Cancer Causes and Control **14**: 367–375, 2003.

Second primary breast and thyroid cancers (Israel)

Siegal Sadetzki[1,*], Ronit Calderon-Margalit[1], Chava Peretz[2], Ilya Novikov[2], Micha Barchana[3] & Moshe Z. Papa[4]
[1]*Cancer Epidemiology Unit, Gertner Institute, Chaim Sheba Medical Center, Tel Hashomer, Israel;* [2]*Biostatistics Unit, Gertner Institute, Chaim Sheba Medical Center, Tel Hashomer, Israel;* [3]*Israel Cancer Registry, Ministry of Health, Jerusalem, Israel;* [4]*Department of Surgical Oncology ('C'), Chaim Sheba Medical Center, Tel Hashomer, Israel*

Received 10 September 2002; accepted in revised form 20 January 2003

Key words: malignant breast neoplasms, second primary malignant neoplasms, thyroid neoplasms.

Abstract

Objective: To evaluate the risk for developing second primary thyroid cancer (TC) following breast cancer (BC) and second primary BC following TC on a nationwide basis.
Methods: All BC and TC Jewish females diagnosed in Israel during 1960–1998 were identified through the Israel Cancer Registry. The expected second primaries were calculated using cancer incidence rates stratified by age, country of birth and period of diagnosis among the Jewish population in Israel. Standardized incidence ratios (SIRs) were estimated using Poisson regression.
Results: A total of 49,207 breast and 4911 thyroid neoplasms were identified. After the exclusion of concomitant disease (diagnosed within 1 year), 59 and 70 second primaries TC and BC yielded SIRs of 1.34 (95% CI: 1.03, 1.72) and 1.07 (95% CI: 0.84, 1.34), respectively. Younger age and earlier calendar year of first primary diagnosis and shorter follow-up period were associated with increased risk for developing second primary neoplasm.
Conclusions: Considering the long latency required for carcinogenesis, excess risk of second primary diagnoses soon after the first cancer, argues against the hypothesis of first primary treatment as an initiator for the second cancer. A detection bias of meticulously followed cancer patients, early exposure to common risk factors or genetic susceptibility of certain subpopulations for both malignancies seem plausible.

Introduction

An association between breast cancer (BC) and thyroid diseases including thyroid carcinoma has been suggested by several investigators, but no definite conclusions were drawn [1–4]. The relatively high survival rates of thyroid cancer (TC) and even that of BC (5 year survival rates of 95 and 85%, respectively) [5] allow sufficient time for developing cancer at another site.

Four possible hypotheses may explain the higher than expected incidence of one of these neoplasms following the other:

(1) Common risk factors may initiate both tumors.
(2) Higher genetic susceptibility of specific subpopulations is responsible for the appearance of both tumors.
(3) Radiotherapy given as a treatment for BC may play a role in the causation of TC; in such a case, only higher incidence of TC following BC is expected.
(4) The higher incidence may be a consequence of a detection-bias; *i.e.*, the first primary diagnosis is preceded by a more careful follow-up. This will yield an elevated incidence of the second primary mainly in a short time following the first diagnosis.

The objective of this study was to explore the possible association between breast and thyroid neoplasms on a nationwide basis. Specifically, we aimed to estimate the standardized incidence ratio (SIR) for developing a second primary BC following TC and for developing second primary TC following BC, compared to the

* Address correspondence to: S. Sadetzki, MD, MPH, Cancer Epidemiology Unit, Gertner Institute for Epidemiology and Health Policy Research, Chaim Sheba Medical Center, Tel Hashomer 52621, Israel. Ph.: +972-3-5303262; Fax: +972-3-5348360; E-mail: siegals@gertner.health.gov.il

Jewish population in Israel. In addition, we tested the influence of age, origin, calendar year at first primary, and time since first diagnosis on the occurrence of a second primary cancer.

Materials and methods

The study population of this nationwide historical prospective study included all BC and TC Jewish female patients diagnosed in Israel during the period of 1960–1998. The target population was identified through the national Israel Cancer Registry that was established in 1960 and is notified by law of all malignancies diagnosed in the country. Completeness of this registry for solid neoplasms was checked and found to be about 95%. Included were all diagnoses of TC and BC as coded in the ICD-9 (193.9 and 174.0–174.9, respectively). The registry includes demographic data, date of diagnosis, site, and vital status. About 2.5% of the BC cohort and 3% of the TC cohort were excluded from the analysis due to some of the above information being missing.

Statistical analysis

Distributions of second primaries were compared to that of the total group of first primary of the respective site using *t*-tests for age and time-related variables.

An in-house program was written to calculate person years for follow-up time. The beginning of follow-up was considered as the date of first primary cancer diagnosis and the end of follow-up was 31.12.1998 or date of second primary diagnosis or death, whichever occurred first. Patients that had more than one diagnosis of BC or TC were included only once, considering the beginning of follow-up as the date of the first diagnosis (1423 BC patients and 35 TC patients).

We defined second primary as cancer diagnoses made at least one year after the first primary. Diagnoses made within one year from date of first primary were considered as concomitant diseases and were included only in the univariate analysis of the effect of follow-up period.

The observed counts of TC and BC were stratified according to age groups at diagnosis (five-year intervals starting from age 25), origin of birth (three groups: Asia–Africa, Europe–America and Israel), period of diagnosis (10-year interval categories since 1960, except for the last one of 1990–1998), and time of follow-up since first primary diagnosis (<1, 1–4, 5–9, 10–14, and 15+ years).

The expected second primary BC and TC cases were calculated by multiplying accumulated person years by cancer incidence rates for the respective sites, in the total female Israeli Jewish population, stratified as the observed counts. These specific incidence rates were derived from the National Cancer Registry. We used the actual observed incidence rates for 1960–1992. Data for the period of 1993–1998 was not available at the time of this analysis. Since the average annual incidence rates for 1993–1997 increased only by 1.9% compared to 1990–1992, extrapolation was used to calculate the rates for the latter period.

The ratio of the observed to expected values yielded SIRs for the second primary cancer. Assuming that the observed counts follow a Poisson distribution, further analyses were based on Poisson regression models [6] with adjustment for the expected number of cases (an offset parameter).

To examine how the SIR varies with the covariates, origin, age at diagnosis, calendar year of diagnosis and time of follow-up, each variable was included separately in a univariate regression model and all of them together in a multivariate model. After correcting for under-dispersion, likelihood-ratio 95% CI for the SIRs were estimated.

Relative risks (RRs) of second primary cancers in each covariate category were calculated as the ratio between SIRs of each specific category and a reference category, this being the one with the minimal SIR. RRs of combination of categories of different covariates were estimated through the coefficients of the multivariate model. SIRs at each combination of covariate categories were estimated by the multiplication of the relevant RRs, derived from the model, with the SIR of the reference categories. Likelihood-ratio 95% CI for the RRs were calculated.

Data analysis was performed using Proc GENMOD in SAS software for Poisson modeling [7].

Results

Study characteristics

A total of 49,207 BC and 4911 TC cases were identified during the study period. Seventy-two first primary BC patients developed subsequent TC and 74 first primary TC patients eventually developed BC. Of those, concomitant disease was defined for 13 BC and 4 TC patients who developed thyroid and BC respectively within one year from their first diagnosis. Therefore our final group defined as second primaries included 59 cases of TC and 70 cases of BC.

Mean age at BC diagnosis was significantly younger for patients who developed second primary TC compared to the total BC cohort (age at BC diagnosis: 51.2

versus 58.4, respectively; $p < 0.001$). No differences in age at TC diagnosis were observed between the total TC cohort and those who subsequently developed BC.

The mean follow up periods for the study groups were: 7.3 (SD 7.2) (range 0–39), 7.1 (SD 6.0) (range 1–26), 9.4 (SD 8.9) (range 0–39) and 11.2 (SD 8.2) (range 1–31) years for the total BC cohort, second primary TC, total TC cohort and second primary BC, respectively.

About 20% of the BC patients were born in Asia–Africa, 20% in Israel and 60% in Europe–America with no significant differences between the total BC cohort and the BC to TC group. Significantly, more European–American and less Israeli born women were observed among the second primary TC group compared with the TC cohort (41.3 *versus* 55.7% European–American born and 32.3 *versus* 15.7% Israeli born, respectively).

Second primary TC following BC

SIR of 1.34 (95% CI: 1.03, 1.72) was found for second primary TC following BC (59 observed *versus* 43.91 expected) (Table 1).

This elevated risk was noted only among patients who were younger than 50 years at time of first BC diagnosis. (SIR = 1.94 and 1.97 for age categories <40 and 40–49 years, respectively).

Patients' origin did not seem to affect the SIR for developing second primary TC and no trend of risk was observed by calendar year of BC diagnosis. However, those diagnosed before 1980 had higher risk (SIR = 1.70 and 1.63 for 1960–1969 and 1970–1979, respectively).

A remarkably elevated risk (SIR = 32.16) was shown within the first year following BC diagnosis (concomitant disease). Whilst the risk remained elevated one to four years following the first primary (SIR = 3.97), it reached an apparently protective value 15 years or more following the diagnosis of first primary cancer (SIR = 0.30).

Table 2 shows the adjusted risks resulting from the multivariate analysis, demonstrating the magnitude of the higher risk for second primary TC for those who were diagnosed for BC at an early age (<50 *versus* ≥50) and at early calendar period (1960–1979 *versus* 1980–1998) (RR = 3.15, and RR = 4.61, respectively). In addition, compared with the protective SIR that was seen 15 and more years following the BC diagnzosis, a 58-fold risk for TC is observed in the first one to four years of follow-up.

Table 1. Observed and expected number of cases, SIRs and 95% CI for developing TC following BC according to different factors

Factor	Observed (n)	Expected (n)	SIR	95% CI
Origin				
Asia–Africa	10	8.03	1.25	0.62–2.18
Israel	12	7.04	1.70	0.91–2.86
Europe–America	37	28.85	1.28	0.91–1.74
Age at BC diagnosis (years)				
<40	9	4.64	1.94	0.93–3.50
40–49	22	11.16	1.97	1.26–2.91
50–59	12	12.12	0.99	0.53–1.66
60+	16	16.01	1.00	0.59–1.57
Calendar year of BC diagnosis				
1960–1969	14	8.24	1.70	0.96–2.75
1970–1979	20	12.29	1.63	1.01–2.45
1980–1989	14	14.99	0.93	0.53–1.51
1990–1998	11	8.39	1.31	0.68–2.25
Total	**59**	**43.91**	**1.34**	**1.03–1.72**
Follow-up period[a] (years)				
<1	13	0.40	32.16	17.69–52.95
1–4	29	7.30	3.97	2.70–5.60
5–9	12	12.51	0.96	0.51–1.61
10–14	12	9.69	1.24	0.66–2.08
⩾15	6	20.08	0.30	0.12–0.61
Total[a]	**72**	**49.98**	**1.44**	**1.13–1.80**

[a] Including concomitant disease (n = 72).

Table 2. Multivariate analysis: RR for developing second primary TC following BC according to different factors

Factor	RR	95% CI	*p*-Value
Age at BC diagnosis (years)			
<50	3.15	1.89–5.29	<0.0001
≥50[a]	1.00		
Calendar year of BC diagnosis			
1960–1979	4.61	2.72–7.89	<0.0001
1980–1998[a]	1.00		
Follow-up[b] (years)			
1–4	58.07	24.87–157.79	<0.0001
5–9	10.90	4.09–31.94	<0.0001
10–14	11.33	4.30–32.94	<0.0001
≥15[a]	1.00		

[a] Reference category.
[b] *p* for trend <0.001.

Estimations of SIR for second primary TC as derived from this model for each combination of categories are presented in Figure 1 (note the different *y*-axis scales used for years 1960–1979 and 1980–1998). The highest SIR of 33.54 (95% CI: 20.01, 56.21) was detected for a profile of a BC patient who was under 50 years at first primary diagnosis, was in the first one to four years following first primary BC diagnosis and was diagnosed before 1980.

Second primary BC following TC

SIR of 1.07 (95% CI: 0.84, 1.34) was yielded by the ratio of 70 observed cases of second primary BC following TC to the 65.25 expected (Table 3).

Similar to the trend shown in the breast-to-thyroid direction, follow-up period showed an inverse association with risk (SIR = 7.55; 95% CI: 2.34, 17.53 for the first year that monotonously declined thereafter, reach-

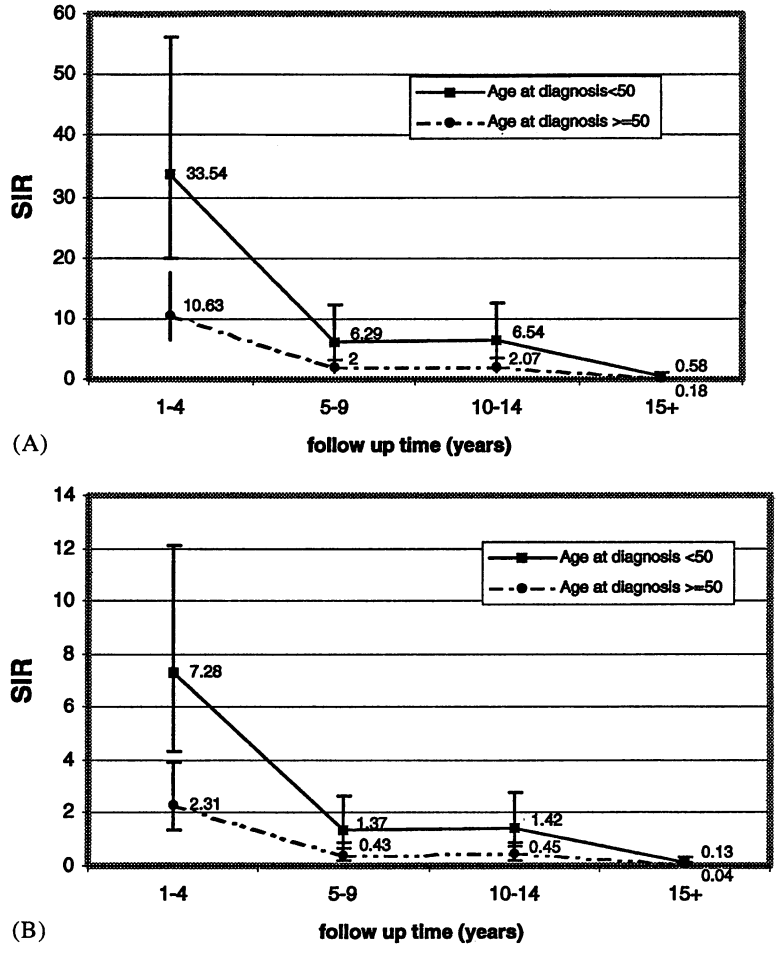

Fig. 1. (A) Estimated SIR for second primary TC following BC for patients diagnosed with BC between 1960 and 1979 according to the multivariate analysis (by years of follow-up and age at BC diagnosis). (B) Estimated SIR for second primary TC following BC for patients diagnosed with BC between 1980 and 1998 according to the multivariate analysis (by years of follow-up and age at BC diagnosis).

Table 3. Observed and expected number of cases, SIRs and 95% CI for developing BC following TC according to different factors

Factor	Observed	Expected	SIR	95% CI
Origin				
Asia–Africa	20	15.65	1.28	0.80–1.92
Israel	11	13.82	0.80	0.41–1.36
Europe–America	39	35.79	1.09	0.78–1.47
Age at TC diagnosis (years)				
<40	21	17.76	1.18	0.75–1.76
40–49	16	17.54	0.91	0.54–1.43
50–59	17	14.44	1.18	0.70–1.83
60+	16	15.51	1.03	0.61–1.62
Calendar year of TC diagnosis				
1960–1969	19	12.23	1.55	0.96–2.36
1970–1979	26	22.07	1.18	0.78–1.69
1980–1989	21	20.71	1.01	0.64–1.51
1990–1998	4	10.25	0.39	0.12–0.91
Total	**70**	**65.25**	**1.07**	**0.84–1.34**
Follow-up[a] (years)				
<1	4	0.53	7.55	2.34–17.53
1–4	23	6.01	3.83	2.47–5.61
5–9	13	12.13	1.07	0.59–1.76
10–14	9	12.37	0.73	0.35–1.31
≥15	25	39.89	0.63	0.41–0.91
Total[a]	**74**	**70.93**	**1.04**	**0.82–1.30**

[a] Including concomitant disease, (n = 74).

Table 4. Multivariate analysis: RR for developing second primary BC following TC according to different factors

Factor	RR	95% CI	*p*-Value
Age at TC diagnosis (years)			
<50	1.93	0.99–3.76	0.052
≥50[a]	1.00		
Calendar year of TC diagnosis			
1960–1979	8.61	4.16–17.83	<0.0001
1980–1998[a]	1.00		
Follow-up[b] (years)			
1–4	52.04	20.94–126.68	<0.0001
5–9	10.86	3.87–28.53	<0.001
10–14	5.47	1.80–14.62	<0.001
≥15[a]	1.00		

[a] Reference category.
[b] *p* for trend <0.001.

ing a SIR of 0.63; 95% CI: 0.41, 0.91 to 15 and more years after TC diagnosis).

Neither patients' age at TC diagnosis nor their origin was found to affect the SIR for second primary BC diagnosis. Higher SIRs were observed among patients who were diagnosed for first primary TC at earlier calendar years (SIR = 1.55, 1.18 for years 1960–1969 and 1970–1979 respectively).

In a multivariate analysis, age at TC diagnosis as well as calendar year and time of follow-up from first primary TC diagnosis were all found to affect the risk for second BC diagnosis (Table 4). The SIR estimations for second primary BC at each combination of categories in a multivariate analysis are presented in Figure 2. The highest SIR of 46.82 (95% CI: 20.33, 107.86) was experienced by TC patients, who were younger than 50 years at first primary diagnosis, during the first one to four years following diagnosis and who were diagnosed before 1980. In all age and follow-up time categories, SIRs were higher in the early calendar period compared with the later period.

Discussion

Our results show an overall significant elevated risk for developing a second primary TC following BC. This elevated risk was negatively associated with age at first primary, calendar year and time passed since BC diagnosis.

Whereas the overall SIR for developing second primary BC following TC was not elevated, specific SIRs derived from the multivariate analysis were also associated with short follow up, earlier calendar years and young age at TC diagnosis.

To the best of our knowledge, three previous studies have focused on the issue of TC and BC multiple primaries in a similar methodology (Table 5) [8–10]. Ron *et al.* [8] and Li *et al.* [10] found excess incidence of TC following BC (SIR of 1.68 and 1.5, respectively). However, the latter association disappeared when the first six months of follow up were excluded from the analysis. In a cohort of about 19,000 BC patients Vassilopoupou-Sellin *et al.* [9] did not find such an elevated risk for developing TC following BC. As opposed to our results, all of these three studies did show an overall excess risk for BC following TC.

Several other studies have discussed the issue of multiple primary cancers at all sites following BC through population-based registers [11–18]. Some also found BC patients to have significant elevated risks for developing TC with RRs in the range of 1.6–3.2 [11, 14–16], others however did not support this association [12–13, 17].

Our finding of higher risk for developing second primary (in both directions) in those who developed the first primary at a relatively young age (<50), is compatible with those of Ron *et al.* [8], Evans *et al.* [18], Harvey *et al.* [16], and Vassilopoulou-Sellin *et al.* [9]. Considering second primary TC following BC, Ron *et al.* found a SIR of 4.37 if BC was diagnosed before age 40 and the

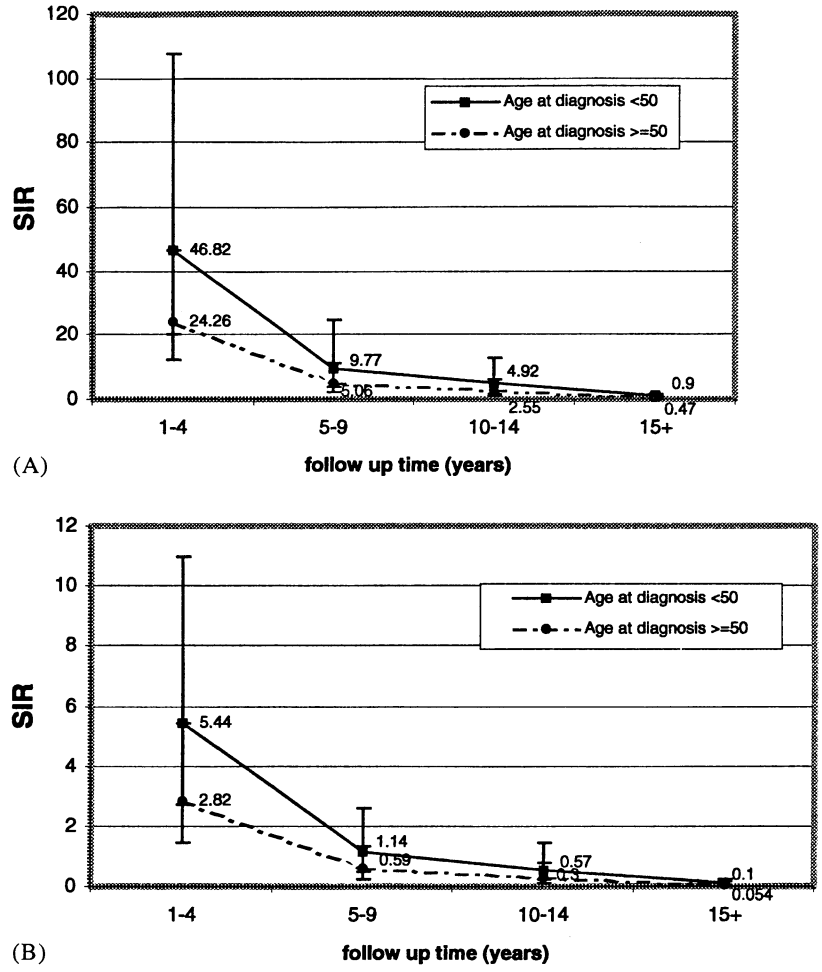

Fig. 2. (A) Estimated SIR for second primary BC following TC for patients diagnosed with TC between 1960 and 1979 according to the multivariate analysis (by years of follow-up and age at TC diagnosis). (B) Estimated SIR for second primary BC following TC for patients diagnosed with TC between 1980 and 1998 according to the multivariate analysis (by years of follow-up and age at TC diagnosis).

risk declined thereafter reaching no excess risk by the age of 55. Evans *et al.* found an elevated SIR (1.74 95% CI: 0.99, 3.07) only when BC was diagnosed before the age of 50. Looking at BC following TC, SIRs of 1.97–2.91 were found for patients younger than 40 years at time of first primary diagnosis [8, 18] and SIRs of 3.2 and 2.8 were demonstrated for patients aged 40–44 and 45–49, respectively, compared with no elevated risk when the first primary presented at older ages (>50) [9].

Familial cancers tend to appear at younger ages than sporadic cases [19]. Thus, the occurrence of second primaries BC and TC in patients who were relatively young at first primary diagnosis may suggest a genetic susceptibility for the development of both tumors. A genetic background was found in the case of the rare Cowden syndrome, which is characterized by high occurrence of both BC and TC. Recently, a mutation in the PTEN gene, which was found in this latter syndrome, was also found in cases of sporadic TC [20]. Indeed, the addition of family history to our data could spread light on this hypothesis.

An alternative explanation may be that a common exogenous risk factor, especially if occurring in childhood, could be responsible for the formation and co-existence of both cancers. The role of ionizing radiation in the causation of both TC and BC is well established [21–24]. Moreover, several studies including the A-bomb [25], Tinea Capitis [26], Chernobyl [27] and others [28], have shown that both BC and TC develop in excess in women who were irradiated in childhood. Vassilopoulou-Selin *et al.* showed that four of the 24 patients they described who developed BC after TC, reported a

Table 5. Literature summary of studies of second primary BC and TC (both directions)

Article	Data source		Time interval following first diagnosis excluded from the analysis	Second primary TC following BC			Second primary BC following TC		
	Obs	Exp		Total BC cohort n	Secondary primary TC, n	SIR (95% CI)	Total TC cohort, n	Secondary primary BC, n	SIR (95% CI)
Ron *et al.* [18]	CTR[a] 1935–1978	CTR[a] 1935–1978	2 months	36,542	24	1.68 (1.08–2.50)	1487	34	1.89 (1.31–2.64)
Vassilopoulou-Sellin et al. [9]	Anderson MD	SEER[b] 1986–1990	2 years	18,931	11	~1[c]	1013	24	Ages: 40–44: SIR = 3.2, (1.2–8.6); 45–49: SIR = 2.8, (1.2–6.9)
	Medical Center, Texas 1976–1997								
Li C *et al.* [10]	CSS[d] 1974–1994	CSS[d] 1974–1994	No time excluded	38,632	33	1.5 (1.1–2.2)	2189	44	1.5 (1.1–2.0)
			First 6 months excluded		20	1.0		38	1.3 (1.0–1.8)
Present report	ICR[e] 1960–1998	ICR[e] 1960–1998	1 year	49,207	59	1.34 (1.03–1.72)	4945	70	1.07 (0.84–1.34)
			No time excluded		72	1.44 (1.13–1.80)		74	1.04 (0.82–1.30)

[a] Connecticut Tumor Registry.
[b] Surveillance Epidemiology and End Results Program.
[c] Exact SIR was not specified.
[d] Cancer Surveillance System.
[e] Israel Cancer Registry.

previous exposure to radiotherapy in childhood; for most of the other patients, such information was missing [9]. It is interesting to mention that a linkage of the 146 women who developed both cancers in our series with lists of people who were treated with ionizing radiation to the head and neck area in childhood due to Tinea Capitis [29, 30] resulted in nine patients. Three developed BC as the first primary, two of them at an age of less than 40 years. The other six patients were diagnosed for TC before BC diagnosis. All of these six patients were diagnosed for TC before the age of 50 years, and four were also diagnosed for BC before the age of 50.

The occurrence of TC following BC may also be a consequence of radiotherapy given for BC. Since our data lacks information regarding cancer treatment, the role of radiotherapy cannot be directly examined in this study. However, since treatment protocols have changed during the study period, and considering the fact that radiation treatment for BC became more localized in Israel by the end of the 1970s, our finding of a RR of 4.61 for developing second primary TC in women diagnosed (and treated) for BC before 1980 compared to subsequent years, may support the role of radiotherapy in the subsequent development of TC. Previous Israeli data covering the period of 1960–1977, reported a RR of 1.7 for the development of TC ($p < 0.05$), either concurrent or subsequent to BC [11]. Our estimation yielded same results for this early period; however, adding 21 more years of follow up demonstrated that the risk decreased in subsequent years. Neither Ron *et al.* [8] nor Li *et al.* [10] found any association between radiotherapy for BC and the development of subsequent TC. It is important to mention that different treatments may also represent different stages of disease, which might influence survival and possibility of developing a second primary tumor.

Nevertheless, the negative association of SIR with calendar year seen in our study was even more prominent for second primary BC following TC. As far as we know no change in treatment protocols for TC was seen during the study years, either in RAI or in external radiation treatments (which was rarely given in Israel). While Ron *et al.* [8] found a SIR of 2.57 (95% CI: 1.11, 5.07) for second primary BC if TC was treated by radiation, Li *et al.* found an elevated SIR only in second primary TC patients who were not treated by ionizing radiation (SIR = 1.4, 95% CI: 1.0, 2.0) [10]. The role of RAI therapy for TC in carcinogenesis is not well established. Hall *et al.* found significantly elevated SIR for developing second primary BC following first primary TC after at least 10 years from first cancer

diagnosis only in those not treated by RAI (SIR = 1.75 *versus* 0.90 in the radio-iodine non-treated *versus* treated, respectively) [31].

The high risk for developing a second primary in a short time interval, as well as the protective SIR 15 years and above following first primary diagnosis, also argues against the role of treatment given for the first primary in the causation of the second primary, since the usual latent period attributed to radiation-induced carcinogenesis for solid tumors is long. This high SIR seen within the first year of the occurrence of the first tumor, could be suggestive of a detection bias. This observation of inverse association between time from first diagnosis to the second was also seen in the BC to TC direction by Ron *et al.* [8] and Harvey *et al.* [16]. Li *et al.* [10] did not report the results by time of follow up, however, only when the first six months were included in the analysis a significantly elevated SIR of 1.5 (95% CI: 1.1, 2.0) was observed for TC following BC. Since elevated risk for TC and BC following radiation stays elevated perhaps throughout life [24, 25], the protective SIR found in the follow up period of 15 and above years following first primary BC and TC, argues against the role of radiotherapy in the causation of the second primary. These results may imply that patients diagnosed for cancer are more meticulously followed. Such thorough medical care may lead to either early diagnosis or to detection of asymptomatic tumors yielding artificially protective SIRs 15 years following first primary diagnosis. This latter possibility is less probable in the case of BC as second primary, but is more plausible for TC that might be asymptomatic for many years.

Other possible common risk factors may also explain the higher prevalence of co-existence of these two tumors. Both BC and TC are known to predominate in females. Thus, female hormones might play a role in the causation of both tumors. The hormonal, probably estrogen related, risk factors for the development of BC are well established [32–36]. Oral contraceptive use as well as hormone replacement therapy were shown to have a moderate but significant effect on the development of BC [35, 36]. A recent pooled analysis of case–control studies that assessed risk factors for TC did not demonstrate higher risks in association with parity, abortions and infertility. However, older age at menarche and older age at first full term pregnancy showed a mild increase of risk for TC. Oral contraceptives demonstrated an odds ratio of 1.5 for current users (compared to never users) that declined with increasing time since stopping [37, 38]. The absence of data regarding past exposure to different possible risk factors, personal, family medical and reproductive history are among the limitations of this study; such information could spread light on our hypotheses.

Obviously, all of the above mentioned hypotheses could be partially responsible for the association observed between these tumors. A combination of factors could play a role in our results; therefore each of these assumptions may contribute to the excess risks observed.

The strength of our study is in its large study population; the fact that the expected incidence rates are derived from the same population and from respective years of those that the study cancer cases came from. While most other studies did not approach the ethnicity of patients, we included information regarding patients' origin, which is known to influence cancer rates in the analysis. Finally, our study used multivariate analysis to estimate adjusted RRs for each of the covariates not shown in any of the others and SIRs based on all four combined covariates creating specific profiles at risk.

Goldman [39] reviewed the association between BC and TC and concluded that they most probably share certain etiological factors. However, she stated, 'the relation between TC and BC continues to be a tantalizing one'. Further research of studies that include personal information with regard to possible risk factors is needed in order to evaluate this association of both tumors.

References

1. Smyth PP (1993) Thyroid disease and breast cancer. *J Endocrinol Invest* **16**: 396–401.
2. Giani C, Fierabracci P, Bonacci R, *et al.* (1996) Relationship between breast cancer and thyroid disease: relevance of autoimmune thyroid disorders in breast malignancy. *J Clin Endocrinol Metab* **81**: 990–994.
3. Brinton LA, Hoffman DA, Hoover R, Fraumeni Jr JF (1984) Relationship of thyroid disease and use of thyroid supplements to breast cancer risk. *J Chronic Dis* **37**: 877–893.
4. Zumoff B, O'Connor J, Levin J, Markham N, Strain GW, Fukushima DK (1981) Plasma levels of thyroxine and triiodothyronine in women with breast cancer. *Anticancer Res* **1**: 287–291.
5. Greenlee RT, Murray T, Bolden S, Wingo PA (2000) Cancer Statistics, 2000. CA *Cancer J Clin* **50**: 7–33.
6. Breslow NE, Day NE (1987) Fitting models to group data. Statistical methods in cancer research: the design and analysis of cohort studies. IARC Scientific Pub. No. 82, Lyon, France, 119–176.
7. SAS/STAT Software (1996) Changes and Enhancements, Release 6.11. SAS Institute, Cary, USA.
8. Ron E, Curtis R, Hoffman DA, Flannery JT (1984) Multiple primary breast and thyroid cancer. *Br J Cancer* **49**: 87–92.
9. Vassilopoulou-Sellin R, Palmer L, Taylor S, Cooksley CS (1999) Incidence of breast carcinoma in women with thyroid carcinoma. *Cancer* **85**: 696–705.

10. Li CI, Rossing MA, Voigt LF, Daling JF (2000) Multiple primary breast and thyroid cancers: role of age at diagnosis and cancer treatments (United States). *Cancer Causes Control* **11**: 805–811.
11. Schenker JG, Levinsky R, Ohel G (1984) Multiple primary malignant neoplasms in breast cancer patients in Israel. *Cancer* **54**: 145–150.
12. Grossbart-Schwartz A, Ragheb NE, Swanson GM, Satariano WA (1989) Racial and age difference in multiple primary cancers after breast cancer: a population-based analysis. *Breast Cancer Res Treat* **14**: 215–254.
13. Buiatti E, Crocetti E, Acciai S, *et al.* (1997) Incidence of second primary cancers in three Italian population-based cancer registries. *Eur J Cancer* **33**: 1829–1834.
14. Murakami R, Hiyama T, Hanai A, Fujimoto I (1987) Second primary cancers following female breast cancer in Osaka, Japan – a population-based cohort study. *Jpn J Clin Oncol* **17**: 293–302.
15. Volk N, Pompe-Kirn V (1997) Second primary cancers in breast cancer patients in Slovenia. *Cancer Causes Control* **8**: 764–770.
16. Harvey EB, Brinton LA (1985) Second cancer following cancer of the breast in Connecticut, 1935–1982. *Natl Cancer Inst Monogr* **68**: 99–112.
17. Ewertz M, Mouridsen H (1985) Second cancer following cancer of the female breast in Denmark 1943–1980. *Natl Cancer Inst Monogr* **68**: 325–329.
18. Evans HS, Lewis CM, Robinson D, *et al.* (2001) Incidence of multiple primary cancers in a cohort of women diagnosed with breast cancer in southeast England. *Br J Cancer* **84**: 435–440.
19. Collaborative Group on Hormonal Factors in Breast Cancer (2001) Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without the disease. *Lancet* **358**: 1389–1399.
20. Dahia PL, Marsh DJ, Zheng Z, *et al.* (1997) Somatic deletions and mutations in the Cowden disease gene, PTEN, in sporadic thyroid tumors. *Cancer Res* **57**: 4710–4713.
21. Ron E, Preston DL, Mabuchi K, Thompson DE, Soda M (1994) Cancer Incidence in Atomic Bomb Survivors. Part IV: Comparison of cancer incidence and mortality. *Radiat Res* **137**: S98–S112.
22. Bhatia S, Robison LL, Oberlin O, Greenberg M, Bunin G, Fossati-Bella Meadows AT (1996) Breast cancer and other second neoplasms after childhood Hodgkin's disease. *N Engl J Med* **334**: 745–751.
23. de Vathaire F, Hardiman C, Shamsaladin A, *et al.* (1999) Thyroid carcinomas after irradiation for a first cancer during childhood. *Arch Int Med* **159**: 2713–2719.
24. Ron E, Lubin JH, Shore RE, *et al.* (1995) Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. *Radiat Res* **14**: 259–277.
25. Tokunaga M, Land CE, Yamamoto T, Asano M, Tokuoka S, Ezaki H (1987) Incidence of female breast cancer among atomic bomb survivors, Hiroshima and Nagasaki, 1950–1980. *Radiat Res* **112**: 243–272.
26. Ron E, Modan B, Preston D, Alfandary E, Stovall M, Boice JD Jr (1989) Thyroid neoplasia following low dose radiation in childhood. *Radiat Res* **120**: 516–531.
27. Baverstock K, Egloff B, Pinchera A, Ruchti C, Williams D (1992) Thyroid cancer after Chernobyl. *Nature* **359**: 21–22.
28. Li FP, Corkery J, Vawter G, Fine W, Sallan SE (1983) Breast carcinoma after cancer therapy in childhood. *Cancer* **51**: 521–523.
29. Modan B, Baidatz D, Mart H, Steinitz R, Levin SG (1974) Radiation Induced Head and Neck Tumors. *Lancet* **1**: 277–279.
30. Sadetzki S, Modan B (1999) Epidemiology as a basis for legislation. How far should epidemiology go? *Lancet* **353**: 2238–2239.
31. Hall P, Holm LE, Lundell G, *et al.* (1991) Cancer risks in thyroid cancer patients. *Br J Cancer* **64**: 159–163.
32. Brinton LA, Schairer C, Hoover RN, Fraumeni JF, Jr (1988) Menstrual factors and risk of breast cancer. *Cancer Invest* **6**: 245–254.
33. Pike MC, Henderson BE, Casagrande JT (1981) The epidemiology of breast cancer as it relates to menarche, pregnancy and menopause. In: Pike MC, Siiteri PJ, Welsch CW, eds. *Hormones and Breast Cancer*. (Banbury Report No. 8). Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, pp. 3–18.
34. Ewertz M, Duffy SW (1988) Risk of breast cancer in relation to reproductive factor in Denmark. *Br J Cancer* **58**: 99–104.
35. Collaborative Group on Hormonal Factors in Breast Cancer (1996) Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53,297 women with breast cancer and 100,239 women without breast cancer from 54 epidemiological studies. *Lancet* **347**: 1713–1727.
36. Collaborative Group on Hormonal Factors in Breast Cancer (1997) Breast cancer and hormonal contraceptives: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 without breast cancer. *Lancet* **350**: 1047–1059.
37. Negri E, Dal Maso L, Ron E, *et al.* (1999) A pooled analysis of case–control studies of thyroid cancer. II. Menstrual and reproductive factors. III. Oral contraceptives, menopausal replacement therapy and other female hormones. *Cancer Causes Control* **10**: 143–166.
38. La Vecchia C, Ron E, Franceschi S, *et al.* (1999) A pooled analysis of case–controls studies of thyroid cancer. III. Oral contraceptives, menopausal replacement therapy and other female hormones. *Cancer Causes Control* **10**: 157–166.
39. Goldman MB (1990) Thyroid disease and breast cancer. *Epi Rev* **12**: 16–28.