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Meta-Analyses of Epidemiologic Associations between Cutaneous Melanoma and Thyroid Cancer

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Abstract

Background: The incidences of cutaneous melanoma (CM) and thyroid cancer (TC) continue to increase in the United States, and recent studies have demonstrated associations between these two malignancies.

Objective: We explore these associations between CM and TC by reviewing, and combining in meta-analyses, population-based studies that assessed risk for TC in individuals with a history of CM, and reciprocally, risk for CM in individuals with a history of TC.

Methods: A literature search was performed using the PubMed databases with the terms "melanoma thyroid cancer." Relevant English-language articles were included. Meta-analyses were conducted for both risk of TC among CM survivors and CM among TC survivors.

Results: Population-based studies demonstrate an increased risk for TC among CM survivors, and likewise, an increased risk of CM among TC survivors. Our meta-analysis suggests a statistically significant standardized incidence ratio (SIR) for TC after CM of 1.88 (95% confidence interval (CI): 1.62-2.15), which was higher among men (2.60, 95% CI=1.65-3.55) compared to women (1.59, 95% CI=1.10-2.09), but this was not statistically significant. Likewise, a significant SIR for CM after TC of 1.49 (95% CI=1.20-1.79) was demonstrated in the meta-analysis; however, the sex-specific SIRs for CM after TC were not statistically significantly different, which may be due to small sample sizes.

Conclusions: The observed bidirectional association between CM and TC raises the possibility of shared risk factors, which should be further explored. Additionally, further studies should be performed to assess the benefit of screening TC patients for melanoma and CM patients for TC.

Keywords: Cutaneous melanoma; Thyroid carcinoma; Meta-analysis; Melanoma

Abbreviation

CM: Cutaneous Melanoma; TC: Thyroid Cancer; PTC: Papillary Thyroid Carcinoma; U.S.: United States; OR: Odds Ratio; RR: Relative Risk; SIR: Standardized Incidence Ratio; CI: Confidence Interval; SEER: Surveillance, Epidemiology, and End Results; MIS: Melanoma In-Situ; FTC: Follicular Thyroid Carcinoma; MTC: Medullary Thyroid Carcinoma; UVR: Ultraviolet Radiation; RAI: Radioactive Iodine; MM: Malignant Melanoma; N: Number; M: Males; F: Females; Mos: Months.

Introduction

The incidences of both cutaneous melanoma (CM) and thyroid cancer (TC) have increased in recent years. TC, with papillary thyroid carcinoma (PTC) the most common subtype, affects women at almost three times the rate of men and is one of the most common cancers in young women under 45 years old [1], and there are estimated to be almost 20,000 new cases in 2016 [2]. CM, one of the most fatal forms of skin cancer, is the fifth and seventh most commonly diagnosed cancer affecting U.S. men and women, respectively, with 76,380 estimated new cases and 10,130 deaths in 2016 [2]. Studies have demonstrated that individuals with CM have an increased risk of subsequent TC, and that those with TC have an increased risk of subsequent CM. Although there are potential genetic links between these two cancer types, CM and TC do not have obvious shared risk factors. Herein, we comprehensively review these studies and perform meta-analyses to further explore the connections between TC and CM.

Methods

We conducted a literature review using the PubMed database and the search terms "melanoma thyroid cancer" for English-language articles. We reviewed the titles and abstracts identified in the literature search and also reviewed references from bibliographies of pertinent articles. We restricted our search to population-based studies reporting risk estimates; family studies and individual case reports were excluded.

Meta-analyses

Results from studies reporting the same measure, relative risk (RR) and standardized incidence ratio (SIR), were combined using standard methods. In the case where multiple reports utilized the same sample population (specifically SEER), only the results from the study with the largest sample size was included. Only studies reporting the ratios, standard deviation/errors or 95% confidence interval (CI), and sample size were included in the meta-analyses calculations.

Result

We identified five population-based studies to date that evaluated the risk of subsequent TC in individuals with a primary CM diagnosis, seven that evaluated the risk of subsequent CM in individuals with a primary TC diagnosis, and five studies that evaluated both the risk of subsequent TC after primary CM and the risk of subsequent CM after primary TC. There were two population-based studies that reported incidence rather than risk-one reported on 8 individuals with TC after primary CM, and one reported on 7 individuals with CM after primary TC; these were excluded [3,4]. Characteristics of the included population-based studies are summarized in Table 1.

Study Location/Database	Number of Cases1	Description of Study Population	Reference
TC after primary CM			
Denmark 1943-1989	CM Total: 12,460 M: 5,061 F: 7,399	Race: not specified Invasive CM only Mean age at CM diagnosis: not specified Time from CM diagnosis: not specified	Swerdlow et al.
U.S. SEER-13 1973-2003	CM Total: 151,996 M: 82,143 F: 69,853	Race: not specified Invasive CM and MIS Mean age at CM diagnosis: 54 years Time from CM diagnosis: 2 months	Spanogle et al.
U.S. SEER-9 1973-2006	CM Total: 89,515 M: 47,804 F: 41,711	Race: Whites Invasive CM only Mean age at CM diagnosis: 54 years Time from CM diagnosis: 2 months	Bradford et al.
U.S. SEER-13 1992-2006	CM Total: 116,922 M: 63,728 F: 53,194	Race: all Invasive CM (65%); MIS (35%) Mean age at CM diagnosis: not specified Time from CM diagnosis: 0 months	Balamurugan et al.
Norway 1955-2008	CM Total: 28,069 M: 12,933 F: 15,136	Race: not specified Invasive CM only Mean age at CM diagnosis: 55.6 years Time from CM diagnosis: not specified	Robsahm et al.
CM after primary TC			
Norway 1955-1985	TC Total: 3,626 M: 906 F: 2,720	Race: not specified TC type: not specified Mean age at TC diagnosis: not specified Time from TC diagnosis: 2 months	Akslen et al.
Germany2 1960-1988	TC Total: 298 M: 90 F: 208	Race: not specified TC type: PTC and FTC Mean age at TC diagnosis: not specified Time from TC diagnosis: not specified	Glanzmann et al.
Sweden, 1951-1977 Italy, 1958-1995 France, 1934-1995	TC Sweden: 1,894 Italy: 1,894	Race: not specified TC type: PTC and FTC Mean age at TC diagnosis: 44 years	Rubino et al.

	France: 3,053	Time from TC diagnosis: 24 months	
France2 1960-1998	TC Total: 875 M: 146 F: 729	Race: not specified TC type: PTC (86%); FTC (14%) Mean age at TC diagnosis: 46 years Time from TC diagnosis: 12 months	Berthe et al.
California3 1988-1999	TC Total: 13,937 M: 0 F: 13,937	Race: all TC type: PTC (100%); FTC (0%) Mean age at CM diagnosis: not specified Time from TC diagnosis: 1 month	Canchola et al.
U.S. SEER-172 1973-2002	TC Total: 30,278 M: 7,219 F: 23,059	Race: not specified TC type: PTC (88%); FTC (12%) Mean age at TC diagnosis: not specified Time from TC diagnosis: 2 months	Brown et al.
U.S. SEER-9 1988-2007	TC Total: not specified	Race: All TC type: not specified Mean age at TC diagnosis: not specified Time from TC diagnosis: 2 months	Yang et al.,
TC after primary CM and CM after primary TC			
Connecticut2 1935-1982	CM Total: 4,693 M: 2,336 F: 2,357 TC Total: 2,284 M: 603 F: 1,681	Race: not specified Invasive CM only TC type: not specified Mean age at CM diagnosis: 52 years Mean age at TC diagnosis: 46 years Time from primary diagnosis: 2 months	Tucker et al.
U.S. SEER-9 1973-2000	CM Total: not specified TC Total: 29,456 M: 7,406 F: 22,050	Race: All Invasive CM only TC type: PTC (78%); FTC (15%); MTC (7%) Mean age at CM diagnosis: not specified Mean age at TC diagnosis: 43 years Time from primary diagnosis: 2 months	Ronckers et al.
U.S. SEER-9 1973-2000	CM Total: 73,274 TC Total: 27,138	Race: Whites Invasive CM only TC type: not specified Mean age at CM diagnosis: not specified Mean age at TC diagnosis: not specified Time from primary diagnosis: 1 month	Goggins et al.
Europe, Canada, Australia, Singapore 1953-19984	CM Total: not specified TC Total: 39,002 M: 9,972 F: 29,030	Race: not specified CM type: not specified TC type: PTC (39.8%), FTC (13.5%), MTC (3%), other/unknown (43.7%) Mean age at CM diagnosis: not specified Mean age at TC diagnosis: not specified Time from primary diagnosis: not specified	Sandeep et al.
Utah 1966-2011	CM Total: 14,569 M: 8,086 F: 6,483 PTC	Race: not specified CM type: not specified PTC only Mean age at CM diagnosis: not specified	Oakley et al

	Total: 4,460 M: 984 F: 3,476	Mean age at TC diagnosis: not specified Time from primary diagnosis: not specified	

TC: Thyroid Cancer; CM: Cutaneous Melanoma; M: Males; F: Females; MIS: Melanoma In-Situ; PTC: Papillary Thyroid carcinoma, FTC: Follicular Thyroid Carcinoma, MTC: Medullary Thyroid Carcinoma

1The number of cases refers to the total number of cases evaluated for subsequent cancer in each study, not necessarily the number of cases with both CM and TC.

2These studies do not specify invasive or MIS.

3Although the total cases include all races and both genders, the subsequent analysis was limited to 10,932 White women with PTC.

4This study included 13 population-based cancer registries; Australia, New South Wales (1972–1997); Canada, British Columbia (1970–1998); Canada, Manitoba (1970–1998); Canada, Saskatchewan (1967–1998); Denmark (1943–1997); Finland (1953–1998); Iceland (1955–2000); Norway (1953–1999); Singapore (1968–1992); Slovenia (1961–1998); Spain, Zaragoza (1978–1998); Sweden (1961–1998); UK, Scotland (1975–1996).

Table 1: Characteristics of identified population-based studies, including those examining risk of TC after primary CM, risk of CM after primary TC, and studies that looked at both populations.

Thyroid Cancer after Cutaneous Melanoma

There were ten population-based studies that assessed the risk ratio of TC in individuals with a history of primary CM (Table 1). The majority were U.S. studies that utilized the cancer registry records from the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute in North America, including a study that analyzed the Connecticut registry, which also contributes to the SEER database [5-13]. One population-based study was from Utah [14,15]. The non-U.S. studies included one from Denmark, one from Norway, and another that included thirteen population-based cancer registries from Europe, Canada, Australia, and Singapore [8,9,13]. Of the ten studies that analysed TC subsequent to CM diagnosis, six included subjects with primary invasive melanoma only, two included both invasive melanoma and melanoma in-situ (MIS), and the remainder did not specify CM type [5-14]. Most subjects were White, with a mean age at CM diagnosis ranging from 52 years to 54 years. Cases with a CM diagnosis and TC diagnosis within the same month or two months were excluded in most studies [6-9].

The risk ratios of TC in individuals with a history of primary CM from ten population-based studies are presented in Table 2a. Among the ten studies, two reported RR, seven reported SIR, and one reported odds ratio (OR). A statistically significantly increased risk of TC after CM diagnosis with a risk ratio ranging from 1.75 to 3.6 was reported in all studies except for one in Denmark [5-8,10-14]. Four studies stratified risk by gender. Three found no statistically significant difference in overall risk in men versus women [5,7,9]. Another found a statistically significantly higher SIR of 2.78 (1.61-4.80) in men in contrast to a non-statistically significant SIR of 1.27 (0.81-1.99) in women [13]. Similarly, in studies that stratified risk by age of CM diagnosis, no differences were found [6,7,9]. In studies that stratified risk of TC by time since primary CM diagnosis, mixed results were observed: three studies reported significantly increased risk of TC within five years following CM diagnosis, one study reported increased TC risk 5 to 9 years after CM diagnosis, and three studies reported an increased risk throughout [5-8,10-12]. One study stratified risk of TC by gender and CM invasiveness [12]. Among invasive melanoma survivors, both men and women had an increased risk of subsequent TC; however, among melanoma in-situ (MIS) survivors, only women had a significantly increased risk for the development of TC [12]. No significant association was found between radiation therapy for CM and subsequent risk of TC [6].

Reference		N	Risk Ratio Measure	Overall Risk Ratio (CI)	Overall Risk Ratio (CI) of TC stratified by time since CM diagnosis			
					<10 years			>10 years
Tucker et al.	Total M F	5 2 3	RR	3.6* 4.8 3.1	<1 year 0.0 0.0 0.0	1-4 years 1.9 6.1 0.0	5-9 years 8.6* 9.8 8.1	>10 years 3.0 0.0 4.1
Ronckers et al.	Total	93	RR	2.01 (1.62-2.47)*	<10 years 2.22*			>10 years 1.53
Goggins et al.	Total M F	101 39 62	SIR	2.17 (1.77-2.63)* 2.49 (1.54-2.57) 2.00 (1.54-2.57)	≤3 years 2.54 (1.78-3.51)*	3-10 years 2.28 (1.67-3.06)*		>10 years 1.65 (1.02-2.53)*
Sandeep et al.	Total	118	SIR	1.84 (1.53-2.21)*	<1 year 1.80 (0.93-3.14)	1-9 years 1.64 (1.26-2.11)*		>10 years 2.23 (1.63-2.99)*
Swerdlow et al.	Total M	6 0	SIR	1.72 (0.63-3.75) 0 .0 (0.0-5.34)				

	F	6		2.15 (0.79-4.68)					
Bradford et al.	Total	170	SIR	1.75 (1.50-2.04)*	2 mos-1 year 5.19*	1-5 years 1.73*	5-10 years 1.39	10-20 years 1.48*	>20 years 0.82
Spanogle et al.	Total	217	SIR	1.90 (1.65-2.17)*	2 mos-1 year 4.06 (2.96-5.43)*	1-5 years 2.20 (1.77-2.71)*	5-10 years 1.37 (0.99-1.85)	>10 years 1.40 (1.00-1.90)	
						Melanoma in situ			
Balamurugan et al.	M F	15 32		1.27 1.58*	2 mos-1 year -- --	1-5 years 1.07 1.76*	5-10 years 1.71 1.00	>10 years 0.0 --	
			SIR			Invasive CM			
	M F	54 67		2.67* 1.77*	2 mos-1 year 7.09* 4.94*	1-5 years 2.19* 1.25	5-10 years 1.12 1.16	>10 years 1.13 --	
Robsahm et al.	M F	13 19	SIR	2.78 (1.61-4.80)* 1.27 (0.81-1.99)*					
Meta-Analysis	Total M F	44252 186	SIR	1.88 (1.62-2.15)* 2.60 (1.65-3.55)* 1.59 (1.10-2.09)*					
Oakley et al.	Total	78	OR	2.3 (1.8-3.0)*					

Data were suppressed if fewer than 6 cases were observed.

TC: Thyroid Cancer; CM: Cutaneous Melanoma; N: Number; M: Males; F: Females; RR: Relative Risk; OR: Odds Ratio; SIR: Standardized Incidence Ratio; CI: 95% Confidence Interval; Mos: Months; *RR/SIR/OR differs significantly from 1 ($p < 0.05$); †These studies also analyzed RR/SIR/OR of CM subsequent to TC and are included in Table 2b.

Table 2a: Risk of thyroid cancer (TC) after cutaneous melanoma (CM).

A meta-analysis of the seven population-based studies reporting SIR revealed, among a combined 612 individuals, a statistically significant SIR for TC after CM of 1.88 (1.62-2.15), the magnitude of which was higher in men compared to women (Table 2a); however, as can be seen by the overlapping confidence intervals, this difference was not statistically significant. A meta-analysis of the two population-based studies reporting RR could not be conducted since only one study provided the necessary statistics.

Cutaneous Melanoma after Thyroid Cancer

There were twelve population-based studies that evaluated the risk ratio of CM in individuals with a history of primary TC diagnosis (Table 1). The majority were U.S.-based studies that utilized the SEER database. The non-U.S. studies included cancer registries from Norway, Germany, France, Swedish, Italy and France; in addition, one study analysed thirteen population-based cancer registries from Europe, Canada, Australia, and Singapore [8,16-19]. Seven studies specified the type of TC; one included PTC only, four included PTC and follicular thyroid carcinoma (FTC), and two included PTC, FTC, and medullary thyroid carcinoma (MTC) [6,8,16,18-21]. The mean age of TC diagnosis ranged from 43 years to 46 years. Exclusion of individuals based on time from primary TC to subsequent CM diagnosis varied with the majority of studies excluding those diagnosed within two months of primary TC, and the remainder excluding those diagnosed within one month, one year, or two years [6,15,16,19-21].

Of the population-based studies that looked at the risk of CM in primary TC survivors, four reported RR, seven reported SIR, and one reported OR (Table 2b). Five studies reported a significantly increased risk ratio ranging from 1.24 to 2.5 [6,7,14,16,20]. In two European studies that stratified risk by gender, a significant SIR in men with TC was found in a Norway study, in contrast to a study from France that found no significant risk in men nor women [17,19]. Risk of CM stratified by time since primary TC diagnosis yielded mixed results with two studies demonstrating an increased risk in the 2-11 months following TC diagnosis, but one study showing an increased risk 10 years after TC diagnosis [15,20,21]. The results were mixed in the studies that stratified risk by age at TC diagnosis: three U.S. SEER studies found no overall difference in risk by age; one study from California found an increased risk in those under 45 years at TC diagnosis; and one U.S. SEER study found an increased risk in those diagnosed over age 45 years [6,7,15,20,21]. Five studies analyzed the

effects of I-131 or radiation therapy for TC and found no role in the development of CM [6,16,18,20,21]. One study stratified risk by calendar year and found similar SIRs for both time frames [7].

Reference		N	Risk Ratio Measure	Overall Risk Ratio (CI)	Overall Risk Ratio (CI) of TC stratified by time since CM diagnosis			
					<10 years			>10 years
Tucker et al.	Total M F	3 2 1	RR	1.5 3.6 0.7	<1 year 7.0 0.0 10.3	1-4 years 1.8 5.8 0.0	5-9 years 0.0 0.0 0.0	>10 years 1.3 5.2 0.0
Glanzmann et al.	Total	1	RR	1.8 (0.04-9.8)				
Ronckers et al.	Total	78	RR	1.24 (0.98-1.55)				
Yang et al.			RR		2 mos-1 year 2.24 (1.07-4.12)*	1-5 years 1.41 (0.89-2.11)	5-9 years 1.42 (0.83-2.28)	>10 years 0.84 (0.31-1.82)
Meta-Analysis	Total	79	RR	1.49 (0.88-2.11)				
Akslen et al.	Total M F	8 5 3	SIR	1.32 (0.57-2.61) 4.17 (1.3-9.72)* 0.62 (0.13-1.81)				
Rubino et al.	Total	25	SIR	2.5 (1.6-3.7)*				
Berthe et al.	M F	1 1	SIR	7.14 (0.8-40) 1.30 (0.3-7.23)				
Canchola et al.	Total	21	SIR	2.1 (1.3-3.2)*	2 mos-1 year 3.9 (1.4-8.4)*	1-3 years 2.3 (0.9-4.7)	3-5 years 2.1 (0.7-5.0)	≥5 years 0.9 (0.2-2.7)
Sandeep et al.	Total	81	SIR	1.09 (0.86-1.35)	<1 year 1.86 (0.93-3.33)	1-9 years 1.07 (0.76-1.45)		>10 years 0.96 (0.65-1.37)
Goggins et al.	Total	79	SIR	1.25 (0.99-1.56)	≤3 years 1.63 (1.05–2.43)*	3-10 years 1.20 (0.81–1.71)		>10 years 1.06 (0.69–1.56)
Brown et al.	Total M F	89 57 32	SIR	1.17 (0.94-1.44) 1.13 (0.86-1.47) 1.24 (0.85-1.75)				
Meta-Analysis	Total M F	224 89 35	SIR	1.49 (1.20-1.79)* 1.44 (0.90-1.98) 0.84 (0.41-1.26)				
Oakley et al.	Total	78	OR	1.8 (1.4-2.3)*				

TC: Thyroid Cancer; CM: Cutaneous Melanoma; N: Number; M: Males; F: Females; RR: Relative Risk; OR: Odds Ratio; SIR: Standardized Incidence Ratio; CI: 95% Confidence Interval; Mos: Months; *RR/SIR/OR differs significantly from 1 ($p < 0.05$); †These studies also analyzed RR/SIR/OR of TC subsequent to CM and are included in Table IIa; ‡This study also analyzed effect of age at TC diagnosis in development of subsequent CM; §This study reported RR for patients over 45 years at age of primary TC diagnosis.

Table 2b: Risk of cutaneous melanoma (CM) after thyroid cancer (TC).

A meta-analysis of the four population-based studies reporting RR for CM after TC revealed no statistically significant association (Table 2b). In the meta-analysis of the seven population-based studies reporting SIR, a statistically significant SIR for CM after TC of 1.49 (1.20-1.79) was observed (Table 2b). When the meta-analysis was performed on results stratified by sex, the SIRs were not significant.

Discussion

We identified several population-based studies from the U.S. and Europe that analyzed cancer registries for epidemiologic connections between CM and TC. Most of the studies utilized data from one cancer registry, the SEER database. A majority demonstrated an increased risk of TC among CM survivors, and reciprocally, an increased risk of CM among TC survivors. Only one population-based study consisting of six observed TC cases from Denmark found a non-significant increased risk of TC after CM [17]. The meta-analysis of results from studies reporting SIR revealed a statistically significant SIR for TC after CM. Likewise, a significant SIR for CM after TC was demonstrated in the meta-analysis; however, sex-specific SIRs for CM after TC were not statistically significant, which may be due to small sample sizes given that only a subset of studies provided data stratified by sex.

Surgery is the foremost treatment modality for primary CM. We found that a majority of CM cases were treated surgically, with 3% to 38% treated with adjuvant radiation [5,6,10]. Similarly, the definitive therapy for TC is complete or partial surgical thyroidectomy with or without adjuvant radioactive iodine (RAI) therapy, as shown in the majority of individuals identified in the population-based studies [5,6,16,18-22]. It is interesting to note that in the small number of CM cases treated with adjuvant radiation therapy, the treatment effects of radiation did not seem to play a role in the development of TC. Similarly, RAI therapy for TC did not appear to play a role in the development of CM. This is consistent with results of a pooled meta-analysis demonstrating no increased risk of melanoma in TC patients treated with RAI in contrast to the association demonstrated for leukemia following high exposure of RAI for TC [23]. Moreover, a study of seven patients with CM treated with thyroidectomizing doses of radioactive iodine or thyroidectomy showed no effect on tumor growth [24].

Most studies reviewed here did not assess outcomes of individuals with both cancer types. A study not included here (published in abstract form only) utilized the SEER database from 1973 to 2004 to analyze the mortality risk for individuals diagnosed with CM only, PTC only, PTC after CM diagnosis and reciprocally, CM after PTC diagnosis [25]. Patients with PTC alone had the best overall survival [25]. This is consistent with reported 10-year survival rates of over 99% for women diagnosed with PTC before the age of 45 years [20]. Those individuals with CM alone had the worst mortality rate; interestingly, those who had both CM and PTC were more likely to survive than those with CM alone [25]. The reasons for this increased survival are unknown.

In any study of a primary malignancy with subsequent cancer development, the possibility of detection or surveillance bias exists, especially if the second cancer was diagnosed concurrently or soon after the diagnosis of the first cancer. In our analysis of the literature, population-based studies that stratified SIR by time yielded mixed and inconclusive results, with some reports of increased risk in the first year and some reports of an increased risk up to ten years following the primary cancer diagnosis. In the six case reports of incidental TC diagnosed among CM patients that were excluded from our analysis, all cases of the subsequent cancer were detected during surveillance for the primary cancer: three cases were identified by FDG-PET for metastatic melanoma evaluation; one case was identified when routine pre-op laboratory exam for melanoma excision revealed abnormal thyroid levels; one case was diagnosed when routine dermatologic exam was significant for enlarged thyroid gland 8 months after excision of CM; and another case was diagnosed when radical neck dissection for CM metastasis to sentinel lymph node revealed metastasis of PTC in four out of thirty-eight lymph nodes [26-30]. Therefore, increased medical surveillance still could explain part of the association between TC and CM.

In conclusion, we report a number of population-based studies that reported an increased risk of TC among patients with a history of CM, and reciprocally, CM among patients with a history of TC. The bidirectional association between CM and TC raises the possibility of shared risk factors between these two malignancies. However, risk factors that are associated with CM, such as ultraviolet radiation (UVR) have not been demonstrated in TC [15-22]. Similarly, risk factors that are known to be associated with TC, such as ionizing radiation, are not known to predispose individuals to CM [16]. Similar genetic pathways between the tumors have been recently implicated. Germline mutations in PTEN, a tumor suppressor gene located on 10q23.3, have been associated with both CM and TC development [31-33]. Likewise, a high prevalence of somatic mutations in the oncogene BRAF V600E have been described in melanoma tumors as well as a substantial portion of papillary thyroid cancers, but not other types of benign or malignant thyroid cancers [34-39]. In two recent studies examining the link between melanoma and thyroid cancer in families (excluded from our analysis), one observed a borderline significantly increased risk for PTC in men and women with a family history of CM, and determined a significant, but not overwhelming risk of CM in those with PTC and, conversely, of PTC in those with CM; this significant association was not observed in spouses, suggesting a familial connection between both cancers [14,40]. There may be underlying genetic or immune risk factors that increase susceptibility to multiple cancers, regardless of the type. Whether shared genetic pathways or as yet unknown common environmental exposures explain the observed associations between melanoma and thyroid cancer, future studies should explore these connections so that we may ultimately improve our ability to counsel patients regarding their risk for subsequent malignancies.

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