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Risk of second primary papillary thyroid cancer among adult cancer survivors in the United States, 2000–2015

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Abstract

Background: While radiotherapy is a major risk factor for thyroid cancer after childhood cancer, factors contributing to increased thyroid cancer risk after adulthood cancer remain unclear.

Methods: We evaluated second primary papillary thyroid cancer (PTC) risk among 3,175,216 1-year adult survivors of non-thyroid malignancies from US population-based cancer registries (2000–2015), using standardized incidence ratios (SIRs). Because heightened surveillance may increase detection of indolent thyroid tumors and earlier detection of advanced tumors, we examined SIRs by PTC stage and time since first cancer (latency).

Results: SIRs for second primary PTC (N=4,333) were statistically-significantly 1.2–3.5-fold elevated overall and after 23/27 first cancer types evaluated, with generally similar risks for localized and regional/distant PTC. SIRs for regional/distant PTC (N=1,501) were highest after pancreatic (SIR=3.7; 95% confidence interval [CI]=1.9–6.5) and soft tissue (SIR=4.2; 95% CI=2.8–6.2) cancers, followed by melanoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), diffuse large B-cell lymphoma, and larynx, kidney, and brain/central nervous system (SIRs=2.0–2.9) cancers. SIRs typically decreased with increasing latency but remained statistically-significantly elevated for regional/distant-PTC 5 years after diagnosis of cancers of the rectum, pancreas, lung/bronchus, soft tissue, female breast, uterine corpus, prostate, and kidney, and after melanoma, Hodgkin lymphoma, CLL/SLL, and follicular

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Authorship contributions

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lymphoma. Neither total nor regional/distant PTC were clearly associated with initial course of radiotherapy or chemotherapy.

Conclusions: PTC risk was elevated after a range of first primary adult cancers but was not clearly related to treatment. Although surveillance may contribute to elevated short-term risks of PTC, longer-term elevations in regional/distant PTC may be attributable to shared risk factors.

Keywords

Papillary thyroid cancer; second primary malignancies; radiotherapy; chemotherapy; cancer survivors; SEER

1. INTRODUCTION

Elevated rates of thyroid cancer have been reported among cancer survivors across a spectrum of first primary cancers diagnosed in both childhood and adulthood [1–4]. Radiotherapy for the first primary cancer is the most well-established risk factor for subsequent thyroid cancer following childhood cancer [3, 5, 6], with additional suggestive evidence for an association with alkylating agent-containing chemotherapy [4, 7]. In contrast, cancer treatments in adult patients have not been consistently associated with risk of second primary thyroid cancer [8–11].

While several explanations for observed elevated thyroid cancer rates among adult cancer survivors have been proposed, including shared genetic, hormonal, and environmental risk factors, along with heightened medical surveillance [1, 2, 12], the relevant factors remain unclear. Comprehensive analyses of second primary thyroid cancer patterns among adulthood cancer survivors may generate new hypotheses about the underlying etiology. Heightened surveillance among cancer survivors compared with the general population increases the likelihood of earlier detection of clinically aggressive disease and incidental detection of clinically indolent tumors, which are more likely to be localized and smaller in size at diagnosis [13, 14]. Thus, consideration of stage of second primary thyroid cancer and time since first primary cancer can help distinguish between heightened surveillance versus biological relationships (e.g., shared etiology or late effects of treatments) to explain higher-than-expected rates of thyroid cancer among cancer survivors.

Using U.S. population-based cancer registry data, we evaluated second primary papillary thyroid cancer (PTC) risk after first primary cancers diagnosed in adulthood, with consideration of stage at PTC diagnosis, time since first primary diagnosis (latency), age at diagnosis, initial (first-course) treatment for the first primary malignancy, and sex. We restricted analyses to PTC, the most common histologic type of thyroid cancer [15].

2. MATERIALS AND METHODS

2.1 Study population

Study data derived from the U.S. population-based cancer registries of the Surveillance, Epidemiology, and End Results (SEER) Program, which collects detailed demographic data and characteristics related to each primary cancer diagnosis among residents within a

geographically defined area, including age at and date of diagnosis, sequence (subsequent cancers are ascertained for patients remaining within their SEER registry area), diagnostic confirmation, site, morphology, stage, and initial treatment (radiotherapy, chemotherapy, and surgery).

We included males and females who were diagnosed with an invasive first primary malignancy at ages 20–84 years and who survived at least 12 months without diagnosis of a second primary malignancy, as reported to one of 17 SEER registries during 2000–2014, representing approximately 25% of the US population [16]. First primary malignancies were classified using the International Classification of Diseases for Oncology (ICD-O-3) morphology and site codes [17] and the World Health Organization (WHO) classification of lymphoid neoplasms [18]. We included a combined group of all first primary cancer types, excluding thyroid cancer and non-melanoma skin cancer, and specific first primary types with at least 15,000 1-year survivors.

2.2 Follow-up and outcome ascertainment

The SEER program collects vital status information through linkage with state and national death registries and active follow-up of living patients, resulting in 97% completeness of vital status information [14, 16]. From the SEER registry files, we identified second primary PTC (ICD-O-3: topography C73.9; histology 8050, 8260, 8340–8344, 8350, 8450–8460), restricting to microscopically-confirmed cases that were not diagnosed at autopsy or on death certificate alone. Study participants were followed from one year after first primary diagnosis date (to minimize the influence of heightened surveillance among cancer survivors) [14] until date of second PTC diagnosis (censoring at diagnosis of any malignancy other than PTC), age 85 (due to concerns about under-ascertainment of cancer in elderly populations), last follow-up, death or end of study (December 31, 2015), whichever occurred first.

2.3 Statistical analysis

We compared second primary PTC rates among cancer survivors with those of the general population using standardized incidence ratios (SIRs) and exact 95% confidence intervals (CIs). The SIR was computed as the ratio of observed number of cases to that expected based on rates of microscopically-confirmed PTC (as defined in 2.2, overall and by stage) in the full SEER program data (i.e., the general population). Expected numbers were obtained by multiplying incidence rates stratified by race (white/unknown, black, other), sex (male/female), attained age groups (20–24, 25–29... 80–84) and attained calendar year (2000–2004, 2005–2009, 2010–2015) by stratum-specific person-years at risk and summing across strata. We also calculated excess absolute risks (EAR; [(observed number of cases – expected number of cases) / person-years] × 10,000). SIRs and 95% CIs as well as EARs were estimated using SEER*Stat software, version 8.3.6 (Surveillance, Research Program, National Cancer Institute, Bethesda, MD).

SIRs and EARs were calculated for total second primary PTC and by stage at PTC diagnosis (localized and the combined groups of regional and distant, based on SEER Historic Stage A [16]). SIRs were further calculated in patient subgroups defined by time since first primary

cancer diagnosis, age at first primary cancer diagnosis (<50 versus ≥50 years, the mean age at thyroid cancer diagnosis in the U.S. [19]), sex, and reported first course of treatment (radiotherapy – yes or no/unknown; chemotherapy – yes or no/unknown). We restricted analyses by initial chemotherapy and radiotherapy treatment to first primary cancers where 10% of patients were reported to have received the treatment. We further restricted radiotherapy analyses to the period of ≥5 years following first primary cancer diagnosis to account for the minimum latency period for solid tumors to develop following radiation exposure [20] and evaluated risk following those first primary cancers for which the thyroid was potentially in the radiation field based on typical treatment approaches. We fitted multivariable Poisson regression models to compare SIRs among patient subgroups, adjusting models for sex, age at first primary malignancy and latency through stratification, with inclusion of the log of the expected number of cases as an offset to indirectly adjust for attained age and calendar year [21]. Two-sided P-values for heterogeneity in SIRs were based on a likelihood ratio statistic comparing model fit with and without the factor of interest. Models were fitted using the Amfit module of Epicure [22]. P-values <0.05 were considered statistically significant.

3. RESULTS

The study population included 3,175,216 adult (ages 20–84 years at first primary diagnosis) 1-year cancer survivors (2,995,314 survivors of 27 specific types of first primary malignancies) diagnosed during 2000–2014 (Table 1). Survivors of prostate (N=687,657), female breast (N=614,688) and lung/bronchus (N=222,723) cancers comprised the largest groups. Mean age at diagnosis was ≥50 years for first primary malignancies other than Hodgkin lymphoma (41.3 years; HL) and cancers of the cervix (48.0 years) and testis (36.1 years). Mean years of follow-up ranged from 1.7 years (pancreatic cancer) to 6.7 years (testicular cancer). There was a male predominance for cancers (excluding sex-specific) other than lung/bronchus and follicular lymphoma (FL; 50% female) and marginal zone lymphoma (MZL; 55% female). Initial treatment varied markedly by first primary cancer type.

We observed 4,333 second primary PTC cases during follow-up, 35% of which (N=1,501) were diagnosed at the regional/distant stage (Table 2). Second PTC were most commonly diagnosed after female breast cancer (N=1,199), prostate cancer (N=561), and melanoma (N=312). Compared with the general population, total PTC risks were statistically significantly 1.2–3.5-fold elevated overall and after each cancer evaluated other than esophagus, liver, cervix and myeloid/monocytic leukemia. SIRs stratified by second primary PTC stage were generally similar across each of the first primary malignancies apart from melanoma (localized SIR=1.5; 95% CI 1.3–1.7; regional/distant SIR=2.0; 95% CI 1.7–2.4; $P_{\text{heterogeneity}}=0.03$). For second primary regional/distant PTC, the SIRs were highest after cancers of the pancreas (SIR=3.7; 95% CI 1.9–6.5) and soft tissue (SIR=4.2; 95% CI 2.8–6.2), with more modest increases (SIRs 2.0–2.9) observed after melanoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), diffuse large B-cell lymphoma (DLBCL), and cancers of the larynx, kidney, and brain/central nervous system (CNS). Lower but statistically significantly elevated risks were observed after HL, plasma cell neoplasms (PCN) and cancers of the oral cavity/pharynx, colon, rectum/rectosigmoid

junction, lung/bronchus, female breast, uterine corpus, ovary, and bladder (SIRs 1.3–1.9). EARs ranged from 0.1–1.9 excess cases of regional/distant PTC per 10,000 person-years with the largest excess observed after cancers of the soft tissue and pancreas.

We then evaluated PTC risk patterns by time since first primary cancer diagnosis and PTC stage (Figure 1, Supplementary Table 1). SIRs for total PTC tended to decrease with increasing time since diagnosis of first primary malignancy, most notably for oral cavity/pharynx, colon, female breast, testis, kidney, larynx, and testis cancers as well as melanoma. Nevertheless, SIRs for both total and regional/distant PTC remained statistically significantly elevated 5 years following diagnosis of cancers of the rectum/rectosigmoid junction, pancreas, soft tissue, female breast, uterine corpus, prostate, and kidney, as well as melanoma, HL, CLL/SLL, and FL. Additionally, total (but not regional/distant) PTC rates remained significantly elevated at 5 years following ovarian cancer and MZL, while regional/distant (but not total) PTC rates were significantly elevated 5 years after lung cancer.

Subsequent analyses investigated patterns of total and regional/distant PTC risk by age at diagnosis and initial treatment for the first primary malignancy and sex. SIRs tended to be higher among patients diagnosed with first primary malignancy at <50 versus 50 years (Table 3). Differences for total PTC by age at first primary diagnosis were statistically significant after cancers of the pancreas, larynx, female breast, uterine corpus, kidney, and melanoma. Differences for regional/distant PTC by age were statistically significant for cancers of the colon and pancreas, as well as melanoma, DLBCL, and FL. Apart from uterine corpus cancer (total PTC only), there was little heterogeneity in the SIRs by initial chemotherapy status (Table 4). Similarly, there was little indication that radiotherapy was associated with increased PTC risks among 5-year survivors of cancers for which the thyroid is potentially in or near the treatment field (Table 5). The results were largely consistent between males and females (Supplementary Table 2), although SIRs were statistically significantly higher among males than females following diagnosis of cancers of the colon, larynx, and pancreas for total PTC, and after melanoma for both total and regional/distant PTC.

4. DISCUSSION

Using large-scale population-based cancer registry data, we evaluated PTC risk among adult cancer survivors by stage at PTC for the first time, while building on previous studies that investigated patterns of subsequent thyroid cancer risk by time since first primary cancer diagnosis [1, 2, 23]. Together, stage at PTC diagnosis and time since first primary cancer can help to distinguish between PTCs that are more likely to be incidentally detected under heightened medical surveillance (localized PTCs and/or PTCs that only occur at higher-than-expected rates shortly after diagnosis of another cancer) versus tumors that are more likely to reflect an underlying biological relationship between the first and second cancer (regional/distant PTCs, particularly those with a long-term elevated risk) [13, 14]. For instance, heightened medical surveillance alone is unlikely to explain the elevated rates for regional/distant PTC that persisted 5 years following melanoma, HL, CLL/SLL, and FL,

and after cancers of the rectum/rectosigmoid junction, pancreas, lung/bronchus, soft tissue, female breast, uterine corpus, prostate, and kidney.

Shared etiology has been hypothesized to contribute to the widely-reported mutually increased risks of female breast and thyroid cancers (reviewed in [12]). The specific relevant risk factors and mechanisms remain unclear, but risk factors associated with both thyroid and breast cancer include ionizing radiation exposure during childhood and adolescence [24], Cowden and related rare syndromes involving *PTEN* mutations [25, 26], hyperthyroidism [27, 28], and obesity (postmenopausal breast) [29]. Obesity [29] and Cowden and related syndromes [25] are also associated with kidney cancer; another site for which reciprocal risks with thyroid cancer have been reported, in SEER [1] and elsewhere [2, 30]. Further, there is a growing body of evidence linking benign thyroid and kidney diseases [31] which, along with reported increased PTC risk following kidney transplantation [32] and end stage renal disease [33, 34], might provide clues about PTC risk among kidney cancer survivors.

Obesity may also have a role in some of the increased PTC risk observed after pancreas, rectum, and uterine corpus [29]. Ionizing radiation has been associated with cancers of the rectum, soft tissue, pancreas, and lung [24], and Cowden and related syndromes have been associated with uterine corpus cancer, rectal cancer, and melanoma [25, 26]. Individual-level data are needed to investigate whether obesity or any of these other factors could explain the patterns observed for second PTC risk in SEER. For prostate cancer, potential shared etiologic factors are not obvious; although surveillance has been suspected to explain observed relationships between these tumors [35], the persistently increased risk that we observed for regional/distant PTC as well as reported increased risks for prostate cancer after thyroid cancer [36, 37] may warrant further investigation. Interestingly, we observed increased risk of regional/PTC after lung/bronchus and a number of other smoking-related cancers [38]. Given that smoking has been associated with a reduced risk of PTC, with the strongest associations observed among current smokers [39], smoking would seem an unlikely explanation for observed increased PTC risk after these cancers.

Our analyses suggest that second PTC risk varies across subtypes of non-Hodgkin lymphoma (NHL), with persistently elevated risks of total and regional/distant PTC observed after CLL/SLL and FL, but less clear associations for DLBCL, PCN, and MZL. Based on a limited number of population-based studies, second thyroid cancer has been most consistently observed after CLL [40–43], including an earlier SEER analysis (1992–2006) [43], whereas previous SEER analyses found no significant increase after FL [43, 44] or DLBCL [43] and only a short-term increase after PCN [45], and an international pooled registry study found no increase after PCN [2]. Possible explanations for potential increased risks of PTC after lymphoid malignancies are unclear. However, a recent cancer-registry study reported increased thyroid cancer risk among patients diagnosed with DLBCL in 2001–2012, corresponding to the introduction of rituximab, but not in earlier years [46]. Thus, thyroid dysfunction related to targeted therapy for lymphoid malignancies may be a pathway to pursue in future research [47]. Disentangling potential biological associations from surveillance, however, is particularly challenging after NHL. CLL/SLL and FL survivors undergo medical surveillance throughout the disease course due to the relapsing/

remitting nature of these indolent lymphomas [48]. The majority of nodal MZL and approximately one-quarter of nodal DLBCL cases occur in the cervical lymph nodes [49, 50], increasing the likelihood of incidental thyroid cancer detection, consistent with our observation of higher SIRs for localized vs regional/distant PTC after MZL.

Unlike childhood cancer studies [3–7], we found no evidence that radiotherapy or chemotherapy for first primary cancers diagnosed in adulthood were associated with subsequent risks of PTC. Other studies have failed to observe associations between radiotherapy among adults and subsequent thyroid cancers [8, 10, 11], consistent with the reduced age-at-exposure effect that has been observed in other radiation-exposed populations [7]. Although we observed elevated SIRs for total PTC among patients who received initial chemotherapy for a variety of cancers, including testicular cancer (as reported previously [9, 51]), SIRs were similarly elevated among individuals with no/unknown initial chemotherapy, except for uterine corpus cancer. Importantly, the lack of information on specific chemotherapeutic agents and doses, specific radiotherapy fields, and subsequent therapy, as well as under-ascertainment of treatment data (particularly chemotherapy) in SEER [52] limits our ability to detect potential modest treatment effects.

For a number of sites, the SIRs for regional/distant PTC were only increased within 5 years following diagnosis (colon, oral cavity/pharynx, larynx, testis, and brain/CNS cancers, as well as DLBCL) or were increased overall but not within specific latency groups (ovary, bladder and PCN). Although the potential for incidental detection may be particularly heightened for cancers where the thyroid is more likely to be in the imaging field (e.g., oral cavity/pharynx and larynx), regional/distant PTC would probably be considered a clinically important finding regardless of the mode of detection. The relatively low survival rates for these first primary malignancies may have limited our ability to detect long-term risks of total or regional/distant PTCs in these patient groups. Continued follow-up of these groups may be warranted.

We found no overall increase for PTC following myeloid/monocytic leukemia or esophageal, liver, or cervical cancers. Total PTC risk was increased after stomach cancer but only during the first 5 years, and there was no increased risk for regional/distant PTC. These null findings are largely consistent with previous studies [2, 53], although thyroid cancer rates were increased in a study of adult acute myeloid leukemia survivors (based on 3 observed cases [40]), and following cervical cancer in an international pooled registry study [2]. Small numbers of survivors and observed events, particularly after esophagus and liver cancer, however, are a limitation of our analyses.

Additional limitations not already mentioned include the inability to capture diagnoses of subsequent malignancies among individuals who migrated out of their original SEER catchment area; this would have led to an under-estimation of second cancer risks (i.e., attenuation of SIRs towards the null) [14]. Lastly, the limited follow-up (2000–2015) precluded assessment of long-term (10+ years) patterns of second PTC. Nonetheless, the expanded set of 17 SEER registries provides a large, contemporary population-based dataset to conduct the first analysis of second primary PTC risk by PTC stage among adult cancer survivors.

In conclusion, we observed increased PTC risks following a broad range of first primary adult cancers that did not appear to be related to first primary cancer treatment. Although medical surveillance may have contributed to elevated PTC risks in the first 5 years after first primary cancer diagnosis, significantly elevated long-term risks for regional/distant PTC after melanoma, HL, CLL/SLL, and FL, and cancers of the rectum/rectosigmoid junction, pancreas, lung/bronchus, soft tissue, female breast, uterine corpus, prostate, and kidney suggest a role for shared etiologic factors. Further investigation of these associations in studies with both detailed risk factor and treatment information is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

- [1]. Lal G, Groff M, Howe JR, Weigel RJ, Sugg SL, Lynch CF, Risk of subsequent primary thyroid cancer after another malignancy: latency trends in a population-based study, *Ann Surg Oncol* 19(6) (2012) 1887–96. [PubMed: 22227921]
- [2]. Sandeep TC, Strachan MW, Reynolds RM, Brewster DH, Scelo G, Pukkala E, Hemminki K, Anderson A, Tracey E, Friis S, McBride ML, Kee-Seng C, Pompe-Kirn V, Kliever EV, Tonita JM, Jonasson JG, Martos C, Boffetta P, Brennan P, Second primary cancers in thyroid cancer patients: a multinational record linkage study, *J Clin Endocrinol Metab* 91(5) (2006) 1819–25. [PubMed: 16478820]
- [3]. Taylor AJ, Croft AP, Palace AM, Winter DL, Reulen RC, Stiller CA, Stevens MC, Hawkins MM, Risk of thyroid cancer in survivors of childhood cancer: results from the British Childhood Cancer Survivor Study, *Int J Cancer* 125(10) (2009) 2400–5. [PubMed: 19610069]
- [4]. Veiga LH, Bhatti P, Ronckers CM, Sigurdson AJ, Stovall M, Smith SA, Weathers R, Leisenring W, Mertens AC, Hammond S, Neglia JP, Meadows AT, Donaldson SS, Sklar CA, Friedman DL, Robison LL, Inskip PD, Chemotherapy and thyroid cancer risk: a report from the childhood cancer survivor study, *Cancer Epidemiol Biomarkers Prev* 21(1) (2012) 92–101. [PubMed: 22028399]
- [5]. de Vathaire F, Haddy N, Allodji RS, Hawkins M, Guibout C, El-Fayech C, Teinturier C, Oberlin O, Pacquement H, Diop F, Kalhouche A, Benadjaoud M, Winter D, Jackson A, Bezin Mai-Quynh G, Benabdennebi A, Llanas D, Veres C, Munzer M, Nguyen TD, Bondiau PY, Berchery D, Laprie A, Deutsch E, Lefkopoulos D, Schlumberger M, Diallo I, Rubino C, Thyroid Radiation Dose and Other Risk Factors of Thyroid Carcinoma Following Childhood Cancer, *J Clin Endocrinol Metab* 100(11) (2015) 4282–90. [PubMed: 26327481]
- [6]. Bhatti P, Veiga LH, Ronckers CM, Sigurdson AJ, Stovall M, Smith SA, Weathers R, Leisenring W, Mertens AC, Hammond S, Friedman DL, Neglia JP, Meadows AT, Donaldson SS, Sklar CA, Robison LL, Inskip PD, Risk of second primary thyroid cancer after radiotherapy for a childhood cancer in a large cohort study: an update from the childhood cancer survivor study, *Radiat Res* 174(6) (2010) 741–52. [PubMed: 21128798]
- [7]. Veiga LH, Holmberg E, Anderson H, Pottern L, Sadetzki S, Adams MJ, Sakata R, Schneider AB, Inskip P, Bhatti P, Johansson R, Neta G, Shore R, de Vathaire F, Damber L, Kleinerman R, Hawkins MM, Tucker M, Lundell M, Lubin JH, Thyroid Cancer after Childhood Exposure to External Radiation: An Updated Pooled Analysis of 12 Studies, *Radiat Res* 185(5) (2016) 473–84. [PubMed: 27128740]

- [8]. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans V, Godwin J, Gray R, Hicks C, James S, MacKinnon E, McGale P, McHugh T, Peto R, Taylor C, Wang Y, Early G Breast Cancer Trialists' Collaborative, Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials, *Lancet* 366(9503) (2005) 2087–106. [PubMed: 16360786]
- [9]. Groot HJ, Lubberts S, de Wit R, Witjes JA, Kerst JM, de Jong IJ, Groenewegen G, van den Eertwegh AJM, Poortmans PM, Klumpen HJ, van den Berg HA, Smilde TJ, Vanneste BGL, Aarts MJ, Incrocci L, van den Bergh ACM, Jozwiak K, van den Belt-Dusebout AW, Horenblas S, Gietema JA, van Leeuwen FE, Schaapveld M, Risk of Solid Cancer After Treatment of Testicular Germ Cell Cancer in the Platinum Era, *J Clin Oncol* 36(24) (2018) 2504–2513. [PubMed: 29989856]
- [10]. Michaelson EM, Chen YH, Silver B, Tishler RB, Marcus KJ, Stevenson MA, Ng AK, Thyroid malignancies in survivors of Hodgkin lymphoma, *Int J Radiat Oncol Biol Phys* 88(3) (2014) 636–41. [PubMed: 24521679]
- [11]. Sun LM, Lin CL, Liang JA, Huang WS, Kao CH, Radiotherapy did not increase thyroid cancer risk among women with breast cancer: A nationwide population-based cohort study, *Int J Cancer* 137(12) (2015) 2896–903. [PubMed: 26135015]
- [12]. Bolf EL, Sprague BL, Carr FE, A Linkage Between Thyroid and Breast Cancer: A Common Etiology?, *Cancer Epidemiol Biomarkers Prev* 28(4) (2019) 643–649. [PubMed: 30541751]
- [13]. Kitahara CM, Sosa JA, The changing incidence of thyroid cancer, *Nat Rev Endocrinol* 12(11) (2016) 646–653. [PubMed: 27418023]
- [14]. Curtis RE, Freedman DM, Ron E, Ries LA, Hacker DG, Edwards BK, Tucker MA, Fraumeni JF, New Malignancies Among Cancer Survivors: SEER Cancer Registries, 1973–2000, National Institute of Health, Bethesda, MD, 2006.
- [15]. Kitahara CM, Schneider AB, Brenner AV, Chapter 44: Thyroid Cancer, in: Thun MJ, Linet MS, Cerhan JR, Haiman CA, Schottenfeld D (Eds.), *Schottenfeld and Fraumeni: Cancer Epidemiology and Prevention*, Oxford University Press, New York, NY, 2018, pp. 839–860.
- [16]. Noone AM, Howlader N, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA, SEER Cancer Statistics Review, 1975–2015, National Cancer Institute Bethesda, MD, https://seer.cancer.gov/csr/1975_2015/, based on November 2017 SEER data submission, posted to the SEER web site, 4 2018.
- [17]. Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM, Whelan S, International Classification of Diseases for Oncology, World Health Organization, Geneva, 2000.
- [18]. Turner JJ, Morton LM, Linet MS, Clarke CA, Kadin ME, Vajdic CM, Monnereau A, Maynadie M, Chiu BC, Marcos-Gragera R, Costantini AS, Cerhan JR, Weisenburger DD, InterLymph hierarchical classification of lymphoid neoplasms for epidemiologic research based on the WHO classification (2008): update and future directions, *Blood* 116(20) (2010) e90–8. [PubMed: 20699439]
- [19]. Lim H, Devesa SS, Sosa JA, Check D, Kitahara CM, Trends in Thyroid Cancer Incidence and Mortality in the United States, 1974–2013, *JAMA* 317(13) (2017) 1338–1348. [PubMed: 28362912]
- [20]. Preston DL, Ron E, Tokuoka S, Funamoto S, Nishi N, Soda M, Mabuchi K, Kodama K, Solid cancer incidence in atomic bomb survivors: 1958–1998, *Radiat Res* 168(1) (2007) 1–64. [PubMed: 17722996]
- [21]. Yasui Y, Liu Y, Neglia JP, Friedman DL, Bhatia S, Meadows AT, Diller LR, Mertens AC, Whitton J, Robison LL, A methodological issue in the analysis of second-primary cancer incidence in long-term survivors of childhood cancers, *Am J Epidemiol* 158(11) (2003) 1108–13. [PubMed: 14630607]
- [22]. Preston D, Lubin J, Pierce D, McConney M, Shilnikova N, *Epicure Risk Regression and Person-Year Computation Software: Command Summary and User Guide*. Ottawa: Risk Sciences International; 2015.
- [23]. Ronckers CM, McCarron P, Ron E, Thyroid cancer and multiple primary tumors in the SEER cancer registries, *Int J Cancer* 117(2) (2005) 281–8. [PubMed: 15880372]

- [24]. Berrington de Gonzalez AB, Bouville A, Rajaraman P, Chapter 13: Ionizing Radiation, in: Thun MJ, Linet MS, Cerhan JR, Haiman CA, Schottenfeld D (Eds.), Schottenfeld and Fraumeni: Cancer Epidemiology and Prevention, Oxford University Press, New York, NY, 2018, pp. 227–48.
- [25]. Mester J, Eng C, Cowden syndrome: recognizing and managing a not-so-rare hereditary cancer syndrome, *J Surg Oncol* 111(1) (2015) 125–30. [PubMed: 25132236]
- [26]. Ngeow J, Stanuch K, Mester JL, Barnholtz-Sloan JS, Eng C, Second malignant neoplasms in patients with Cowden syndrome with underlying germline PTEN mutations, *J Clin Oncol* 32(17) (2014) 1818–24. [PubMed: 24778394]
- [27]. Kitahara CM, Farkas DK, Jorgensen JOL, Cronin-Fenton D, Sorensen HT, Benign Thyroid Diseases and Risk of Thyroid Cancer: A Nationwide Cohort Study, *J Clin Endocrinol Metab* 103(6) (2018) 2216–2224. [PubMed: 29590402]
- [28]. Sogaard M, Farkas DK, Ehrenstein V, Jorgensen JO, Dekkers OM, Sorensen HT, Hypothyroidism and hyperthyroidism and breast cancer risk: a nationwide cohort study, *Eur J Endocrinol* 174(4) (2016) 409–14. [PubMed: 26863886]
- [29]. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K, International G Agency for Research on Cancer Handbook Working, Body Fatness and Cancer--Viewpoint of the IARC Working Group, *N Engl J Med* 375(8) (2016) 794–8. [PubMed: 27557308]
- [30]. Van Fossen VL, Wilhelm SM, Eaton JL, McHenry CR, Association of thyroid, breast and renal cell cancer: a population-based study of the prevalence of second malignancies, *Ann Surg Oncol* 20(4) (2013) 1341–7. [PubMed: 23263698]
- [31]. Iglesias P, Bajo MA, Selgas R, Diez JJ, Thyroid dysfunction and kidney disease: An update, *Rev Endocr Metab Disord* 18(1) (2017) 131–144. [PubMed: 27864708]
- [32]. Kitahara CM, Yanik EL, Ladenson PW, Hernandez BY, Lynch CF, Pawlish KS, Engels EA, Risk of Thyroid Cancer Among Solid Organ Transplant Recipients, *Am J Transplant* 17(11) (2017) 2911–2921. [PubMed: 28397388]
- [33]. Maisonneuve P, Agodoa L, Gellert R, Stewart JH, Buccianti G, Lowenfels AB, Wolfe RA, Jones E, Disney AP, Briggs D, McCredie M, Boyle P, Cancer in patients on dialysis for end-stage renal disease: an international collaborative study, *Lancet* 354(9173) (1999) 93–9. [PubMed: 10408483]
- [34]. Vajdic CM, McDonald SP, McCredie MR, van Leeuwen MT, Stewart JH, Law M, Chapman JR, Webster AC, Kaldor JM, Grulich AE, Cancer incidence before and after kidney transplantation, *JAMA* 296(23) (2006) 2823–31. [PubMed: 17179459]
- [35]. Tomaszewski JJ, Uzzo RG, Eggleston B, Corcoran AT, Mehrazin R, Geynisman DM, Ridge JA, Veloski C, Kocher N, Smaldone MC, Kutikov A, Coupling of prostate and thyroid cancer diagnoses in the United States, *Ann Surg Oncol* 22(3) (2015) 1043–9. [PubMed: 25205302]
- [36]. Kim C, Bi X, Pan D, Chen Y, Carling T, Ma S, Udelsman R, Zhang Y, The risk of second cancers after diagnosis of primary thyroid cancer is elevated in thyroid microcarcinomas, *Thyroid* 23(5) (2013) 575–82. [PubMed: 23237308]
- [37]. Cho YY, Lim J, Oh CM, Ryu J, Jung KW, Chung JH, Won YJ, Kim SW, Elevated risks of subsequent primary malignancies in patients with thyroid cancer: a nationwide, population-based study in Korea, *Cancer* 121(2) (2015) 259–68. [PubMed: 25223713]
- [38]. Sasco AJ, Secretan MB, Straif K, Tobacco smoking and cancer: a brief review of recent epidemiological evidence, *Lung Cancer* 45 Suppl 2 (2004) S3–9.
- [39]. Cho A, Chang Y, Ahn J, Shin H, Ryu S, Cigarette smoking and thyroid cancer risk: a cohort study, *British journal of cancer* 119(5) (2018) 638–645. [PubMed: 30111870]
- [40]. Nielsen SF, Bojesen SE, Birgens HS, Nordestgaard BG, Risk of thyroid cancer, brain cancer, and non-Hodgkin lymphoma after adult leukemia: a nationwide study, *Blood* 118(15) (2011) 4062–9. [PubMed: 21841167]
- [41]. Schöllkopf C, Rosendahl D, Rostgaard K, Pipper C, Hjalgrim H, Risk of second cancer after chronic lymphocytic leukemia, *Int J Cancer* 121(1) (2007) 151–156. [PubMed: 17351903]
- [42]. Royle JA, Baade PD, Joske D, Girschik J, Fritschi L, Second cancer incidence and cancer mortality among chronic lymphocytic leukaemia patients: a population-based study, *British journal of cancer* 105(7) (2011) 1076–81. [PubMed: 21847118]

- [43]. Morton LM, Curtis RE, Linet MS, Bluhm EC, Tucker MA, Caporaso N, Ries LAG, Fraumeni JF, Second Malignancy Risks After Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukemia: Differences by Lymphoma Subtype, *Journal of Clinical Oncology* (2010).
- [44]. Giri S, Bhatt VR, Verma V, Pathak R, Bociek RG, Vose JM, Armitage JO, Risk of Second Primary Malignancies in Patients With Follicular Lymphoma: A United States Population-based Study, *Clin Lymphoma Myeloma Leuk* 17(9) (2017) 569–574. [PubMed: 28709798]
- [45]. Razavi P, Rand K, Cozen W, Chanan-Khan A, Usmani S, Ailawadhi S, Patterns of second primary malignancy risk in multiple myeloma patients before and after the introduction of novel therapeutics, *Blood Cancer J* 3(6) (2013) e121. [PubMed: 23811785]
- [46]. Tao L, Clarke CA, Rosenberg AS, Advani RH, Jonas BA, Flowers CR, Keegan THM, Subsequent primary malignancies after diffuse large B-cell lymphoma in the modern treatment era, *Br J Haematol* 178(1) (2017) 72–80. [PubMed: 28542862]
- [47]. Mancuso S, Carlisi M, Napolitano M, Siragusa S, Lymphomas and thyroid: Bridging the gap, *Hematol Oncol* (2018).
- [48]. Jaffe ES, Harris NL, Stein H, Vardiman JW, Pathology and genetics: tumours of haematopoietic and lymphoid tissues, IARC2001.
- [49]. van den Brand M, van Krieken JH, Recognizing nodal marginal zone lymphoma: recent advances and pitfalls. A systematic review, *Haematologica* 98(7) (2013) 1003–13. [PubMed: 23813646]
- [50]. Lontos K, Tsagianni A, Yuan JM, Normolle DP, Boyiadzis M, Hou JZ, Swerdlow SH, Dorritie KA, Location matters in early stage nodal diffuse large B-cell lymphoma, *Leuk Lymphoma* 60(1) (2019) 250–253. [PubMed: 29932787]
- [51]. Fung C, Fossa SD, Milano MT, Oldenburg J, Travis LB, Solid tumors after chemotherapy or surgery for testicular nonseminoma: a population-based study, *J Clin Oncol* 31(30) (2013) 3807–14. [PubMed: 24043737]
- [52]. Noone AM, Lund JL, Mariotto A, Cronin K, McNeel T, Deapen D, Warren JL, Comparison of SEER Treatment Data With Medicare Claims, *Med Care* 54(9) (2016) e55–64. [PubMed: 24638121]
- [53]. Ghimire KB, Shah BK, Second primary malignancies in adult acute myeloid leukemia--A US population-based study, *Anticancer Res* 34(7) (2014) 3855–9. [PubMed: 24982414]

Highlights

- Risks for second primary papillary thyroid cancer were elevated after a broad range of first primary cancer types.
- Risks for second primary papillary thyroid cancer appeared to decrease with increasing time since the first primary cancer but remained statistically-significantly elevated following a number of first primary types.
- Risks were generally similar for localized- and regional/distant- second primary papillary thyroid cancers.

Figure 1.

Risk of second primary papillary thyroid cancer among adults (20–84 years) who survived 1 year after diagnosis, 17 Surveillance, Epidemiology, and End Results Program registries (SEER), 2000–2015, by time since diagnosis of first primary malignancy and papillary thyroid cancer stage. SIR=observed/expected. Expected numbers of cases were derived from incidence rates for papillary thyroid cancer, overall and by stage at diagnosis in the total population of the same 17 SEER registries, stratified by age (5-year groups), race (white/unknown, black, other), sex, and calendar year (5-year groups), multiplied by the appropriate person-years at risk. SIRs were suppressed to protect patient confidentiality when observed <3. CNS=Central nervous system, PTC=papillary thyroid cancer, NMSC=non-melanoma skin cancer, CLL/SLL=chronic lymphocytic leukemia/small lymphocytic lymphoma, DLBCL=diffuse large B-cell lymphoma, MZL=marginal zone lymphoma, PCN=plasma cell neoplasms.

Table 1.

Selected characteristics of adults (aged 20–84) who were diagnosed with first primary malignancy and survived 1 year after diagnosis, 17 SEER registries^a, 2000–2014

	Total (N)	Mean age at diagnosis (years)	Mean person-years at risk ^b	Proportion remaining 5 years ^c	Female (%)	Initial treatment			
First primary malignancy						RT, no/UK CT (%)	RT and CT (%)	CT, no/UK RT (%)	No/UK RT CT (%)
All excluding NMSC and thyroid	3,175,216	61.5	4.9	50%	48%	18%	15%	17%	51%
Oral cavity/pharynx	83,407	59.1	4.4	44%	28%	23%	42%	2%	33%
Esophagus	18,578	64.0	2.5	22%	20%	4%	61%	12%	24%
Stomach	35,039	63.2	3.2	29%	39%	2%	28%	24%	46%
Colon	213,514	64.5	4.5	45%	49%	0%	2%	36%	62%
Rectum/rectosigmoid junction	104,509	60.8	4.7	47%	42%	3%	41%	13%	44%
Liver	29,025	61.5	2.5	21%	25%	3%	3%	44%	49%
Pancreas	30,688	63.5	1.7	13%	49%	2%	29%	38%	32%
Larynx	26,996	62.5	4.3	44%	19%	51%	30%	1%	18%
Lung/bronchus	222,723	65.9	2.5	22%	50%	9%	32%	20%	39%
Soft tissue (including heart)	21,946	54.1	4.8	47%	44%	31%	13%	9%	47%
Melanoma	171,472	56.5	5.6	56%	45%	1%	0%	1%	97%
Female breast	614,668	59.1	5.6	57%	100%	27%	27%	18%	27%
Cervix	39,013	48.0	5.5	54%	100%	10%	42%	2%	45%
Uterine corpus	119,819	60.7	5.3	53%	100%	18%	8%	7%	66%
Ovary	48,887	58.5	4.1	38%	100%	0%	1%	73%	25%
Prostate	687,657	66.1	5.8	62%	0%	38%	0%	0%	62%
Testis	29,136	36.1	6.7	67%	0%	26%	1%	30%	42%
Bladder	133,136	67.0	4.7	48%	24%	1%	2%	14%	83%
Kidney	102,114	60.3	4.7	49%	37%	1%	1%	4%	94%
Brain/CNS	31,953	49.6	3.4	32%	43%	17%	50%	4%	28%

	Total (N)	Mean age at diagnosis (years)	Mean person-years at risk ^b	Proportion remaining 5 years ^c	Female (%)	Initial treatment			
First primary malignancy						RT, no/UK CT (%)	RT and CT (%)	CT, no/UK RT (%)	No/UK RT CT (%)
Myeloid/monocytic leukemia	26,352	54.6	4.1	40%	44%	0%	4%	78%	17%
Hodgkin lymphoma	23,534	41.3	6.3	63%	46%	4%	32%	53%	11%
CLL/SLL	46,018	65.9	4.7	49%	39%	1%	1%	21%	78%
DLBCL	44,847	59.7	4.8	49%	45%	2%	24%	63%	11%
Marginal zone lymphoma	15,222	62.4	5.1	53%	55%	20%	4%	28%	48%
Follicular lymphoma	31,729	60.5	5.5	57%	50%	9%	7%	49%	35%
Plasma cell neoplasms ^d	43,332	64.2	3.5	33%	45%	8%	15%	48%	29%

Abbreviations: central nervous system (CNS); chemotherapy (CT); chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); diffuse large B-cell lymphoma (DLBCL); non-melanoma skin cancer (NMSC); radiotherapy (RT); Surveillance, Epidemiology, and End Results Program (SEER); unknown (UK)

^a17 SEER registries [metropolitan areas of Atlanta, Detroit, Seattle-Puget Sound; states of Connecticut, Hawaii, Iowa, New Mexico, California (San Francisco-Oakland, Los Angeles, San Jose-Monterey, Greater California), Georgia (Rural Georgia, Greater Georgia), Utah, Kentucky, Louisiana, and New Jersey].

^bPatients were followed from one year after first primary malignancy until the first of: second malignancy diagnosis, death, age 85 years, loss to follow-up, or end of the study period (December 31, 2015).

^cProportion of 1 year survivors who contribute person-time of follow-up 5 years after diagnosis of the first primary malignancy.

^dIncludes plasmacytoma and multiple myeloma/plasma cell leukemia

Risk of second primary thyroid cancer (PTC) among adults (20–84 years) who survived 1 year after diagnosis, 17 SEER registries, 2000–2015, overall and by stage of PTC

Table 2.

	Total PTC			Localized PTC			Regional/Distant PTC			P_{het}^c
	Obs	SIR (95% CI) ^a	EAR ^b	Obs	SIR (95% CI) ^a	EAR ^b	Obs	SIR (95% CI) ^a	EAR ^b	
First primary malignancy										
All excluding NMSC and thyroid	4,333	1.5 (1.5 – 1.6)	0.9	2,777	1.5 (1.4 – 2.0)	0.6	1,501	1.6 (1.5 – 1.6)	0.3	0.20
Oral cavity/pharynx	101	1.7 (1.4 – 2.1)	1.2	64	1.8 (1.4 – 2.3)	0.8	34	1.6 (1.1 – 2.3)	0.4	0.75
Esophagus	7	1.0 (0.4 – 2.1)	0.1	3	0.7 (0.2 – 2.1)	–0.3	4	1.6 (0.4 – 4.1)	0.3	0.34
Stomach	34	1.9 (1.3 – 2.7)	1.5	26	2.3 (1.5 – 3.4)	1.3	8	1.3 (0.5 – 2.5)	0.2	0.09
Colon	265	1.6 (1.4 – 1.8)	1.0	170	1.6 (1.4 – 1.9)	0.7	90	1.6 (1.3 – 2.0)	0.4	0.86
Rectum/rectosigmoid junction	144	1.7 (1.4 – 2.0)	1.2	97	1.8 (1.4 – 2.2)	0.9	46	1.6 (1.1 – 2.1)	0.3	0.63
Liver	16	1.5 (0.8 – 2.4)	0.7	9	1.3 (0.6 – 2.5)	0.3	6	1.5 (0.5 – 3.2)	0.3	0.86
Pancreas	32	3.3 (2.3 – 4.7)	4.2	20	3.2 (2.0 – 4.9)	2.6	12	3.7 (1.9 – 6.5)	1.7	0.93
Larynx	33	2.0 (1.4 – 2.8)	1.4	21	2.1 (1.3 – 3.1)	0.9	12	2.0 (1.0 – 3.5)	0.5	0.75
Lung/bronchus	155	1.5 (1.3 – 1.8)	1.0	96	1.5 (1.2 – 1.8)	0.5	53	1.6 (1.2 – 2.1)	0.4	0.59
Soft tissue (including heart)	63	3.5 (2.7 – 4.5)	4.3	36	3.1 (2.2 – 4.3)	2.3	26	4.2 (2.8 – 6.2)	1.9	0.36
Melanoma	312	1.7 (1.5 – 1.9)	1.3	181	1.5 (1.3 – 1.7)	0.6	129	2.0 (1.7 – 2.4)	0.7	0.03
Female breast	1,199	1.3 (1.2 – 1.4)	0.8	821	1.3 (1.2 – 1.4)	0.6	369	1.4 (1.2 – 1.5)	0.3	0.49
Cervix	65	1.1 (0.9 – 1.4)	0.3	42	1.0 (0.8 – 1.4)	0.1	23	1.3 (0.8 – 1.9)	0.2	0.48
Uterine corpus	247	1.5 (1.3 – 1.7)	1.2	168	1.4 (1.2 – 1.7)	0.8	75	1.5 (1.2 – 1.9)	0.4	0.80
Ovary	77	1.5 (1.2 – 1.8)	1.2	49	1.4 (1.0 – 1.8)	0.6	28	1.8 (1.2 – 2.5)	0.6	0.29
Prostate	561	1.2 (1.1 – 1.3)	0.2	309	1.1 (1.0 – 1.2)	0.1	245	1.3 (1.1 – 1.4)	0.1	0.10
Testis	31	2.1 (1.5 – 3.0)	0.9	20	2.6 (1.6 – 4.1)	0.6	10	1.5 (0.7 – 2.8)	0.2	0.12
Bladder	119	1.3 (1.1 – 1.5)	0.4	69	1.2 (0.9 – 1.5)	0.2	48	1.4 (1.0 – 1.8)	0.2	0.41
Kidney	252	3.1 (2.7 – 3.5)	3.5	168	3.2 (2.7 – 3.7)	2.4	82	2.9 (2.3 – 3.6)	1.1	0.49
Brain/CNS	36	1.9 (1.3 – 2.6)	1.6	18	1.5 (0.9 – 2.4)	0.5	17	2.6 (1.5 – 4.1)	1.0	0.12
Myeloid/monocytic leukemia	24	1.3 (0.8 – 1.9)	0.5	15	1.3 (0.7 – 2.1)	0.3	9	1.4 (0.6 – 2.7)	0.2	0.86
Hodgkin lymphoma	44	1.9 (1.4 – 2.5)	1.4	28	1.9 (1.3 – 2.8)	0.9	16	1.9 (1.1 – 3.1)	0.5	0.89
CLL/SLL	73	2.0 (1.6 – 2.5)	1.7	43	1.8 (1.3 – 2.5)	0.9	27	2.1 (1.4 – 3.1)	0.7	0.46

	Total PTC			Localized PTC			Regional/Distant PTC			P_{het}^c
	Obs	SIR (95% CI) ^a	EAR ^b	Obs	SIR (95% CI) ^a	EAR ^b	Obs	SIR (95% CI) ^a	EAR ^b	
First primary malignancy										
DLBCL	61	1.7 (1.3 – 2.1)	1.1	34	1.4 (1.0 – 2.0)	0.5	26	2.0 (1.3 – 3.0)	0.6	0.21
Marginal zone lymphoma	42	2.9 (2.1 – 3.9)	3.5	33	3.4 (2.4 – 4.8)	3.0	8	1.6 (0.7 – 3.2)	0.4	0.06
Follicular lymphoma	49	1.5 (1.1 – 2.0)	0.9	32	1.5 (1.0 – 2.1)	0.6	17	1.6 (0.9 – 2.5)	0.4	1.00
Plasma cell neoplasms	40	1.6 (1.1 – 2.2)	1.0	24	1.5 (0.9 – 2.2)	0.5	15	1.8 (1.0 – 3.0)	0.4	0.54

Abbreviations: central nervous system (CNS); confidence interval (CI); observed (Obs); heterogeneity (het); papillary thyroid cancer (PTC); non-melanoma skin cancer (NMSC); standardized incidence ratio (SIR); Surveillance, Epidemiology, and End Results Program (SEER); chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); diffuse large B-cell lymphoma (DLBCL);

^a SIR=observed/expected. Expected numbers of cases were derived from incidence rates for papillary thyroid cancer, overall and by stage at diagnosis (based on SEER Historic Stage A) in the total population of the same 17 SEER registries, stratified by age (5-year groups), race (white/unknown, black, other), sex, and calendar year (5-year groups), multiplied by the appropriate person-years at risk.

^b EAR = excess absolute risk per 10,000 person-years: [(observed – expected number of cases) / person-years] × 10,000.

^c Two-sided P-value for heterogeneity in SIRs by stage (localized versus regional/distant) at papillary thyroid cancer based on a likelihood ratio statistic from multivariable Poisson regression models adjusted for age, sex and time since first primary cancer diagnosis. Inclusion of the log of the expected number of cases as an offset indirectly adjusted for attained age and calendar year.

Table 3.

Risk of second primary papillary thyroid cancer (PTC) among adults (20–84 years) who survived 1 year after diagnosis, 17 SEER registries, 2000–2015, by age at first primary malignancy and stage at thyroid cancer

	Total PTC					Regional/Distant PTC					
	Age <50 years at first primary cancer		Age 50 years at first primary cancer			Age <50 years at first primary cancer		Age 50 years at first primary cancer			
	Obs	SIR (95% CI) ^a	Obs	SIR (95% CI) ^a		P _{het} ^b	Obs	SIR (95% CI) ^a	Obs		SIR (95% CI) ^a
First primary malignancy											
All excluding NMSC and thyroid	1285	1.8 (1.7 – 1.9)	3048	1.4 (1.4 – 1.5)	<0.001	459	1.9 (1.7 – 2.1)	1042	1.4 (1.4 – 1.5)	<0.001	
Oral cavity/pharynx	34	2.2 (1.5 – 3.1)	67	1.6 (1.2 – 2.0)	0.06	14	2.5 (1.4 – 4.2)	20	1.3 (0.8 – 2.0)	0.07	
Esophagus	<3		6	1.0 (0.4 – 2.2)		0		4	1.8 (0.5 – 4.6)		
Stomach	7	2.0 (0.8 – 4.0)	27	1.9 (1.2 – 2.7)	0.62	0		8	1.6 (0.7 – 3.1)		
Colon	46	1.8 (1.3 – 2.5)	219	1.6 (1.4 – 1.8)	0.14	21	2.5 (1.6 – 3.8)	69	1.5 (1.1 – 1.8)	0.02	
Rectum/rectosigmoid junction	27	1.5 (1.0 – 2.2)	117	1.7 (1.4 – 2.1)	0.46	9	1.5 (0.7 – 2.8)	37	1.6 (1.1 – 2.2)	0.80	
Liver	<3		14	1.5 (0.8 – 2.5)		<3		4	1.1 (0.3 – 2.9)		
Pancreas	14	7.2 (3.9 – 12.1)	18	2.3 (1.4 – 3.7)	0.001	6	9.2 (3.4 – 19.9)	6	2.3 (0.9 – 5.1)	0.02	
Larynx	9	3.6 (1.7 – 6.9)	24	1.7 (1.1 – 2.5)	0.01	3	3.4 (0.7 – 9.9)	9	1.8 (0.8 – 3.3)	0.24	
Lung/bronchus	23	2.0 (1.3 – 3.1)	132	1.5 (1.2 – 1.8)	0.13	11	3.0 (1.5 – 5.4)	42	1.4 (1.0 – 1.9)	0.06	
Soft tissue (including heart)	33	4.2 (2.9 – 5.9)	30	3.0 (2.0 – 4.2)	0.07	10	3.6 (1.7 – 6.7)	16	4.7 (2.7 – 7.6)	0.74	
Melanoma	154	1.9 (1.6 – 2.2)	158	1.5 (1.3 – 1.8)	0.003	68	2.4 (1.9 – 3.1)	61	1.7 (1.3 – 2.2)	0.02	
Female breast	426	1.4 (1.3 – 1.6)	773	1.3 (1.2 – 1.4)	0.04	132	1.5 (1.2 – 1.7)	237	1.3 (1.2 – 1.5)	0.34	
Cervix	42	1.0 (0.7 – 1.4)	23	1.2 (0.8 – 1.9)	0.56	13	1.0 (0.5 – 1.7)	10	1.8 (0.9 – 3.4)	0.18	
Uterine corpus	69	1.9 (1.5 – 2.4)	178	1.3 (1.2 – 1.6)	0.02	24	2.1 (1.4 – 3.1)	51	1.3 (1.0 – 1.7)	0.07	
Ovary	33	1.7 (1.2 – 2.4)	44	1.3 (1.0 – 1.8)	0.26	13	2.2 (1.2 – 3.7)	15	1.5 (0.9 – 2.5)	0.36	
Prostate	22	1.6 (1.0 – 2.4)	539	1.2 (1.1 – 1.3)	0.17	8	1.4 (0.6 – 2.7)	237	1.3 (1.1 – 1.4)	0.84	
Testis	25	2.1 (1.3 – 3.0)	6	2.6 (0.9 – 5.6)	0.82	8	1.4 (0.6 – 2.8)	<3			
Bladder	14	1.4 (0.8 – 2.4)	105	1.3 (1.0 – 1.5)	0.78	6	1.7 (0.6 – 3.6)	42	1.4 (1 – 1.8)	0.66	
Kidney	83	4.1 (3.3 – 5.1)	169	2.7 (2.3 – 3.1)	0.001	26	3.7 (2.4 – 5.5)	56	2.6 (2.0 – 3.4)	0.09	

First primary malignancy	Total PTC			Regional/Distant PTC				
	Age <50 years at first primary cancer		Age 50 years at first primary cancer		Age <50 years at first primary cancer		Age 50 years at first primary cancer	
	Obs	SIR (95% CI) ^a	Obs	SIR (95% CI) ^a	Obs	SIR (95% CI) ^a	Obs	P _{het}
Brain/CNS	23	1.9 (1.2 – 2.9)	13	1.9 (1.0 – 3.2)	11	2.6 (1.3 – 4.6)	6	<i>0.94</i>
Myeloid/monocytic leukemia	11	1.3 (0.6 – 2.3)	13	1.3 (0.7 – 2.2)	5	1.6 (0.5 – 3.8)	4	<i>0.63</i>
Hodgkin lymphoma	36	2.1 (1.4 – 2.9)	8	1.4 (0.6 – 2.7)	15	2.3 (1.3 – 3.8)	<3	
CLL/SLL	12	2.8 (1.5 – 5.0)	61	1.9 (1.4 – 2.4)	5	3.5 (1.1 – 8.1)	22	<i>0.29</i>
DLBCL	23	2.1 (1.3 – 3.1)	38	1.5 (1.0 – 2.0)	13	3.3 (1.8 – 5.7)	13	0.04
Marginal zone lymphoma	9	2.7 (1.3 – 5.2)	33	2.9 (2.0 – 4.1)	<3		6	
Follicular lymphoma	16	1.9 (1.1 – 3.0)	33	1.4 (0.9 – 1.9)	9	3.1 (1.4 – 5.9)	8	0.03
Plasma cell neoplasms	5	1.3 (0.4 – 3.0)	35	1.6 (1.1 – 2.3)	<3		13	

Abbreviations: central nervous system (CNS); confidence interval (CI); heterogeneity (het); observed (Obs); papillary thyroid cancer (PTC); standardized incidence ratio (SIR); non-melanoma skin cancer (NMSC); Surveillance, Epidemiology, and End Results Program (SEER); chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); diffuse large B-cell lymphoma (DLBCL);

^a SIR=observed/expected. Expected numbers of cases were derived from incidence rates for papillary thyroid cancer, overall and by stage at diagnosis in the total population of the same 17 SEER registries, stratified by age (5-year groups), race (white/unknown, black, other), sex, and calendar year (5-year groups), multiplied by the appropriate person-years at risk. Exact numbers of observed cases <3 and accompanying SIRs were suppressed to protect patient confidentiality.

^b Two-sided P-value for heterogeneity in SIRs by age at first primary malignancy based on a likelihood ratio statistic from multivariable Poisson regression models adjusted for sex and time since first primary cancer diagnosis. Inclusion of the log of the expected number of cases as an offset indirectly adjusted for attained age and calendar year. Models were not fitted when one group had <3 cases. Models were fitted separately for total and regional/distant PTC

Table 4.

Risk of second primary papillary thyroid cancer (PTC) among adults (20–84 years) who survived 1 year after diagnosis, 17 SEER registries, 2000–2015, by stage at papillary thyroid cancer and initial chemotherapy

	Total PTC				Regional/Distant PTC					
	Any Chemotherapy		No/UK Chemotherapy		Any Chemotherapy		No/UK Chemotherapy		P_{het}	P_{het}^b
	Obs	SIR (95% CI) ^a	Obs	SIR (95% CI) ^a	Obs	SIR (95% CI) ^a	Obs	SIR (95% CI) ^a		
First primary malignancy										
All excluding NMSC and thyroid	1392	1.5 (1.5 – 1.6)	2941	1.5 (1.4 – 1.5)	444	1.6 (1.4 – 1.7)	1057	1.6 (1.5 – 1.7)	<i>0.87</i>	<i>0.31</i>
Oral cavity/pharynx	38	1.9 (1.3 – 2.5)	63	1.7 (1.3 – 2.2)	14	1.8 (1.0 – 3.1)	20	1.5 (0.9 – 2.3)	<i>0.69</i>	<i>0.58</i>
Esophagus	4	0.9 (0.3 – 2.4)	3	1.2 (0.3 – 3.5)	<3		<3		<i>0.87</i>	
Stomach	15	2.1 (1.2 – 3.4)	19	1.8 (1.1 – 2.8)	4	1.5 (0.4 – 3.9)	4	1.1 (0.3 – 2.7)	<i>0.97</i>	<i>0.62</i>
Colon	105	1.8 (1.5 – 2.2)	160	1.5 (1.3 – 1.8)	38	2.0 (1.4 – 2.7)	52	1.4 (1.1 – 1.9)	<i>0.27</i>	<i>0.29</i>
Rectum/rectosigmoid junction	78	1.9 (1.5 – 2.4)	66	1.5 (1.2 – 1.9)	21	1.5 (0.9 – 2.3)	25	1.7 (1.1 – 2.4)	<i>0.17</i>	<i>0.66</i>
Liver	9	1.9 (0.9 – 3.7)	7	1.1 (0.4 – 2.3)	<3		5	2.1 (0.7 – 4.9)	<i>0.27</i>	
Pancreas	10	2.0 (1.0 – 3.7)	22	4.7 (2.9 – 7.1)	5	3.0 (1.0 – 7.1)	7	4.4 (1.8 – 9.1)	<i>0.07</i>	<i>0.84</i>
Larynx	7	1.6 (0.7 – 3.3)	26	2.1 (1.4 – 3.1)	<3		10	2.2 (1.1 – 4.1)	<i>0.41</i>	
Lung/bronchus	53	1.3 (1.0 – 1.7)	102	1.7 (1.4 – 2.1)	18	1.4 (0.8 – 2.1)	35	1.8 (1.2 – 2.4)	<i>0.09</i>	<i>0.31</i>
Soft tissue (including heart)	11	3.6 (1.8 – 6.4)	52	3.5 (2.6 – 4.6)	4	3.8 (1.0 – 9.7)	22	4.3 (2.7 – 6.5)	<i>0.89</i>	<i>0.79</i>
Female breast	614	1.4 (1.3 – 1.5)	585	1.3 (1.2 – 1.4)	184	1.4 (1.2 – 1.6)	185	1.4 (1.2 – 1.6)	<i>0.37</i>	<i>0.91</i>
Cervix	26	1.3 (0.8 – 1.9)	39	1.0 (0.7 – 1.4)	7	1.1 (0.5 – 2.3)	16	1.3 (0.8 – 2.1)	<i>0.47</i>	<i>0.54</i>
Uterine corpus	39	2.4 (1.7 – 3.2)	208	1.4 (1.2 – 1.6)	9	1.8 (0.8 – 3.5)	66	1.5 (1.1 – 1.9)	<i>0.004</i>	<i>0.48</i>
Ovary	53	1.5 (1.1 – 2.0)	24	1.4 (0.9 – 2.0)	19	1.8 (1.1 – 2.8)	9	1.7 (0.8 – 3.2)	<i>0.54</i>	<i>0.76</i>
Testis	11	3.0 (1.5 – 5.5)	20	1.8 (1.1 – 2.9)	5	2.9 (1.0 – 6.9)	5	1.0 (0.3 – 2.4)	<i>0.26</i>	<i>0.12</i>
Bladder	10	0.9 (0.5 – 1.7)	109	1.3 (1.1 – 1.6)	5	1.3 (0.4 – 2.9)	43	1.4 (1.0 – 1.9)	<i>0.27</i>	<i>0.79</i>
Brain/CNS	11	1.6 (0.8 – 2.9)	25	2.1 (1.3 – 3.0)	6	2.5 (0.9 – 5.5)	11	2.6 (1.3 – 4.6)	<i>0.38</i>	<i>0.91</i>
Myeloid/monocytic leukemia	22	1.4 (0.9 – 2.1)	<3		9	1.7 (0.8 – 3.2)	0			
Hodgkin lymphoma	38	1.9 (1.4 – 2.6)	6	1.7 (0.6 – 3.7)	15	2.1 (1.2 – 3.5)	<3		<i>0.83</i>	
CLL/SLL	18	2.5 (1.5 – 4.0)	55	1.9 (1.4 – 2.4)	<3		25	2.5 (1.6 – 3.6)	<i>0.30</i>	
DLBCL	50	1.6 (1.2 – 2.1)	11	2.1 (1.1 – 3.8)	23	2.1 (1.3 – 3.1)	3	1.7 (0.4 – 5.0)	<i>0.28</i>	<i>0.81</i>
Marginal zone lymphoma	16	3.5 (2.0 – 5.7)	26	2.6 (1.7 – 3.8)	3	2.0 (0.4 – 5.8)	5	1.5 (0.5 – 3.5)	<i>0.35</i>	<i>0.63</i>

	Total PTC			Regional/Distant PTC			
	Any Chemotherapy		No/UK Chemotherapy		Any Chemotherapy		No/UK Chemotherapy
	Obs	SIR (95% CI) ^a	Obs	SIR (95% CI) ^a	Obs	SIR (95% CI) ^a	P _{het} ^b
First primary malignancy							
Follicular lymphoma	27	1.4 (1.0 – 2.1)	22	1.5 (1.0 – 2.3)	10	1.6 (0.8 – 3.0)	0.94
Plasma cell neoplasms	25	1.6 (1.1 – 2.4)	15	1.5 (0.9 – 2.5)	11	2.2 (1.1 – 3.9)	0.39

Abbreviations: central nervous system (CNS); confidence interval (CI); heterogeneity (het); observed (Obs); papillary thyroid cancer (PTC); standardized incidence ratio (SIR); non-melanoma skin cancer (NMSC); Surveillance, Epidemiology, and End Results Program (SEER); chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); diffuse large B-cell lymphoma (DLBCL);

Note: Restricted to those first primary sites where at least 10% of individuals reported to have received initial treatment with chemotherapy.

^aSIR=observed/expected. Expected numbers of cases were derived from incidence rates for papillary thyroid cancer in the total population of the same 17 SEER registries, stratified by age (5-year groups), race (white/unknown, black, other), sex, and calendar year (5-year groups), multiplied by the appropriate person-years at risk. Exact numbers of observed cases <3 and accompanying SIRs were suppressed to protect patient confidentiality.

^bTwo-sided P-value for heterogeneity in SIRs by reported initial chemotherapy based on a likelihood ratio statistic from multivariable Poisson regression models adjusted for sex, age at diagnosis and time since first primary cancer diagnosis. Inclusion of the log of the expected number of cases as an offset indirectly adjusted for attained age and calendar year. Models were not fitted when one group had <3 cases. Models were fitted separately for total and regional/distant PTC.

Table 5.

Risk of second primary papillary thyroid cancer (PTC) among adults (20–84 years) who survived 5 years after diagnosis, 17 SEER registries, 2000–2015, by stage at papillary thyroid cancer and initial radiotherapy for first primary types where thyroid potentially in or near the radiotherapy field.

	Total PTC				Regional/Distant PTC			
	Radiation Yes		Radiation No/UK		Radiation Yes		Radiation No/UK	
	Obs	SIR (95% CI) ^a	Obs	SIR (95% CI) ^a	Obs	SIR (95% CI) ^a	Obs	P _{het}
First primary malignancy								
Oral cavity/pharynx	14	1.0 (0.5 – 1.7)	12	1.1 (0.6 – 1.9)	3	0.6 (0.1 – 1.7)	7	1.8 (0.7 – 3.8)
Esophagus	<3		<3		0		<3	0.10
Larynx	4	0.7 (0.2 – 1.9)	<3		<3		0	
Lung/bronchus	4	0.6 (0.2 – 1.5)	38	1.6 (1.1 – 2.2)	0		18	2.3 (1.3 – 3.6)
Soft tissue (including heart)	7	2.0 (0.8 – 4.2)	18	3.6 (2.1 – 5.7)	<3		9	5.3 (2.4 – 10.0)
Female breast	253	1.0 (0.9 – 1.2)	239	1.3 (1.1 – 1.5)	78	1.1 (0.9 – 1.3)	79	1.4 (1.1 – 1.8)
Brain/CNS	6	1.7 (0.6 – 3.7)	7	1.5 (0.6 – 3.1)	<3		5	3.1 (1.0 – 7.2)
Brain	6	1.9 (0.7 – 4.1)	5	1.4 (0.5 – 3.3)	<3		4	3.3 (0.9 – 8.4)
Hodgkin lymphoma	11	1.9 (0.9 – 3.4)	11	1.6 (0.8 – 2.8)	5	2.4 (0.8 – 5.6)	6	2.4 (0.9 – 5.2)
DLBCL	10	1.8 (0.9 – 3.3)	11	1.0 (0.5 – 1.8)	6	3.2 (1.2 – 6.9)	5	1.3 (0.4 – 3.0)
Marginal zone lymphoma	4	2.1 (0.6 – 5.5)	10	2.2 (1.0 – 4.0)	3	4.8 (1.0 – 14.0)	<3	
Follicular lymphoma	4	1.3 (0.4 – 3.4)	23	1.8 (1.2 – 2.8)	<3		9	2.2 (1.0 – 4.1)
Plasma cell neoplasms	<3		8	1.3 (0.6 – 2.6)	<3		3	1.5 (0.3 – 4.4)

Abbreviations: central nervous system (CNS); confidence interval (CI); heterogeneity (het); observed (Obs); papillary thyroid cancer (PTC); standardized incidence ratio (SIR); Surveillance, Epidemiology, and End Results Program (SEER); diffuse large B-cell lymphoma (DLBCL); unknown (UK)

Note: Restricted to those first primary sites where at least 10% of individuals reported to have received initial treatment with radiotherapy.

^a SIR=observed/expected. Expected numbers of cases were derived from incidence rates for papillary thyroid cancer in the total population of the same 17 SEER registries, stratified by age (5-year groups), race (white/unknown, black, other), sex, and calendar year (5-year groups), multiplied by the appropriate person-years at risk. Follow-up for this analysis began at 5-years after diagnosis of first primary cancer. Exact numbers of observed cases <3 and accompanying SIRs were suppressed to protect patient confidentiality.

^b Two-sided P-value for heterogeneity in SIRs by reported initial radiotherapy based on a likelihood ratio statistic from multivariable Poisson regression models adjusted for sex, age at diagnosis and time since first primary cancer diagnosis. Inclusion of the log of the expected number of cases as an offset indirectly adjusted for attained age and calendar year. Models were not fitted when one group had <3 cases. Models were fitted separately for total and regional/distant PTC.