

Risk of Second Primary Cancer Among Patients with Thyroid Carcinoma in Finland: A Nationwide Population-Based Study

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Purpose: Thyroid cancer (TC) survivors face an increased risk of second primary cancers (SPCs). While previous research on the risk of SPCs among TC patients has been conducted in other regions, comprehensive data from Northern Europe remain limited. Our register-based cohort study aimed to evaluate the risk of SPCs among Finnish TC survivors.

Patients and Methods: We obtained data on all patients diagnosed with TC in Finland in 1953–2022 from the Finnish Cancer Registry (FCR). Standardized incidence ratios (SIRs) of SPCs were calculated relative to the risk of cancer in the general population.

Results: We identified 14,520 patients with TC (3,212 males, 22%; 11,308 females, 78%), with a median follow-up of 12.1 years. A metachronous SPC was diagnosed in 16.4% (n=527) of males and 15.5% (n=1,744) of females. The overall SPC risk was elevated for both males (SIR 1.23, 95% CI 1.12–1.34; EAR 2.39/1,000 PYs) and females (1.24, 1.19–1.30; EAR 1.92/1,000 PYs). Female patients with papillary TC (PTC) displayed increased SIRs for breast (SIR 1.26, 95% CI:1.15–1.37), urinary organ (1.50, 1.19–1.86), brain (1.85, 1.48–2.29), and hematolymphoid cancers (1.31, 1.10–1.54). Males with PTC showed an increased risk of urinary organ (SIR 1.39, 1.01–1.85), brain (2.73, 1.69–4.17), and hematolymphoid cancers (1.52, 1.12–2.01). The elevated SPC risk of the breast and brain persisted even after 20 years of follow-up. An increased incidence of SPCs of the urinary organs, brain, and hematolymphoid tissues was observed in females diagnosed with follicular TC (FTC) or medullary TC (MTC) in 1953–1985.

Conclusion: Our results indicate an excess risk of cancers of the breast, urinary organs, brain and hematolymphoid tissues for Finnish patients with a history of PTC. For FTC and MTC risk of cancers of the urinary organs, brain, and hematolymphoid tissues is specific for female patients diagnosed in 1953–1985.

Keywords: thyroid cancer, papillary thyroid cancer, second primary cancer

Introduction

Thyroid cancer (TC) encompasses a heterogeneous group of various histologic subtypes. They vary from indolent to highly aggressive tumors and are classified into four main groups: papillary (PTC) and follicular (FTC) (both classified as differentiated TC; DTC), medullary (MTC), and anaplastic (ATC). DTC is considered the sixth most common cancer with an increasing overall incidence in the past decades owing especially to improved diagnostics.¹ In Finland, since 1953 the annual number of new TC cases has steadily increased in both sexes with an age-adjusted incidence rate of 9.16 per 100,000 in 2022.² Nevertheless, DTC-related mortality remains low, with a 10-year survival exceeding 90%: 5-year survival in Finland 94% for females and 91% for males.¹⁻³ Primary treatment entails surgery, followed in select cases by treatment with radioactive iodine (RAI), either as adjuvant therapy or for ablation of remnant disease.⁴

Overall, TC survivors have a 20% higher risk of developing a second primary cancer (SPC) compared with the general population, with follow-up up to 14 years.^{5,6} Suggested risk factors include shared genetic and environmental factors, toxicity from diagnostic radiography and prior anticancer therapies, as well as enhanced screening and lengthy follow-up potentially revealing dormant pathologies. The use of RAI has several recognized adverse effects and an associated risk of secondary malignancy.^{7,8} Further, the Chernobyl disaster in 1986 caused substantial radioactive contamination in its immediate vicinity and extending to vast areas in Europe, and its carcinogenic effects and impact on thyroid and other cancers have been acknowledged in prior studies.^{4,9,10} In Finland, its impact on the incidence of other cancers has been deemed insignificant.¹¹

Prior reports on the risk and types of SPC following DTC have shown considerable variability and some conflicting findings.^{5,6,8,12–16} This is the first comprehensive, registry-based study to evaluate the incidence and type of SPCs in Finnish TC survivors, with over 20 years of follow-up and findings stratified by specific time intervals before and after the Chernobyl accident in 1986. Given the increasingly favorable prognosis of TC, acknowledging the risk of secondary malignancies, along with their key shared and possibly treatment-related risk factors, is of utmost importance.

Materials and Methods

Study Cohort

We retrieved data on patients diagnosed with TC in Finland between the 1st of January 1953 and the 31st of December 2022 from the Finnish Cancer Registry (FCR). The FCR documents all new primary cancer cases diagnosed in Finland since 1953, with details on the primary tumor location, histology, and complete follow-up until death or emigration. We identified TC cases using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) topography codes C739 and morphology codes as follows: Papillary M8260/3, M8340/3–M8344/3, M8265/3; Follicular M8330/3, M8335/3, M8339/3, M8331/3; Medullary M8345/3, M8347/3, M8510/3; Anaplastic M8020/3, M8021/3. Other histologies were grouped as Other histology or unknown M8010/3, 8000/3, M8800/3, M8810/3, M9120/3, M8802/3, M8890/3; Other carcinoma M8290/3, M8070/3, M8140/3, M8337/3, M8054/3, M8240/3, M8246/3, M8310/3, M8350/3, M8430/3. Histology codes prior to 2000 (before use of ICD-O-3) were converted as follows: Papillary adenocarcinomas; Medullary carcinomas; Follicular adenocarcinomas; and Carcinoma, NOS or No histology or unknown. Lymphomas, sarcomas and other rare histologies (such as carcinoids, epidermoid ca) were also converted to their respective ICD-O-3 codes. We excluded all patients with a history of any previous cancer, except for basal cell carcinoma of the skin, which is common, not systematically registered as a first primary cancer in the FCR and not considered to influence the risk of subsequent malignancies. Patients whose first primary cancer diagnosis and death occurred on the same date were also excluded.

Second Primary Cancer Data

We limited the analysis to metachronous SPCs (ie malignant tumors diagnosed at six months or later after the initial diagnosis of primary TC). Therefore, we did not include synchronous SPCs (ie malignant tumors diagnosed within six months of the primary TC diagnosis). Of note, the FCR does not record cases of SPCs occurring at the same site as the index tumor, unless the cancer is of a different histological type. Follow-up for each patient started 6 months after the date of the primary TC diagnosis and ended at diagnosis of an SPC, death, emigration or December 31st, 2022; whichever came first. Only one patient emigrated during the follow-up.

Statistical Analyses

To estimate the risk of SPCs, we calculated standardized incidence ratios (SIRs) and their associated 95% confidence intervals (CIs) for each TC type. This involved comparing the observed number of SPC cases among patients with TC to the expected number of cancer cases among the Finnish general population, adjusted for age, sex, and calendar year, using patient years (PYs) of observations (until the first primary cancer in the general population and second primary in TC patients) and assuming a Poisson distribution for the observed cases. The expected numbers of cancers in the general population were derived by multiplying the accumulated person-years at risk in each stratum (defined by sex, 5-year age group, and 5-year calendar period) by the corresponding site-specific cancer incidence rates in the Finnish general population. To evaluate the

influence of demographic and clinical factors on SPC risk, we performed stratified analyses by age at thyroid cancer diagnosis, sex, extent of the primary disease (localized vs non-localized), time since the primary cancer diagnosis, and calendar period of diagnosis (1953–1969, 1970–1985, 1986–1995, 1996–2010, 2011–2022). SIRs were calculated separately for each stratum, with the expected numbers of cancers derived from the corresponding Finnish population rates for that subgroup. This approach enabled assessment of how the SPC risk varied across different demographic categories and time periods. Additionally, we calculated the excess absolute risk (EAR) to quantify the burden of SPCs among TC survivors compared to the general population. The EAR is expressed as the number of excess cancers per 1,000 PYs at risk. All SPCs recorded in the FCR were included in the analysis. For data privacy reasons, we do not show numerical data or risk estimates for categories with less than five observed cancer cases. We conducted all statistical analyses using R software (The R Project for Statistical Computing), version 4.2.2 and the *popEpi* and *forestplot* packages.

Results

A total of 14,520 patients with TC (3,212 males, 22%; 11,308 females, 78%) were identified from 1953 to 2022 adding to 218,762 PYs of follow-up. The median follow-up time was 12.06 years (first quartile 5.16 years, third quartile 22.80 years). PTC, FTC, MTC and ATC constituted 78.8% (n=11,436), 13.6% (n=1,974), 2.5% (n=366), and 0.4% (n=63) of all cases, respectively (Table 1). A total of 681 cases (4.7%) had either a different or unknown histology or represented a different carcinoma type. All primary cancers and 86.9% of second primary cancers were histologically confirmed.

Figure 1 provides a summary of the SIRs and EARs for SPC among all TC patients categorically stratified. A metachronous SPC was diagnosed in 2,271 patients (15.6% of all TC patients) over the entire follow-up: in 16.4% (n=527) of males and 15.5% (n=1,744) of females. Out of all SPCs, 59.2% (n=1,346) were diagnosed after 10 years from the initial TC diagnosis. For male patients with TC, the overall SIR for an SPC at any primary site was 1.23 (95% CI: 1.12–1.34), yielding 2.39 (1.51–3.79) excess SPCs per 1,000 PYs, when compared to the cancer risk of the general population. Similarly, for females, the corresponding SIR and EAR were 1.24 (95% CI: 1.19–1.30) and 1.92 (1.51–2.44), respectively. The risk of SPC remained elevated in all age categories and throughout follow-up, except for the first period in 1953–1969, when the SIR was 1.00.

Papillary Thyroid Carcinoma (PTC)

Of all patients with a PTC, a metachronous SPC was diagnosed in 17.1% (n=399) and 15.3% (n=1,389) of males and females, respectively, translating to elevated SIRs of 1.27 (95% CI: 1.15–1.40) and 1.24 (95% CI: 1.17–1.31), respectively, when compared with the cancer risk in the general population (Figure 2). The excess risk equated to 2.70 (95% CI: 1.71–4.27) and 1.84 (1.40–2.242) excess SPCs per 1,000 PYs among males and females, respectively. The increased risk of SPC was seen across all age categories, in each calendar period after 1970, and for both localized and non-localized primary diseases, and remained elevated even after 20 years.

The breast and digestive organs harbored most SPCs among females, with 34.6% (n=481) and 17% (n=236) of all diagnosed SPCs, respectively (Figure 3). Females displayed increased SIRs for cancers of the breast (SIR 1.26, 95% CI: 1.15–1.37), urinary organs (1.50, 1.19–1.86), brain (1.85, 1.48–2.29), and hematolymphoid tissues (1.31, 1.10–1.54). Similarly, males showed an increased SPC risk of the urinary organs (SIR 1.39, 95% CI: 1.01–1.85), brain (2.73, 1.69–4.17), and hematolymphoid tissues (1.52, 1.12–2.01). Whereas the risk of the urinary organs and hematolymphoid tissues was elevated only during the 10 first years of follow-up, the risk of breast and brain cancers was elevated even beyond 20 years.

Follicular Thyroid Carcinoma (FTC)

Of all FTC patients, a metachronous SPC was diagnosed in 18.3% (n=94) and 17.3% (n=253) of males and females, respectively (Figure 4). An overall increased risk of SPC was only observed among females (SIR 1.22, 95% CI: 1.08–1.38) when compared with the cancer risk in the general population. Females displayed increased SIRs for cancers of the urinary organs (SIR 1.90, 95% CI: 1.17–2.90), brain (2.18, 1.25–3.54), and hematolymphoid tissues (1.66, 1.15–2.32) (Figure 5). The risk of urinary organ cancer among females was elevated only after 20 years of follow-up, specifically among those whose primary TC was diagnosed between 1953 and 1969. Likewise, the risk of brain and hematolymphoid cancers was elevated only in females diagnosed with

Table 1 Finnish Individuals with Primary Thyroid Cancer in 1953–2022

Cancer Subtype	1953–1969		1970–1985		1986–1995		1996–2010		2011–2022		1953–2022			
	n	%	n	%	n	%	n	%	n	%	M	F	All	
Papillary thyroid carcinoma	257	32.6	1,543	66.4	1,893	81.6	3,810	86.2	3,933	84.3	2,339	9,097	11,436	78.80%
Follicular thyroid carcinoma	315	40.0	530	22.8	274	11.8	396	9.0	459	9.8	515	1,459	1,974	13.60%
Medullary thyroid carcinoma	3	0.4	70	3.0	75	3.2	126	2.9	92	2.0	136	230	366	2.50%
Anaplastic thyroid carcinoma									59	1.3	30	33	63	0.40%
Other histology or unknown	206	26.1	171	7.4	53	2.3	35	0.8	21	0.5	136	350	486	3.30%
Other carcinoma	7	0.9	10	0.4	25	1.1	51	1.2	102	2.2	56	139	195	1.30%
All	788	100.0	2,324	100.0	2,320	100.0	4,418	100.0	4,666	100.0	3,212	11,308	14,520	100.00%

Abbreviations: M, males; F, females.

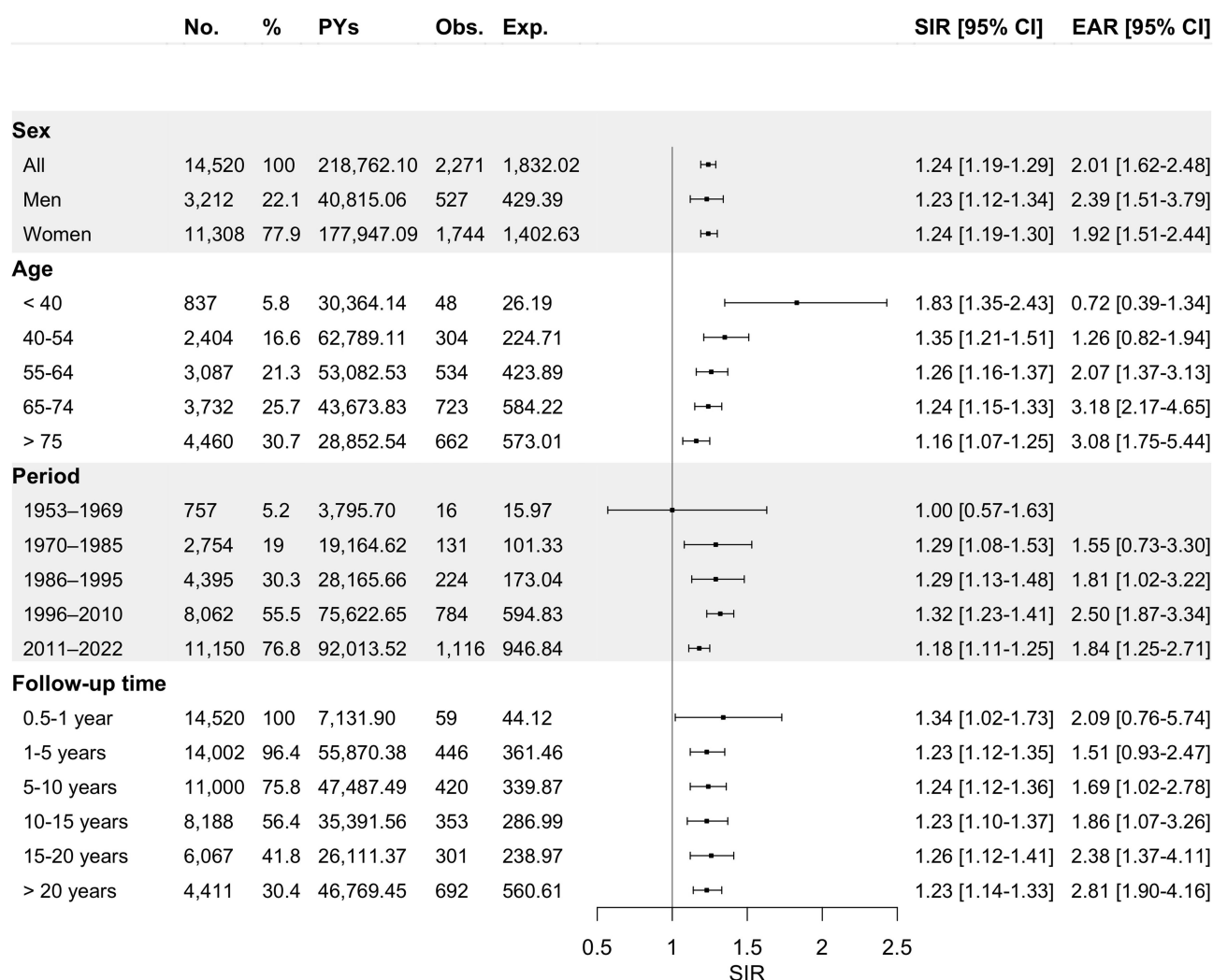


Figure 1 Standardized incidence ratios and excess absolute risk per 1,000 person-years for any metachronous second primary cancer among 14,520 thyroid carcinoma patients diagnosed in Finland during 1953–2022. Results are stratified by sex, age at diagnosis of primary tumor, follow-up period (number of patients alive), follow-up time, and primary disease stage.

Abbreviations: CI, confidence interval; Exp, expected; EAR, excess absolute risk; n.s., non-significant; No, number; Obs, observed; PYs, person-years; SIR, standardized incidence ratio.

primary TC specifically between 1970 and 1985. Males showed an increased risk only for hematolymphoid cancers (SIR 1.90, 95% CI: 1.04–3.18), and specifically during the initial five years of follow-up (SIR 2.94, 95% CI: 1.65–4.85).

Medullary Thyroid Carcinoma (MTC)

Of all MTC patients, a metachronous SPC was diagnosed in 14% of males (n=19) and 17.8% of females (n=41). Only females showed an overall increased risk of SPC (SIR = 1.55, 95% CI: 1.1–2.10), which corresponded to 4.66 (1.96–11.07) excess SPCs per 1,000 PYs, when compared with the cancer risk in the general population (Figure 6). The risk of SPC was elevated only during the first five years of follow-up, and specifically among females diagnosed with primary MTC during 1970–1985. When stratified by SPC site, males displayed an increased risk for hematolymphoid cancers (SIR 3.38, 95% CI: 1.10–7.89), (Figure 7).

Discussion

To the best of our knowledge, this is the first comprehensive, nationwide study on the incidence and types of SPCs among Finnish TC survivors, with over 20 years of follow-up, and results stratified by specific time intervals. Our data suggest that

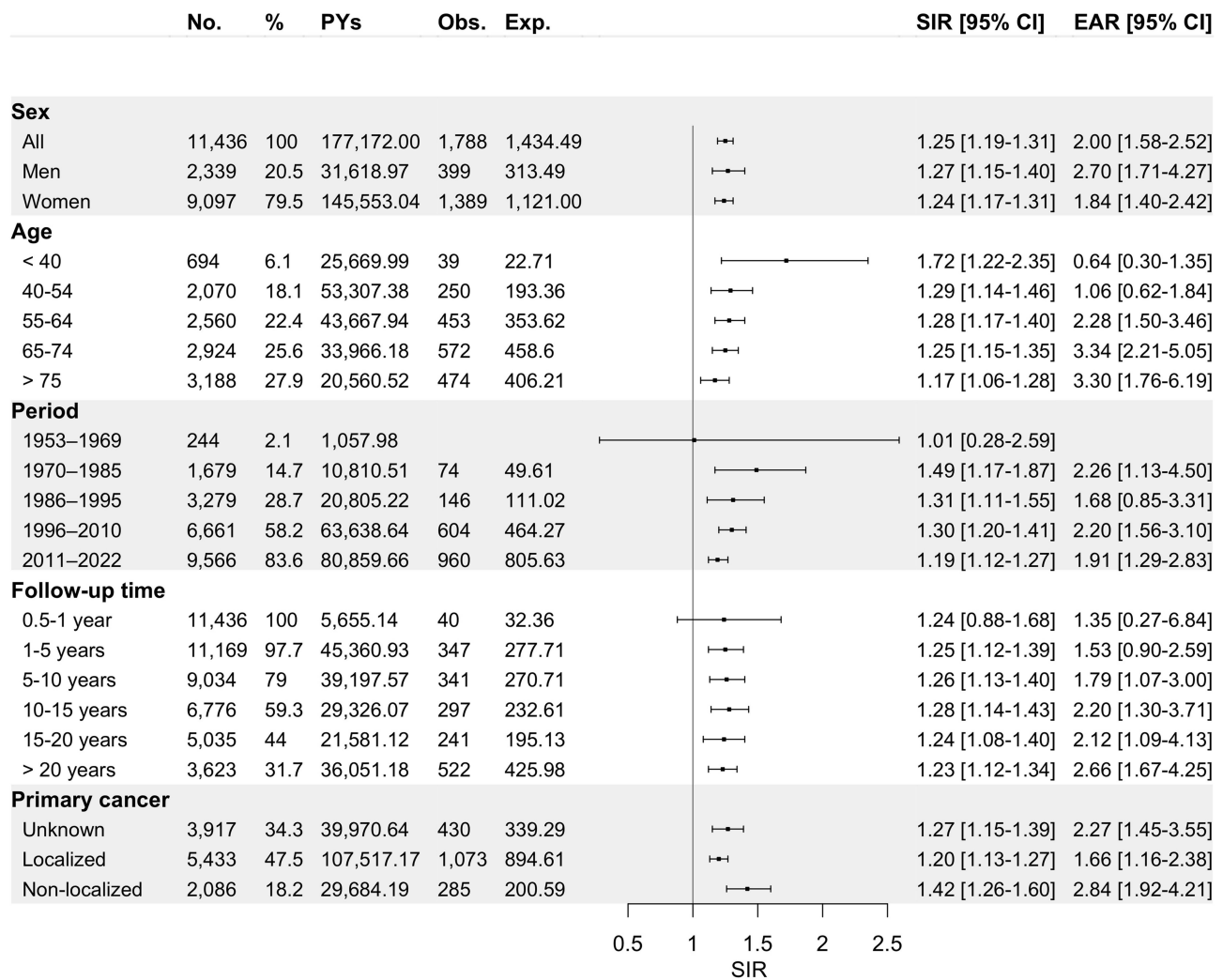


Figure 2 Standardized incidence ratios and excess absolute risk per 1,000 person-years for any metachronous second primary cancer among 11,436 papillary thyroid carcinoma patients diagnosed in Finland during 1953–2022 stratified by sex, age at diagnosis of primary tumor, follow-up period (number of patients alive), follow-up time, and primary disease stage.
Abbreviations: CI, confidence interval; Exp, expected; EAR, excess absolute risk; n.s, non-significant; No, number; Obs, observed; PYs, person-years; SIR, standardized incidence ratio.

patients with a history of PTC have an increased risk of SPCs of the breast (SIR 1.26 for females), urinary organs (SIR 1.39 and 1.50 for males and females, respectively), brain (SIR 2.73 and 1.85), and hematolymphoid tissues (SIR 1.52 and 1.31), when compared with the general Finnish population. Our findings further indicate that the elevated risk of breast and brain SPCs persists even beyond 20 years following the diagnosis of primary PTC (SIR 1.39 and 1.80 for breast and brain cancers, respectively, after 20 years). An increased incidence of SPCs of the urinary organs, brain, and hematolymphoid tissues was seen among FTC and MTC female patients diagnosed with primary TC during 1953–1985.

Several prior epidemiological and registry-based studies have shown that TC patients have an elevated risk of developing subsequent malignancies, with reported SPC rates ranging from 26 to 30% among TC survivors followed for up to 30 years.^{6,8,12,15,17,18} However, results vary considerably, reflecting differences across populations, methodologies, follow-up durations, and study periods, and are not often categorized by specific tumor histology. Debated risk factors range from bidirectional association of shared risk factors to treatment-related adverse events—such as added radio-toxicity and malignant tissue transformation from prior oncogenic treatments and radiographic surveillance—and increased diagnostic scrutiny leading to a higher detection rate of indolent tumors.^{6,19} Nevertheless, with an increasingly favorable prognosis and low age-standardized mortality of TC, SPCs are associated with a worse prognosis and are considered a leading cause of death in TC survivors.^{8,20,21}

The largest studies to date are reports from the United States, using data from the US Surveillance, Epidemiology, and End Results (SEER) Program, and from a few Asian countries. In 2008, Brown et al analyzed a cohort of 30,278 SEER TC patients diagnosed in 1973–2002 and reported an increased SPC risk of the breast (SIR 1.22), but only within 10 years of the initial TC diagnosis, prostate (1.34), salivary glands (2.72), hematolymphoid system (1.24), and kidney (2.4), and no notable risk for gastrointestinal malignancies.⁶ Later in 2013, Kim et al similarly reported a significant SPC risk across all sites in their cohort of over 50,000 SEER TC survivors from 1973–2008, with the highest risks observed for salivary gland (SIR 3.11) and kidney cancers (2.30).²² Further analysis by tumor size indicated a higher SPC risk for microcarcinomas, supporting the role of escalated treatment in secondary tumorigenesis. Most recently, in 2018, Endo et al reported data on 75,992 SEER TC patients diagnosed between 1992–2013, of whom 4.2% developed an SPC.²³ They noted that the bone and joints, salivary glands, hematolymphoid organs, and the ureter had the highest risk of SPC (SIR 4.25, 4.15, 3.98, 2.72, respectively), while the risk of colorectal cancer was decreased compared with the reference population.²³

Findings from Asian countries are alike. A large Korean study by Kim et al included over 290,000 TC survivors from the Korean national registry and reported a significant SPC risk (SIR 1.26), specifically of myeloid leukemia and 13 solid organ cancers, during a 6-year follow-up. The presence of an SPC was also associated with a significantly poorer survival rate.⁸ A Taiwanese study, using data from the Taiwanese Cancer Registry (1979–2006) covering 19,068 TC survivors, reported the highest risks of SPC for the major salivary glands (SIR 4.39), brain (4.02), thymus (3.38), and hematolymphoid tissues (2.66).²⁴

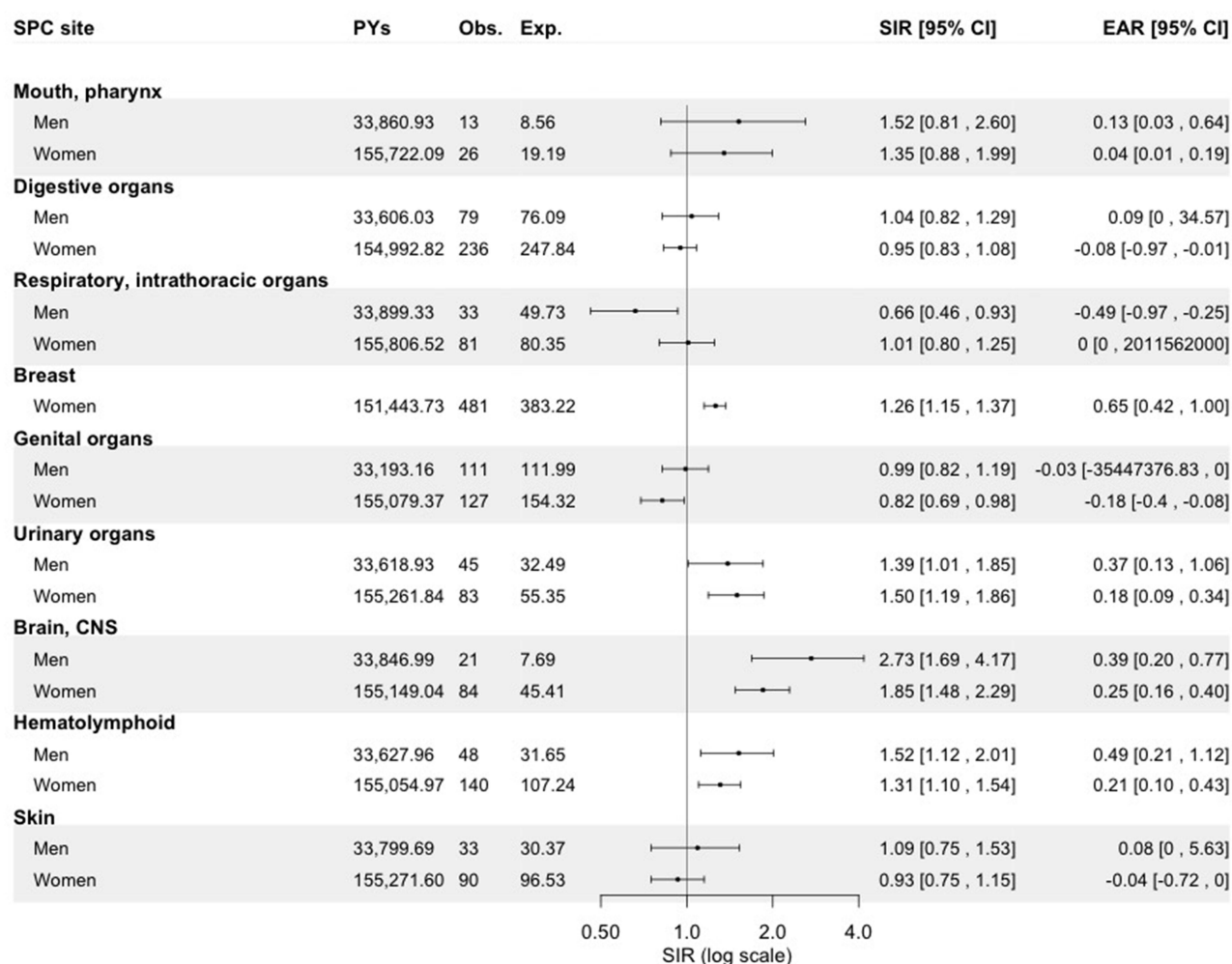


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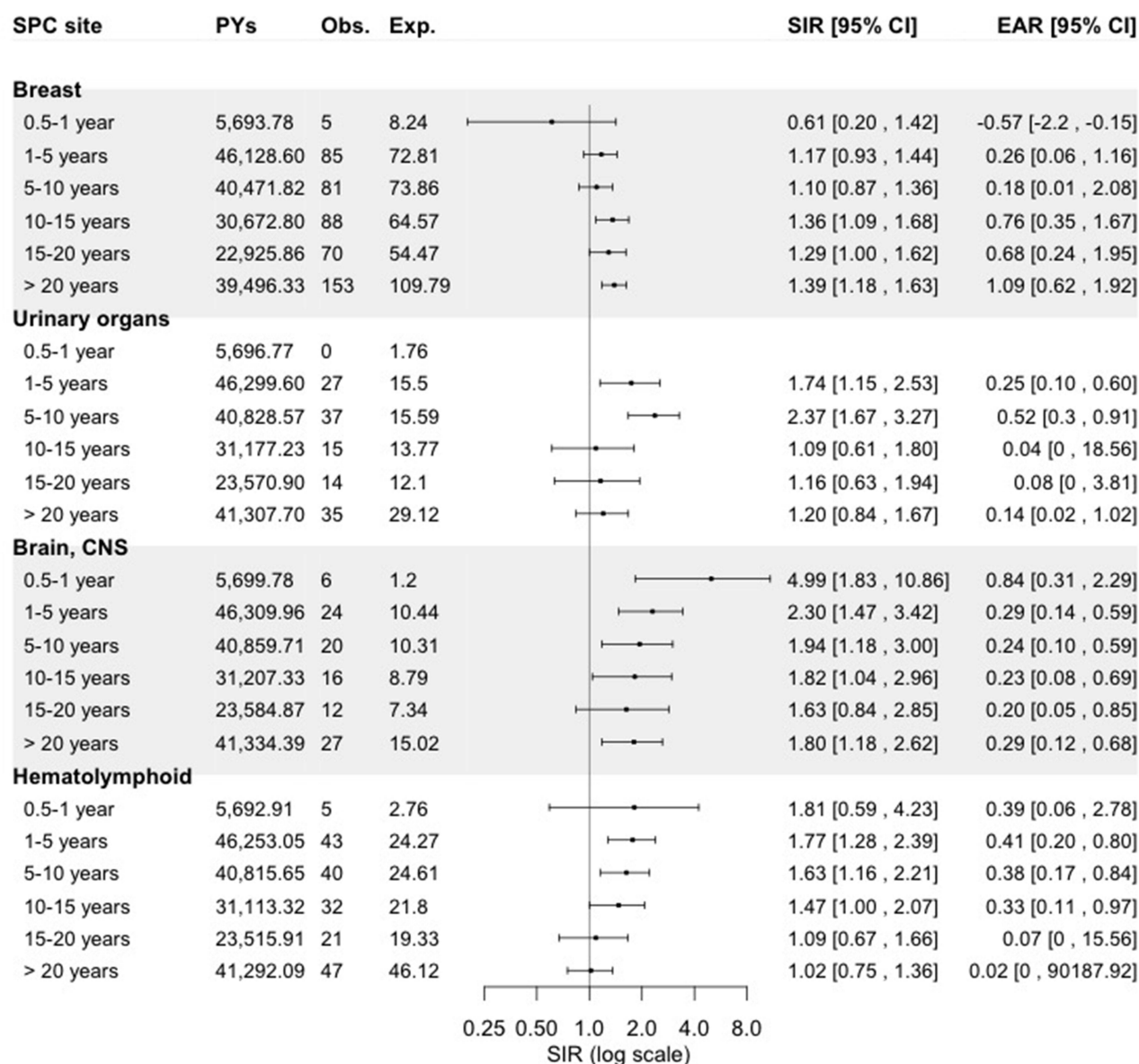


Figure 3 Standardized incidence ratios and excess absolute risk per 1,000 person-years for second primary cancer by site (if more than four cases recorded) among patients with papillary thyroid carcinoma in Finland during 1953–2021 stratified by sex and follow-up time for SPC sites with an elevated risk.

Abbreviations: CI, confidence interval; Exp, expected; EAR, excess absolute risk; n.s., non-significant; No, number; Obs, observed; PYs, person-years; SIR, standardized incidence ratio.

Lastly, one large-scale study conducted in 2006 by Sandeep et al included collated data from 13 countries from Europe, Canada, Australia, and Singapore. Their data indicated a significantly elevated risk for most malignancies, with the highest risks observed for the salivary gland (SIR 3.15), bone (3.62), and adrenal gland (8.34) cancers, as well as for soft tissue sarcoma (3.63) and leukemia (2.26).¹²

Prior reports from Finland or neighboring Nordic countries are limited, somewhat dated, and based on relatively small cohorts. A study by Hakala et al in 2015, comprising 910 DTC patients from two university hospitals (1981–2002), reported an increased risk of SPC, specifically sarcomas and lymphomas (SIR 4.37), in patients under 40 years or diagnosed after 1996.²⁵ A study from Sweden, by Hall et al from 2009, analyzed a cohort of 2,968 TC patients recorded in the national cancer registry between 1958 and 1975 and found an elevated SPC risk of the kidneys (SIR 1.53), endocrine glands (SIR 3.21), and the nervous system (SIR 2.86) (mean follow-up time 12 years), especially in younger patients; no differences in the incidence of leukemia or breast cancer were observed.¹⁸ Akslen and Glattre in 1992

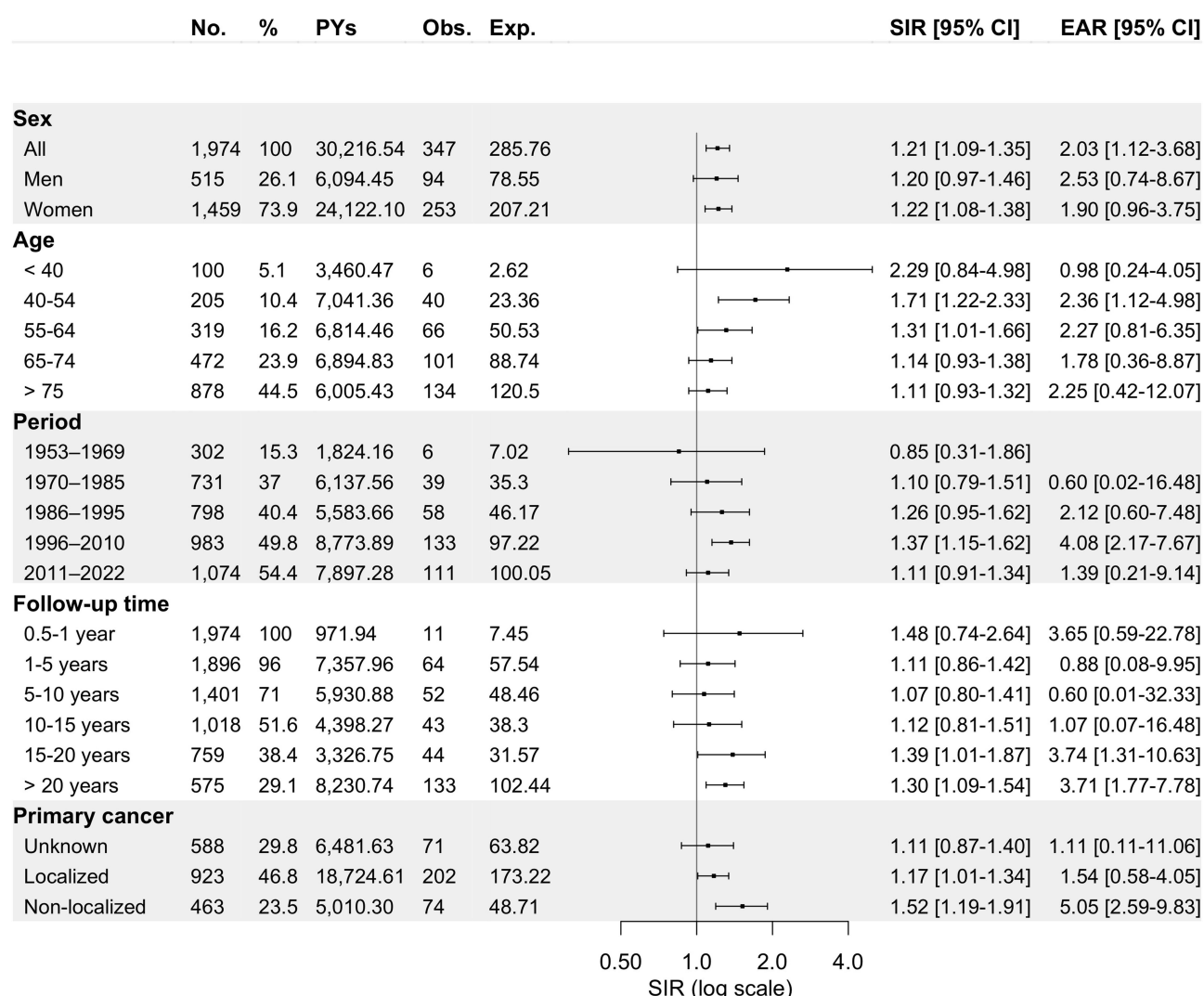


Figure 4 Standardized incidence ratios and excess absolute risk per 1,000 person-years for any metachronous second primary cancer among 1,974 follicular thyroid carcinoma patients diagnosed in Finland during 1953–2022 stratified by sex, age at diagnosis of primary tumor, follow-up period (number of patients alive), follow-up time, and primary disease stage.

Abbreviations: CI, confidence interval; Exp, expected; EAR, excess absolute risk; n.s, non-significant; No, number; Obs, observed; PYs, person-years; SIR, standardized incidence ratio.

described 3,658 Norwegian patients with TC diagnosed in 1955–1985 and reported an increased risk of urogenital cancer in males (SIR 1.96) and melanoma (SIR 4.2) (mean follow-up time 8.4 years).¹⁷ Although one prior study has utilized the Finnish Cancer Registry—as part of a large multinational study that pooled patients from several European registries and reported a 30% increase in SPCs—no subgroup analyses were performed for individual countries.¹²

Our results indicate an increased risk of breast cancer in Finnish patients with PTC. Several prior studies have established an association between thyroid and breast cancer, and an increased risk of either occurring as an SPC.^{6,26–29} While most studies have not specified findings for different TC subtypes,^{6,8,21} PTC typically represents the majority of TC cases and some have indicated a PTC-specific association.^{27,28} Some have postulated radioisotope therapy due to its excretion in breast milk, but no systematic differences have been observed between irradiated and nonirradiated patients.^{6,7} These together suggest a more relevant role for other factors rather than treatment-related events or surveillance bias.²⁸ Identification of shared genetic variants (eg *FOXO1*, *PTEN*, *CHEK2*) might imply a common genetic susceptibility between breast and thyroid cancers. Further, sex hormones, particularly estrogen, might also facilitate thyroidal carcinogenesis given the crosslinks in their molecular pathways and the expression of their receptors in both

normal and malignant thyroid tissue, and *vice versa*.^{27,30} Findings on an association between PTC and pregnancy, menstrual and reproductive phases, however, remain inconsistent.^{31,32} Of note, in contrast to several American and other studies, none of the aforementioned studies from the Nordic countries have shown an elevated risk of breast cancer in their TC survivors.^{17,18,25} The incongruency with prior Finnish data might relate to differences in study settings, ie smaller cohort size, years analyzed, lack of histological subanalyses and comparison to a control group matched for age, sex and inhabitancy.

Our findings also indicate a risk of hematologic and urinary tract malignancies in Finnish PTC survivors. Prior studies have reported similar patterns following TC,^{6,8,12,15,22,33} as well as an increased incidence of second primary TC after leukemia or lymphoma.^{19,26,34} The multinational study by Sandeep et al found an overall increased risk of non-Hodgkin's lymphoma and leukemia (SIR 1.68 and 2.26, respectively), especially within the first year after TC diagnosis, suggestive of a potential surveillance bias. Yuan et al reported that in a cohort of 7,066 patients with a second primary TC—consisting mainly of PTC—leukemia and lymphoma were the most frequent primary cancers contributing to TC development.²⁶ In contrast, prior Scandinavian studies found no elevated risk of hematolymphoid malignancies among TC survivors. Though the role of prior radioiodine treatment remains unknown, the reciprocal association between the two malignancies, and the partly inconsistent findings in prior studies suggest other factors may contribute.^{6,12,26,35} These may include for example shared genetic predisposition to neoplasms, such as the proto-oncogene *RET* linked to both PTC and leukemia and the multisite cancer susceptibility gene *CHEK2*,^{36,37} but current data remains scarce and the exact molecular bases unknown.

In contrast to our findings, both earlier studies from Norway and Sweden showed that the increased risk of urinary tract cancers was specific to males and middle-age patients,^{17,18} while Hakala et al found no elevated risk during 16 years

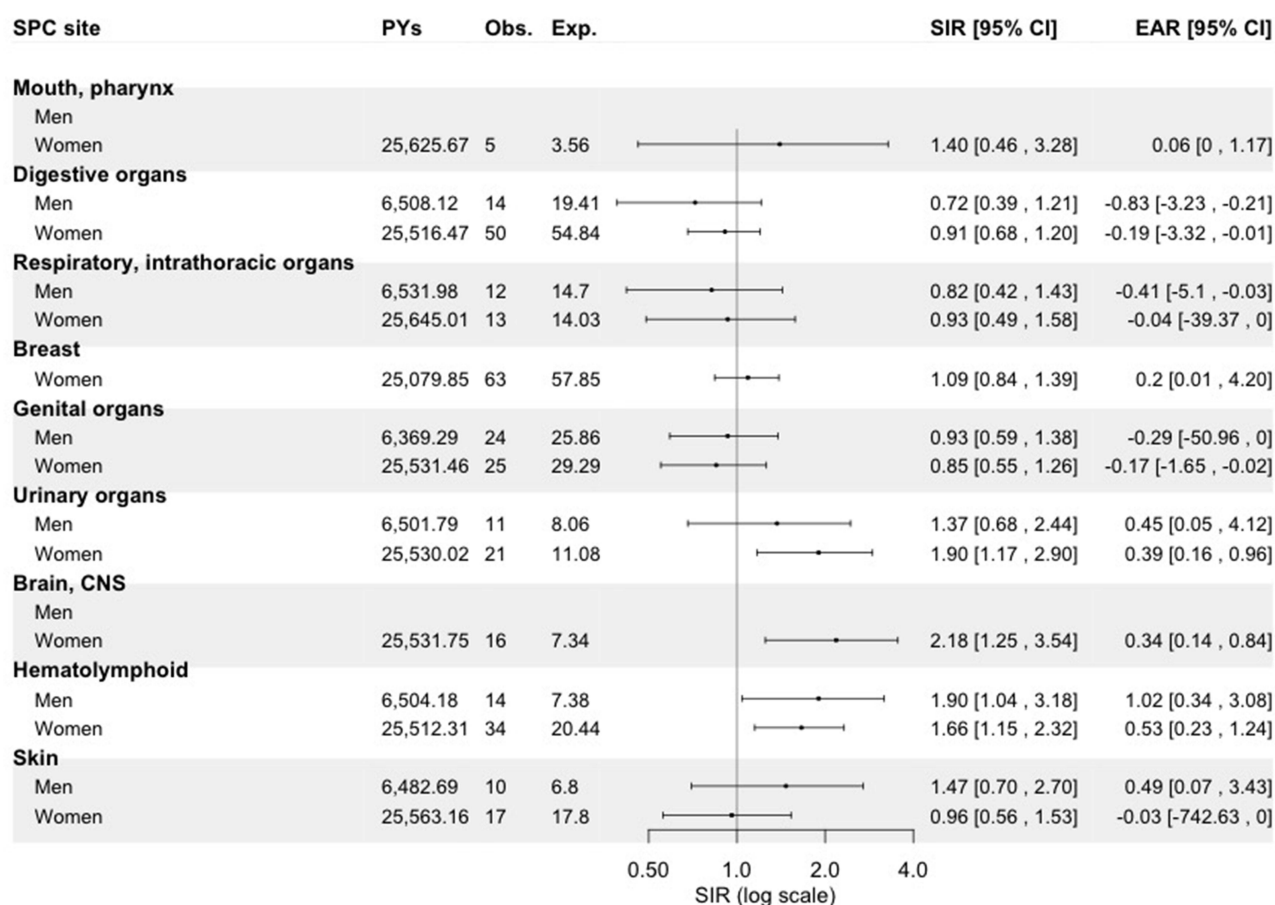


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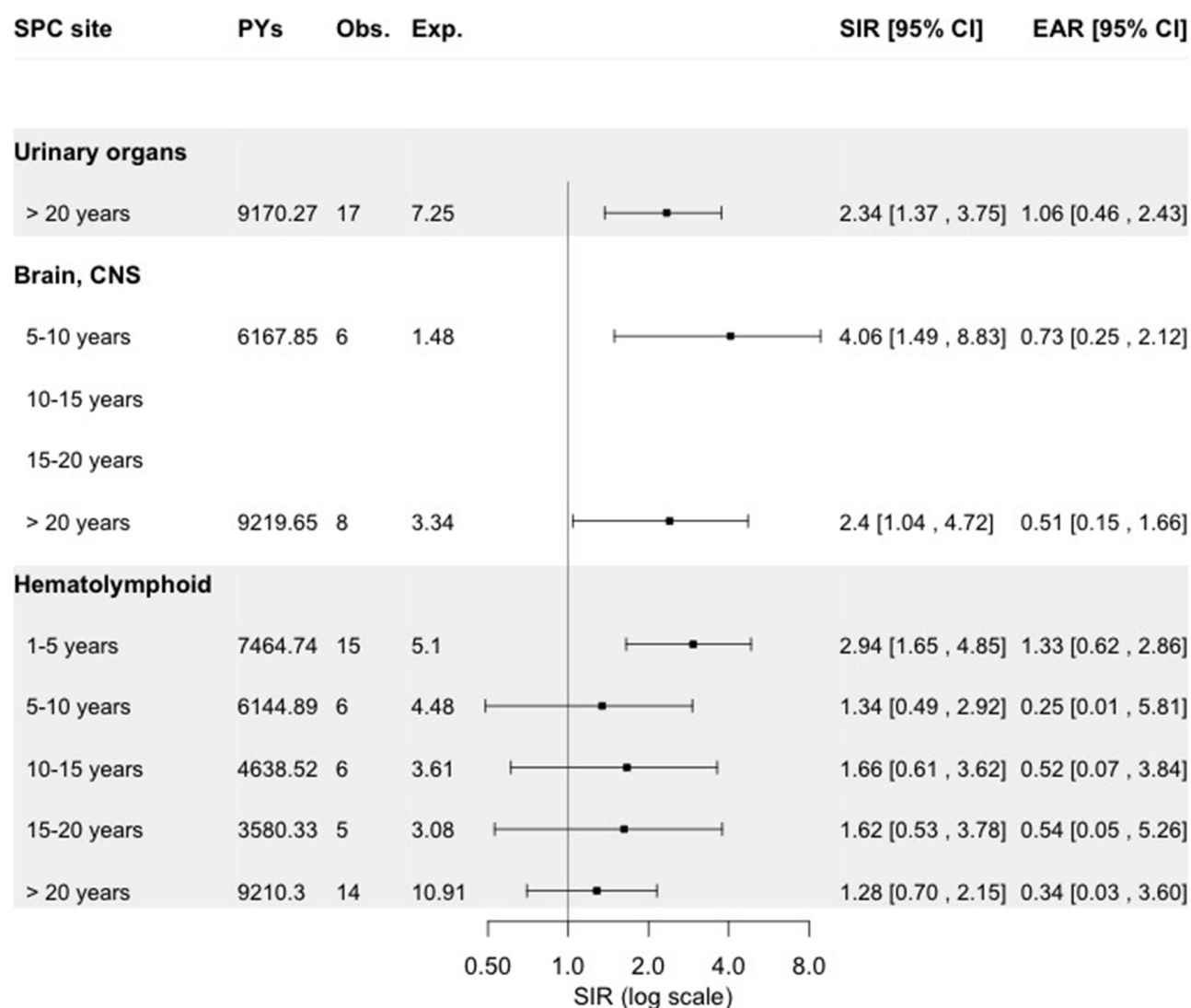


Figure 5 Standardized incidence ratios and excess absolute risk per 1,000 person-years for second primary cancer by site (if more than four cases recorded) among patients with follicular thyroid carcinoma in Finland during 1953–2021 stratified by sex and follow-up time for SPC sites with an elevated risk.

Abbreviations: CI, confidence interval; Exp, expected; EAR, excess absolute risk; n.s., non-significant; No, number; Obs, observed; PYs, person-years; SIR, standardized incidence ratio.

of follow-up.²⁵ Similarly, Canchola et al reported an excess risk of kidney cancers in a cohort of over 10,000 Californian female PTC survivors (SIR 3.9, 5-year follow-up).³³ Others have observed similar patterns in females, although the risk is often lower than that in males and not specific to PTC.⁶ Risk factors for TC-related urinary malignancies remain unclear; the role of prior anticancer therapies and on other shared factors remain inconclusive.^{19,22,33}

The observed risk of brain cancer is important, especially given our finding of an association specifically following PTC. While others have reported an increased risk of cancers of the central nervous system (CNS) following TC, the link to TC itself or its adjuvant therapies has not been extensively explored. Although RAI therapy can induce carcinogenesis in the nervous system, the association appears weaker and the arising tumors often benign.³⁸ Histological verification, to distinguish a true SPC from a metastasis, is also challenging, and hence many prior studies have either overlooked this finding or excluded brain cancer for risk of misclassification.^{8,10,15} Metastases from TC are rare and, if present, typically manifest in the follicular or poorly differentiated forms and affect primarily the lungs or bone.^{39–41} In the Swedish cohort, the SPC risk of the nervous system was significantly increased (SIR 3.82), particularly in 46–65-year-olds and during the first 5 years of follow-up (16). The Danish study also observed an increased SPC risk, though only in females (SIR 1.33).¹⁷ Other studies, such as from

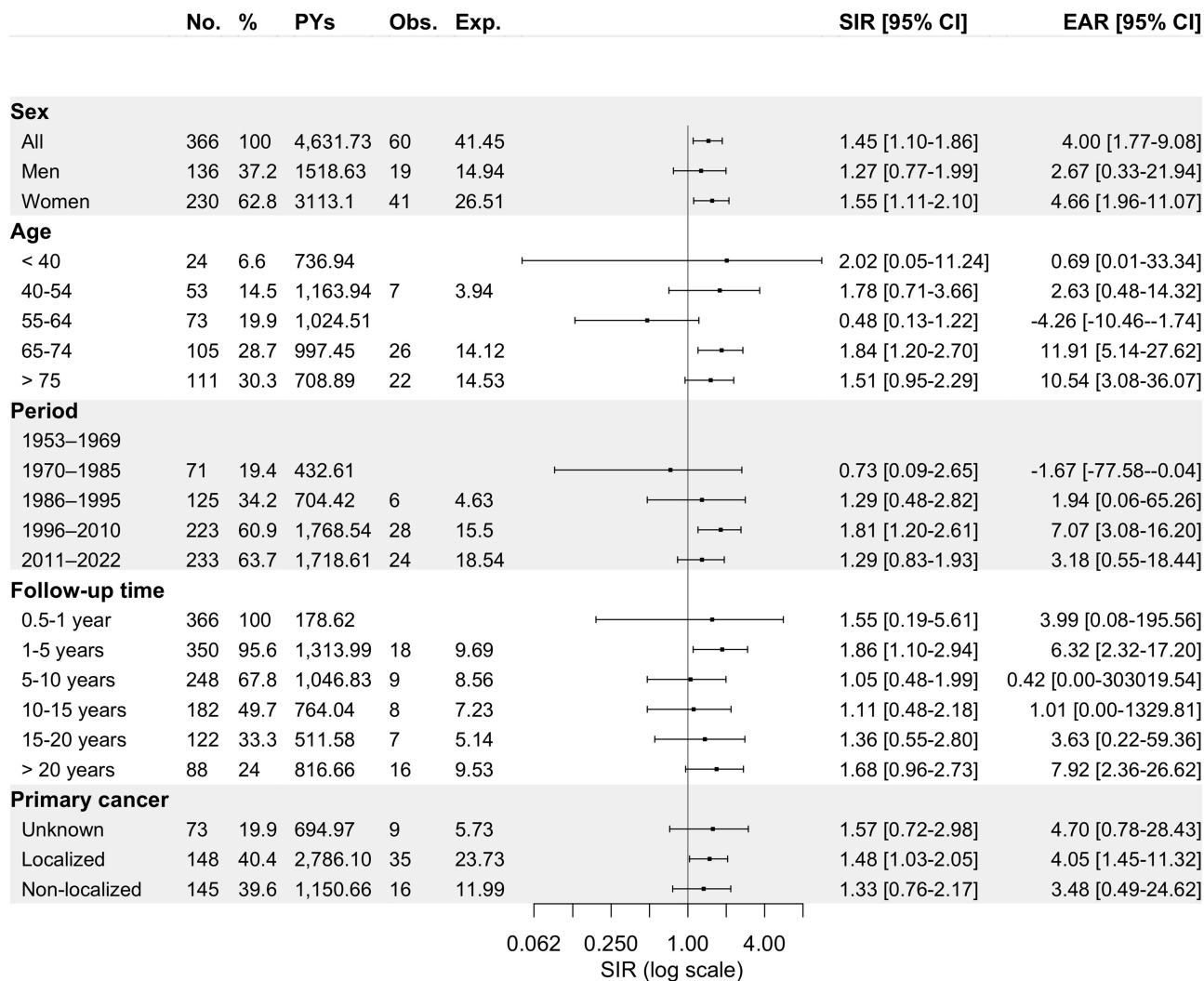


Figure 6 Standardized incidence ratios and excess absolute risk per 1,000 person-years for any metachronous second primary cancer among 1,974 medullary thyroid carcinoma patients diagnosed in Finland during 1953–2022 stratified by sex, age at diagnosis of primary tumor, follow-up period (number of patients alive), follow-up time, and primary disease stage.
Abbreviations: CI, confidence interval; Exp, expected; EAR, excess absolute risk; n.s., non-significant; No, number; Obs, observed; PYs, person-years; SIR, standardized incidence ratio.

Taiwan and the United States, have reported similar findings, though not specific to PTC.^{6,15,22,24} The earlier Finnish study found no significant differences with the control group.²⁵ Although the risk of SPC of the brain persisted even beyond 20 years and the fact that cases with immediate diagnosis within the first 6 months were excluded, these findings should be approached with caution acknowledging the risk of possible misdiagnosed metastases.

Lastly, we observed an increased risk of certain SPCs specifically among females with a primary diagnosis of FTC or MTC in 1953–1985. The reasons for such period-specific differences remain unclear and have not been previously explored, as most studies have not stratified their data by time periods. Brown et al reported that among PTC and FTC patients, identified from the SEER database (1973–2002), an excess risk of salivary gland malignancies was observed only in patients diagnosed in 1973–1988,⁶ suggesting possible treatment-related effects from earlier practices of more widespread irradiation, or statistical bias. In contrast, Kim et al observed that among all TC patients from the SEER database, the risk of SPC was highest in more recent years and especially among patients with an initial diagnosis after 1994.²² Hakala et al also found that Finnish patients diagnosed more recently, specifically after 1996, had an increased SPC risk.²⁵ Notably, they also analyzed RAI dosage across different time periods and observed an increasing trend over time, which would argue against treatment-related bias in our findings. Although not stratifying by diagnosis year,

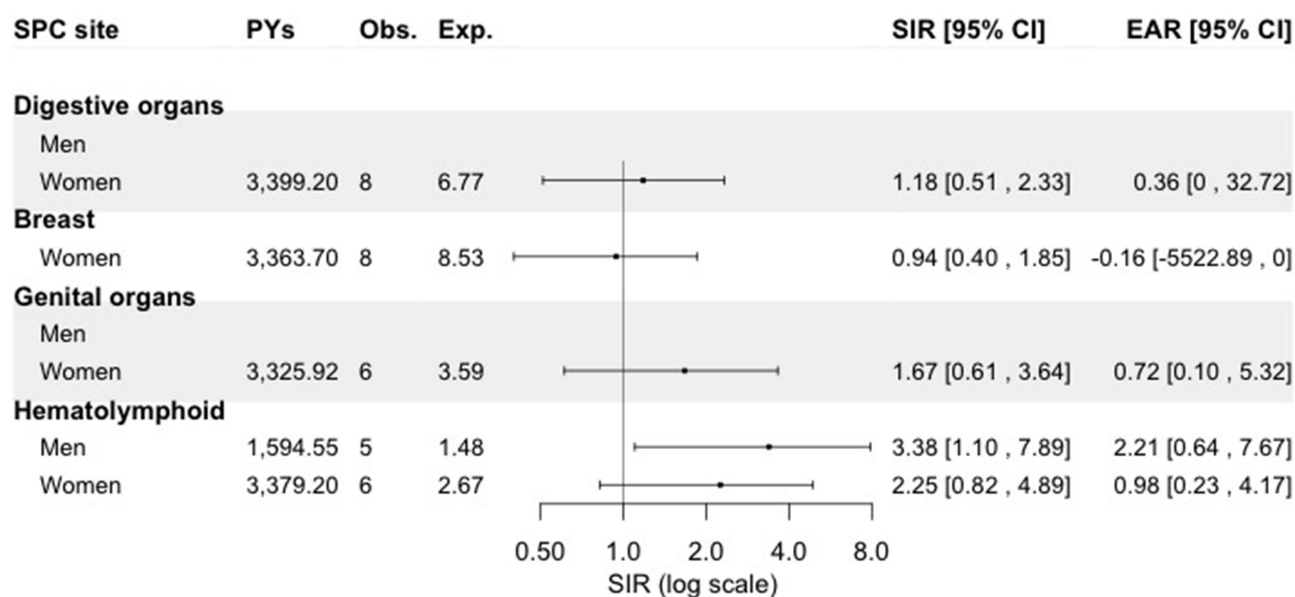


Figure 7 Standardized incidence ratios and excess absolute risk per 1,000 person-years for second primary cancer by site (if more than four cases recorded) among patients with medullary thyroid carcinoma in Finland during 1953–2021 stratified by sex.

Abbreviations: CI, confidence interval; Exp, expected; EAR, excess absolute risk; n.s., non-significant; No, number; Obs, observed; PYs, person-years; SIR, standardized incidence ratio.

Sandeep et al reported that for certain cancers—such as nonmelanoma skin, prostate, and kidney cancer—the risk was highest within the first year of TC diagnosis, whereas for others (gastrointestinal and breast cancer), the risk increased with longer follow-up.¹² Brown et al similarly observed the risk to be highest within the immediate five years following TC diagnosis—but including an elevated risk of breast cancer.⁶ These contrasting findings could be explained by surveillance bias and variations in follow-up modalities. Regardless, while these differences are intriguing, the underlying causes remain unclear, as changes in clinical practices, diagnostic means, and environmental factors would be expected to produce similar trends over time.

The relationship between prior RAI and the development of SPCs remains controversial as prior studies have reported varying and partly contradicting results.^{5,6,14–16,42} Though generally the risk is considered low, cumulative doses could increase its impact with longer follow-up periods.^{5,8,14} Some studies have reported an increased incidence of SPCs after RAI therapy, especially in organs subjected to accumulation of high RAI concentrations through excretion (namely the gastrointestinal tract, urinary organs and salivary glands). Pasqual et al reported an increased incidence of salivary gland and breast cancers, especially after 20 years of follow-up.⁷ Similarly, the risk for hematologic malignancies, specifically acute and chronic myeloid leukemia, was increased, and more pronouncedly in children. Despite high RAI uptake, no elevated risk of stomach or kidney cancer was observed. Similarly, Rubino et al reported an increased risk of solid tumors and leukemia associated with cumulative RAI doses (excess 4% risk per GBq).¹⁵ However, other studies have not observed such consistent associations.^{6,18} Lastly, Reinecke et al conducted a comprehensive review of existing evidence on SPCs in relation to RAI therapy. While the overall findings do suggest an increased SPC risk following RAI administration, the reviewed studies showed great heterogeneity, differences in cohort characteristics, and a substantial risk of bias, warranting further investigations.⁴³

Radioactive contamination from the Chernobyl accident in 1986 is a unique, independent risk factor for malignancies. Radiation exposure and consumption of contaminated foods in areas with greatest fallouts resulted in high thyroidal levels of radioiodine, particularly in children, and later also in adults.^{44–46} Several studies have further reported an increased incidence, earlier onset, and more advanced stage of TC and other malignancies in the exposed areas.^{4,9,10,47} Taha et al analyzed a cohort of over 30,000 PTC patients from the Belarussian Cancer Registry in 1990–2021 and reported that in 31 years of follow-up 9.2% developed an SPC (such as gastrointestinal (SIR 1.32), urinary (SIR 2.79), breast in women (1.72), various hematolymphoid malignancies (combined SIR 2.24), and brain cancer (SIR 1.41)).¹⁰

Finland was among the most heavily affected countries but no increased incidence of thyroid or other cancers has been observed.^{11,48,49} Lastly, our study did not find an increase in the risk of SPCs in FTC or MTC patients after 1986, and the elevated risk among PTC patients was already present prior to the Chernobyl disaster.

We recognize certain limitations to our study. The lack of information on etiological factors, such as tobacco and alcohol use, along with the absence of details on primary treatment protocols, such as RAI administration, prevents us from assessing their association with SPCs. Moreover, our study may be affected by potential site misclassification, a common challenge in clinical practice, and metastases from the primary tumor may have been mistakenly recorded as SPCs as 13% of them lacked histological verification. This type of diagnostic bias alone, however, is unlikely to account for the observed association between PTC and elevated SPC risk, as the increased risk persisted even after 20 years after the initial PTC diagnosis. Despite these limitations, considering the limited prior data from the Nordic countries, the size of our cohort, and the extensive follow-up, we consider our findings unique and valuable.

Conclusion

In conclusion, our nationwide registry-based study indicates an SPC risk of the breast, urinary organs, brain and hematolymphoid tissues in Finnish patients with PTC. The risk of second primary breast and brain cancers seems to persist beyond 20 years post primary diagnosis of PTC, while the SPC risk of the urinary organs, brain, and hematolymphoid tissues seems to be specific to FTC and MTC female patients diagnosed between 1953–1985. In light of these findings, the rising number of TC survivors and their risk of subsequent SPCs have important implications both for the individual patient and for the health care system as a whole. Active surveillance and careful consideration of postoperative adjuvant treatment are warranted to prevent carcinogenesis in secondary organs. Future advances in genetic diagnostics and targeted treatments may enable more tailored strategies for screening and managing SPCs in TC survivors.

Data Sharing Statement

Data sharing is not available due to privacy/ethical restrictions.

Ethics Approval

The current study was based on data from existing registries and did not include any human intervention. Study participants were not contacted during the execution of the study. All parts of the study involving patient data were in accordance with institutional and/or national research committee ethical standards and with the 1964 Helsinki declaration or comparable ethical standards. Approval from any institutional review board or ethics committee was not required for this research according to the Finnish Legislation, and specifically on the Act on the Secondary use of health and social data.

Author Contributions

All authors made a contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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