and kidney cancers. To compute the excess risk of second cancers, that is, the average additional number of cancer patients per 10,000 cancer survivors per year, the expected number was subtracted from the number of observed cases, and the difference divided by the Person-years (PY) at risk. The number of excess cases was then expressed per 10,000 PY.

Patients with a malignancy who survived at least 2 months after initial diagnosis are included in the present analyses; second cancers identified within the first 2 months after diagnosis were excluded as these likely represent latent lesions present prior to diagnosis of the index cancer. PY at risk in the study cohort were accumulated by 5-year age groups and latency periods (2–11, 12–59, 60–119, and ≥ 120 months) after the date of diagnosis of the first cancer (i.e. index cancer) to the date of either their diagnosis of the targeted second cancer, last known follow-up, death, or December 31, 2010, whichever occurred first. We used varying time windows because later diagnoses were more likely to represent incident cases rather than latent ones that existed prior to the index cancer. Site-specific cancer incidence rates from the U.S. population were obtained from SEER by ethnic group, sex, 5-year age groups, and 5-year calendar periods, and were multiplied by the accumulated PY in the study cohort to estimate the expected number of cancer cases. To calculate the excess risks of second cancers, the expected number was subtracted from the number of observed cases, and the difference divided by the PY at risk. The number of excess cases was then expressed per 10,000 PY. P values <0.05 were considered statistically significant for all comparisons.

Results

A total of 330,079 and 5,399 patients diagnosed with primary clinically localized prostate and thyroid cancers, respectively, were identified from the SEER database between 1995 and 2010 (Table 1). Patients with primary prostate and thyroid cancer were monitored for a second primary cancer for 2,097,867 and 34,992 PY's of follow-up, respectively. 23,226 second primary cancers were diagnosed during the observation period. In patients with CAP, the risk of diagnosis with one of the second primary cancers examined was 6.9%. During the total duration of follow-up, patients with CAP had significantly elevated risks of subsequent diagnosis with thyroid (SIR 1.3 [95% CI 1.16–1.44]; $p<0.05$), kidney (SIR 1.25 [95% CI 1.19–1.31]; $p<0.05$), and bladder (SIR 1.10 [95% CI 1.07–1.14]; $p<0.05$) cancers following adjustment for age, gender, race and year of diagnosis. There was no significant increase in the diagnosis of leukemia, Hodgkin or Non-Hodgkin lymphoma, esophageal, colorectal, lung/bronchus, and pancreatic cancer among patients with primary CAP (Table 2).

Patients with known prostate cancer were 30% more likely to be diagnosed with thyroid cancer (1.5% of secondary cancer diagnoses) compared to the general U.S. population. Examination of the latency trends revealed that 4 of 10 evaluated cancer types (thyroid, kidney, bladder, and Non-Hodgkin lymphoma) had significantly elevated SIR's at 2–11 months following CAP diagnosis (Fig 1). Beyond this period, only the increased risk of subsequent thyroid cancer persisted at 2–11 (SIR 1.83 [95% CI 1.38–2.39]; $p<0.05$), 12–59 (SIR 1.24 [95% CI 1.04–1.45]; $p<0.05$) and 60–119 (SIR 1.25 [95% CI 1.03–1.51]; $p<0.05$) months. The risk of bladder cancer detection remained persistently elevated 120 months after CAP diagnosis (SIR 1.12 [95% CI 1.03–1.22]; $p<0.05$), but no significant association was observed between 60–119 months.

In patients with primary localized thyroid carcinoma, CAP was the most common second malignancy diagnosed (45.4%). Thyroid cancer patients had a 28% higher than expected overall risk of subsequent CAP diagnosis (SIR 1.28 [95% CI 1.08–1.5]; $p<0.05$). When stratified by follow-up interval, the observed CAP diagnosis rate among men with thyroid cancer was significantly higher than expected at 12–59 months of follow-up (SIR 1.42 [CI 1.1–1.79]; $p<0.05$). Most cases of subsequent CAP occurred within 5 (62.5%) and 10 (95.1%) years of thyroid cancer diagnosis, whereas the risk of CAP detection (SIR 0.52 [95%CI 0.21–1.07]) was no longer statistically significant among long-term (≥ 10 years) survivors of thyroid cancer. The overall risks of subsequent kidney cancer (SIR 2.53 [95% CI 1.71–3.62]; $p>0.05$) and non-Hodgkin lymphoma (SIR 1.61 [95% CI 1.03–2.39]; $p<0.05$) were also increased (Table 3). There was, however, a latency effect on the diagnosis of both cancers, with a sharp increase in kidney cancer risk at 60–119 months of follow-up (SIR 4.49 [95% CI 2.66–7.1]; $p<0.05$), and at 12–59 months for non-Hodgkin's lymphoma (SIR 2.0 [95% CI 1.07–3.42]; $p<0.05$). The aggregate excess risk of prostate cancer was 9.28/10,000 PY, however the most pronounced excess was for CAP's detected in the first 1 (18.1/10,000 PY) to 5 (13.1/10,000 PY) years following primary cancer diagnosis.

Discussion

Large national registry data demonstrate an association of prostate and thyroid cancer diagnoses, regardless of which cancer was diagnosed first. Patients with CAP had a 30% excess risk of subsequent thyroid cancer, while those with primary thyroid cancer had a similar 28% increase in subsequent CAP diagnosis when compared to the general population (controls). In both cases, the increased risk of identifying second primary malignancy was greatest shortly after the primary cancer diagnosis, with a lower-than-expected risk found at later follow-up. Other studies have evaluated the risk of second primary malignancy in prostate cancer patients;[24–27] however, this report is novel in that it focuses on the short and long-latency of the risks rather than aggregate hazards alone and examines the role of diagnosis and surveillance bias in associated cancers.

Several hypotheses can explain the apparent association between two cancer diagnoses. For instance, bidirectional associations between malignancies raise the possibility of shared genetic or environmental risk factors, or a treatment effect (but an increase in treatment-related cancers usually only becomes apparent years after the first primary cancer).[28] Meanwhile, the unidirectional association trends, as observed between thyroid and prostate cancer in our study, are most likely to indicate an effect of treatment or surveillance bias.[28]

Surveillance bias, a nonrandom type of information bias, refers to the notion that “the more you look, the more you find”.[16] This phenomenon occurs when some patients are followed more closely or have more diagnostic tests performed than others, which leads to a more frequent diagnosis assignment in the more closely monitored group.[15] Although overall population-wide rates of recommended screening are low,[14] cancer survivors are more likely to undergo cancer screening compared to the general population.[29–31] Among cancer survivors, increased understanding of the disease, risk perception, and mode of primary cancer detection are associated with screening for second primary cancers, and screen-detected cancer survivors are approximately twice as likely to receive all appropriate second primary cancer surveillance, even after controlling for other covariates known to affect cancer screening behaviors.[14] Heightened detection efforts may increase compliance with screening guidelines, but could also result in diagnosis of cancers of limited clinical significance. Such surveillance bias likely contributes to diagnosis of secondary malignancy in patients with thyroid and prostate cancer.

Of course, cancer survivors are not solely responsible for second malignancy screening; providers play a large role in directing follow-up care. Characteristics of primary-care providers affect patient participation in cancer screening.[32,33] Importantly, some physicians are “screening-prone.” Systematic recommendation for both breast and prostate cancer screening are strongly linked with systematic recommendation for colorectal cancer screening.[33] Cancer preventive services are more likely to be provided when an oncologist and a primary care physician manage a survivor together (rather than pursuing follow-up with a single provider alone).[32] Coordination between urology, oncology, and primary care providers has been identified as a metric of quality cancer survivorship care and has been suggested as a mechanism to improve appropriate screening utilization.[32]

Heightened diagnostic focus may explain the increase in second primary cancers after CAP.[25] For all malignant cancers diagnosed between 1989 and 2006 in the Netherlands, 7% of all men with CAP developed additional malignancies; urinary cancers (27%) represented the most common cancer diagnoses after CAP.[34] In patients diagnosed with primary cancers of the urinary system, CAP was the most commonly diagnosed second primary cancer (30%).[34] Similarly, a 2-fold increased risk of a second neoplasm was reported among men with CAP in the Netherlands, Belgium and the United Kingdom.[25] The risk of second primary urologic cancers among men with CAP suggests a strong detection bias for urologic cancers.[18,27,35] In this study's cohort, the increased rates of kidney and bladder cancer detected 2–11 months following CAP diagnosis are consistent with these prior findings.

For cancers of the prostate and thyroid, the increased risk of secondary diagnosis was observed regardless of which tumor type was diagnosed first. However, in a Swedish cohort where systematic CAP screening has not been adopted, no association between thyroid and prostate cancer diagnosis appears to exist.[35] Thyroid and prostate cancer are arguably the two most overtreated malignancies, and the observed relationship may be explained by coupling of screening for both cancers in the United States.[8] In the U.S., the incidence of thyroid cancer has tripled in the past 30 years, making it one of the fastest growing diagnoses; in contrast, the incidence in Sweden, Japan and China has increased only minimally, with no significant change in mortality.[19] Ready access to portable ultrasound machines, wider access to healthcare, financial incentives, and greater use of new imaging technology for other indications have fueled an 80% increase in neck imaging[36] and have produced a 2.4-fold increase in the reported incidence of thyroid nodules over the past 30 years. Yet, thyroid cancer-specific mortality has remained static.[19] Similar trends can be seen in the prostate cancer with the exception that CAP-specific mortality has significantly decreased over the last 2 decades. Nevertheless, some estimates of overtreatment in response to early diagnosis suggest rates that exceed 50%, and validated risk-based CAP screening strategies are urgently needed.[437]

Among patients with primary CAP, the incidence of second primary lung/bronchus and colorectal cancers was significantly lower than expected. Some long-term follow-up studies have reported a modestly increased risk of colorectal cancer in men who have received external-beam radiation therapy for CAP,[38] but the observation time in the current study probably is too short to reflect such an association, as the latency period for second primary cancer development following CAP treatment is typically at least 5 to 10 years and may well exceed 15 years.[39] The decreased lung cancer incidence may indicate selection, as the high morbidity in patients with a history of smoking presents as a contraindication for definitive prostate cancer treatment.[27] Patients with primary thyroid and CAP not only face overtreatment risks from the primary malignancy, but also appear subject to similar challenges from a second cancer. This study highlights the importance of careful patient selection for screening and reduction of overdiagnosis to preserve the benefits and reduce the harms of cancer screening.[4]

Some methodological limitations warrant consideration. The data suggest strong trends over time but it is not possible to make firm conclusions surrounding causality using them. Alternative mechanisms could explain the increased detection of additional cancers after a

diagnosis of prostate or thyroid cancer within this limited observational cohort. An unequal distribution of risk factors between groups could have biased the results. Observational studies are further prone to the possibility of residual confounding by unmeasured or imperfectly measured confounders. Furthermore, underestimation of second cancers can result from migration of subjects from SEER Program areas, and, despite the large study population, the relative rarity of some cancers included in the analysis reduces the precision of some hazard estimates presented. Nevertheless, this study is strengthened by a large patient population with extensive follow-up and in-depth evaluation of the latency course of risks. The work incorporates SIR and multivariable methodologies rather than solely an assessment of overall risks. Moreover, our findings may have potential implications for thyroid and prostate cancer screening policies.

Conclusions

This monograph reports a significant association between prostate and thyroid cancer diagnoses in the U.S. The data suggest that patients with these malignancies are not only exposed to challenges of overtreatment of the primary cancer, but also face long-term risks of overtreatment of a secondary low risk malignancy.

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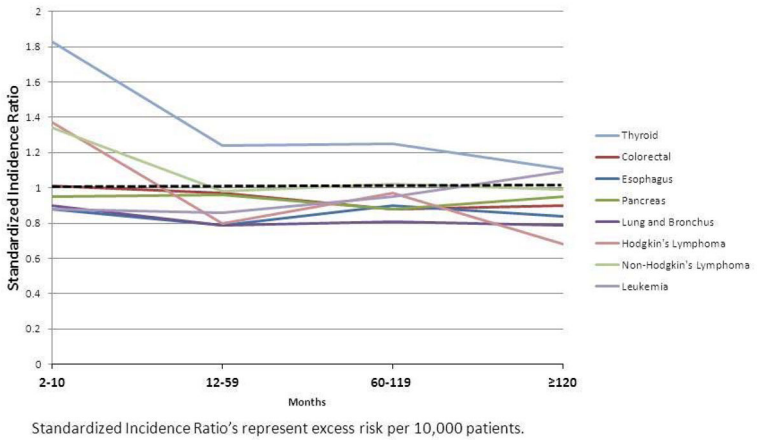

Standardized Incidence Ratio's represent excess risk per 10,000 patients.

Figure 1.

Latency course of risk of second primary non-urologic tumor diagnosis among men with clinically localized prostate cancer.

Table 1

Cohort demographic data.

	Prostate Cancer n (%)	Thyroid Cancer n (%)
Total Patients	330,079	5,399
Age at Diagnosis (yrs) (mean ± SD)	66.7±9.4	50.3±14.2
Marital Status		
Single	30,425 (9.2)	981 (18.2)
Married	230,739 (69.9)	3,835 (71.0)
Divorced/Widowed	38,038 (11.5)	362 (6.7)
Unknown	30,877 (9.4)	221 (4.1)
Year of Diagnosis		
1995–1998	71,996 (21.8)	887 (16.4)
1999–2002	88,330 (26.8)	1,256 (23.3)
2003–2006	85,539 (25.9)	1,493 (27.7)
2007–2010	84,214 (25.5)	1,763 (32.7)
Race		
Caucasian	258,786 (78.4)	4,547 (84.2)
African American	42,853 (13.0)	255 (4.7)
Other	20,944 (6.4)	534 (9.9)
Unknown	7,496 (2.3)	63 (1.2)
Gleason Score		n/a
6	66,633 (46.1)	
7	58,150 (40.3)	
8	10,360 (7.2)	
9	6,532 (4.5)	
10	598 (0.41)	

Table 2

Standardized incidence ratios of secondary malignancy in patients diagnosed with primary clinically localized CAP, stratified by follow-up intervals after diagnosis of primary malignancy. **Bold** typeface indicates p<0.05.

	Time after diagnosis of primary malignancy									
	2–11 months		12–59 months		60–119 months		≥120 months		Total	
	Obs/Exp	SIR (95% CI)	Obs/Exp	SIR (95% CI)	Obs/Exp	SIR (95% CI)	Obs/Exp	SIR (95% CI)	Obs/Exp	SIR (95% CI)
Thyroid	54/29.5	**1.83** (1.4–2.4)	146/118	**1.24** (1.0–1.5)	109/87	**1.25** (1.0–1.5)	29/26	1.11 (0.7–1.6)	338/261	**1.30** (1.2–1.4)
Kidney	399/160	**2.49** (2.3–2.8)	712/653	**1.09** (1.01–1.17)	534/491	1.09 (1–1.2)	177/152	1.16 (1–1.4)	1822/1457	**1.25** (1.19–1.31)
Urinary Bladder	552/390	**1.41** (1.3–1.5)	1812/1673	**1.08** (1.03–1.13)	1401/1360	1.03 (0.98–1.09)	523/466	**1.12** (1.0–1.2)	4288/3891	**1.10** (1.07–1.14)
Colorectal	595/592	1.01 (0.9–1.1)	2308/2384	0.97 (0.93–1.01)	1507/1718	**0.88** (0.83–0.92)	478/530	**0.90** (0.8–0.99)	4888/5223	**0.94** (0.91–0.96)
Lung and Bronchus	767/849	**0.90** (0.84–.097)	2717/3446	**0.79** (0.76–0.82)	2075/2550	**0.81** (0.78–0.85)	631/803	**0.79** (0.73–0.85)	6190/7648	**0.81** (0.79–0.83)
Esophagus	72/82	0.88 (0.69–1.11)	262/332	**0.79** (0.7–0.89)	221/246	0.9 (0.79–1.03)	64/76	0.84 (0.65–1.08)	619/736	**0.84** (0.78–0.91)
Pancreas	132/140	0.95 (0.8–1.1)	561/586	0.96 (0.88–1.0)	407/464	**0.88** (0.79–0.97)	147/156	0.95 (0.8–1.11)	1247/1345	**0.93** (0.88–0.98)
Hodgkin's Lymphoma	16/12	1.37 (0.8–2.2)	37/46	0.8 (0.6–1.1)	32/33	0.97 (0.66–1.4)	7/10	0.68 (0.3–1.4)	92/101	0.91 (0.73–1.12)
Non-Hodgkin's Lymphoma	284/213	**1.34** (1.2–1.5)	871/887	0.98 (0.92–1.1)	706/692	1.02 (0.95–1.1)	226/227	0.99 (0.87–1.1)	2087/2019	1.03 (0.99–1.08)
Leukemia	133/150	0.88 (0.74–1.1)	545/633	**0.86** (0.79–0.94)	476/500	0.95 (0.87–1.04)	184/168	1.09 (0.94–1.26)	1338/1451	**0.92** (0.87–0.97)

Table 3

Standardized incidence ratios of secondary malignancy in patients diagnosed with primary thyroid cancer, stratified by follow-up intervals after diagnosis of primary malignancy. **Bold** typeface indicates $p<0.05$.

	Time after diagnosis of primary malignancy									
	2–11 months		12–59 months		60–119 months		≥120 months		Total	
	Obs/Exp	SIR (95% CI)	Obs/Exp	SIR (95% CI)	Obs/Exp	SIR (95% CI)	Obs/Exp	SIR (95% CI)	Obs/Exp	SIR (95% CI)
Prostate	20/12	1.64 (1–2.5)	70/49	**1.42** (1.1–1.8)	47/38	1.25 (0.9–1.7)	7/13	0.52 (0.2–1.1)	144/113	**1.28** (1.1–1.5)
Urinary Bladder	4/2	1.75 (0.5–4.5)	8/10	0.84 (0.4–1.7)	5/8	0.65 (0.2–1.5)	2/3	0.69 (0.1–2.5)	19/22	0.84 (0.5–1.3)
Kidney	2/1	1.59 (0.2–5.8)	8/5	1.57 (0.7–3.1)	18/4	**4.49** (2.7–7.1)	2/1.5	1.36 (0.2–4.9)	30/12	**2.53** (1.7–3.6)
Colorectal	2/4	0.55 (0.1–2.0)	19/15	1.29 (0.8–2.0)	3/11	**0.27** (0.1–0.8)	5/3.9	1.28 (0.4–3.0)	29/33	0.87 (0.6–1.3)
Lung and Bronchus	3/5	0.62 (0.1–1.8)	18/19	0.93 (0.6–1.5)	15/15	1.01 (0.6–1.7)	4/5	0.75 (0.2–1.9)	40/44	0.9 (0.6–1.2)
Esophagus	2/0.5	3.71 (0.5–13)	0/2	0 (0–1.7)	3/2	1.76 (0.4–5.2)	0/0.6	0 (0–6.0)	5/5.1	0.99 (0.3–2.3)
Pancreas	2/0.9	2.3 (0.3–8)	2/4	0.55 (0–2)	5/3	1.73 (0.6–4.0)	2/1	1.84 (0.2–6.6)	11/8.5	1.3 (0.7–2.3)
Hodgkin's Lymphoma	1/0.16	6.18 (0.2–34)	0/0.6	0 (0–6)	0/0.4	0 (0–9)	0/0.1	0 (0–28)	1/1.3	0.77 (0–4.3)
Non-Hodgkin's Lymphoma	4/1.6	2.48 (0.7–6.4)	13/7	**2.00** (1.0–3.4)	6/5	1.2 (0.4–2.6)	1/1.8	0.55 (0.0–3.1)	24/14.9	**1.61** (1.0–2.4)
Leukemia	0/0.99	0 (0–3.7)	9/4	**2.21** (1.0–4.2)	4/3	1.26 (0.3–3.2)	1/1.2	0.86 (0.0–4.8)	14/9	1.49 (0.8–2.5)