The Laryngoscope

Thyroid Cancer Characteristics in the Population Surrounding Three Mile Island

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Objectives/Hypothesis: To determine differences in disease characteristics between the thyroid cancer populations in the area around the Three Mile Island (TMI) nuclear power plant and the rest of the state of Pennsylvania.

Study Design: Retrospective cross-sectional study.

Methods: Data from the Pennsylvania Cancer Registry from 1985 to 2008 were reviewed and information regarding age at diagnosis, sex, race, residential status, county of residence, thyroid pathology, thyroid surgery, and staging was recorded. Dauphin, Lancaster, and York counties were defined as the TMI area.

Results: Records of 26,357 thyroid cancer patients were reviewed, with 2,611 patients within the TMI area. A higher proportion of papillary thyroid cancer ($P < .001$) and lower proportion of follicular thyroid cancer ($P < .001$) were noted in the TMI area population. Thyroid cancer cases from the TMI area were found to be more likely to be diagnosed before the age of 65 years ($P < .001$), be Pennsylvania born ($P < .001$), be well differentiated ($P < .001$), be <10 mm in size ($P < .001$), and be localized without spread ($P < .001$). Although the TMI area shows a higher incidence of thyroid cancer as compared to the rest of the state, this was not statistically significant.

Conclusions: The TMI population showed a higher proportion of papillary thyroid cancer and less aggressive pathology and earlier diagnosis compared to the rest of Pennsylvania. No statistically significant difference in thyroid cancer incidence was noted. Overall, the study does not show a clear link with more advanced thyroid cancer and proximity to the TMI nuclear reactors.

Key Words: Thyroid cancer, thyroid carcinoma, ionizing radiation, Three Mile Island, nuclear power plant, papillary thyroid carcinoma, Pennsylvania Cancer Registry.

Level of Evidence: 2b.

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INTRODUCTION

A variety of cancers have been associated with ionizing radiation exposure. These include colorectal carcinoma, sarcomas, parotid neoplasms, and perhaps most commonly associated with radiation, thyroid carcinoma. Large cohort studies evaluating the effects of ionizing radiation following the atomic bomb sites at Hiroshima and Nagasaki and the nuclear plant disaster at Chernobyl have identified a significantly increased risk of cancer in the radiation-exposed populations.[1,2] The data from Chernobyl, looking specifically at thyroid cancer, demonstrated an increased dose-dependent risk of papillary thyroid cancer (PTC) with approximately a 4-year latency period.[1] Evaluation of low dose ionizing radiation exposure has also demonstrated associations with thyroid neoplasm and radiation. Historically, patients have received radiation treatments for acne, tinea capitis, and benign thyroid disease, and currently radiation therapy is a mainstay of treatment of childhood lymphomas. Although the total dose of radiation to the cervical region has decreased for lymphoma treatment, long-term follow-up of these individuals demonstrates a higher relative risk of thyroid neoplasm as compared to the general population.[3,4]

One of the worst releases of radioactive gasses in the United States, the Three Mile Island (TMI) incident involved a nuclear power plant core meltdown in one of its units in 1979. An estimated 2.5 million to 10 million curies of radioactivity was released into the atmosphere, mostly consisting of xenon and krypton but also including approximately 15 curies of iodine-131 (^{131}I).[5] Immediately after the incident, a tumor registry was formed to study the effects of the radiation exposure to the surrounding community.[6] In 2008, Levin published a study on the incidence of thyroid cancer in residents surrounding TMI. This study aimed to determine whether

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an association could be made between ionizing radiation exposure in the area and thyroid cancer. The study described increasing incidences of thyroid cancer in Lancaster and York counties starting 10 and 15 years after the TMI incident, but not in Dauphin County, where TMI is located. This increased incidence, however, did not correlate with the level of estimated ionizing radiation exposure in these counties.[7]

Our current study examines the thyroid cancer outcomes in these three high-risk counties between 1985 and 2008, using the updated data provided by the Pennsylvania Cancer Registry (PCR). Given the latency of thyroid cancer presentation in populations exposed to low doses of ionizing radiation, the additional information may provide unique insights into this population. The United States has a rising incidence of thyroid carcinoma, and Pennsylvania as a state has one of the highest incidences of thyroid cancer. Anecdotally, there continues to be a perception in the community surrounding TMI that the incidence of thyroid cancer is intimately linked to the radiation exposure from TMI. We compared the thyroid cancer population in Dauphin, Lancaster, and York counties to the rest of the state of Pennsylvania to determine if there are differences present in disease characteristics such as tumor invasiveness, histology, and presence of metastasis. Additionally, we compared mortality and incidence rates between the TMI area, Pennsylvania and the United States based on information from the Surveillance Epidemiology and End Results (SEER) Program database. We hypothesize that differences in disease behavior exist between the population surrounding TMI and the rest of the state.

MATERIALS AND METHODS

Institutional review board approval was obtained from the Pennsylvania State University–Milton S. Hershey Medical Center for this study. The PCR is a publicly available database of new cases of cancer diagnosed or treated within Pennsylvania beginning in 1985. Data are included from hospitals, clinics, laboratories, radiation facilities, surgical centers, cancer centers, doctors' offices, death certificates, as well as information exchange when Pennsylvania residents are diagnosed or treated in other states. Due to its comprehensive nature, it serves as a representative population for retrospective cross-sectional studies such as this one.

Data were collected from the PCR, which provided information on each case of thyroid cancer diagnosed in Pennsylvania residents from 1985 to 2008 for a total of 26,357 patients. Thyroid cancer was identified by an International Classification of Diseases, 9th Revision (ICD–9 O-2 and 3 primary site code of C739. Variables included in the analysis were derived from North American Association of Central Cancer Registries standard items and included age at diagnosis, gender, place of birth, ethnicity/race, cancer grade, tumor size, histology (categorized by ICD–9 O-2 and 3 codes: anaplastic 8021, follicular 8330-8335, lymphoma 9590-9728, medullary 8510, oxyphilic adenocarcinoma 8290, papillary 8340-8344, 8050, 8130, 8260, and other), focality (solitary or multifocal tumor), SEER summary stage (in situ, local, regional, distant), surgery type, scheduled chemotherapy, radiation therapy scheduled and type, cancer sequence (those with prior cancer), and vital status (alive at last contact). Some variables had a large proportion of missing cases (>10%) because they were not available or recorded in the PCR during the earlier years of the study time frame. For each comparison, missing cases were excluded.

The area closest to TMI was defined to include three counties (Dauphin, Lancaster, and York), as previously described.[7,8] These counties are also consistent with the regions that received the highest doses of radiation exposure.[9] We first examined local characteristics comparing the aggregate of the three counties with all other 64 Pennsylvania counties combined. Each category of the comparison variable was individually tested using χ^2 tests. We considered only P values $<.005$ as significant to minimize type 1 error resulting from multiple comparisons.

The second analysis examined trends across selected characteristics of thyroid cancer cases. The 24-year period was divided into two 12-year periods (1985–1996 and 1997–2008). Trends were calculated for place of birth, grade, histology, and SEER summary stage. Using a log-binomial regression, a likelihood ratio test for the homogeneity of relative risk across region strata (an interaction test) was conducted to examine if the TMI area profile exhibited a different pattern of change as compared to the regional profile. To understand temporal trends in thyroid cancer cases, a third analysis was conducted in which age-adjusted thyroid cancer incidence rates for TMI, Pennsylvania, and the United States were calculated and compared from 1985 to 2008. Thyroid cancer cases for Pennsylvania were taken from the state cancer registry, for each of the 5-year age groups. The population by 5-year groups was taken from US Census data (1980, 1990, and 2000), using intracensal estimates for noncensus years. From 2001 to 2006, the US Center for Disease Control (CDC)-calculated rates were used, and for 2007 to 2008, population estimates from the Pennsylvania State Data Center were used. The US thyroid cancer incidence rates were calculated from data available in SEER reports, for nine states and metropolitan areas (10% of the United States). These included Connecticut, Hawaii, Iowa, New Mexico, Utah, Atlanta, Detroit, San Francisco, and Seattle.

Last, mortality from thyroid cancer in the TMI area was compared to the rest of Pennsylvania to assess whether local death rates exceeded state rates. The CDC data system was used to collect available data on all US deaths (by primary cause of death) from 1979 to 2007. Crude and age-adjusted rates were reviewed for the three-county area and all other PA counties. The ICD-9 code 193 (1979–1998) and the ICD-10 code 73.9 were used to identify thyroid cancer deaths.

RESULTS

The comparison of characteristics of thyroid cancer cases from the TMI area versus other residents in Pennsylvania is shown in Table I. The total number of cases consisted of 2,611 in the three-county area and 23,746 for the rest of the state. The percentages listed are the number of cases in a category divided by total cases, excluding those that were unknown. Results suggest the TMI cohort had a significantly lower proportion of the cancer population that was 65 years or older (all $P < .001$), had a significantly higher portion of persons born in PA (72.6% vs. 63.6%, $P < .001$), a lower rate of black non-Hispanic cases (3.7 vs. 6.4, $P < .001$), a higher percentage of white non-Hispanic cases (93.6% vs. 91.0%, $P < .001$), and a higher proportion still alive at last contact (87.3% vs. 84.6%, $P < .001$).

TABLE I.
Comparison of Cancer Registry Characteristics Between Three Mile Island and Other Pennsylvania Counties, 1985–2008.

Patient Demographics	TMI Area, No. (%), n = 2,611	Rest of PA, No. (%), n = 23,746	*P* Value
Age at diagnosis, yr			
0–39	768 (29.4)	6,539 (27.5)	.04
40–64	1,303 (49.9)	11,492 (48.4)	.14
65+	540 (20.7)	5,715 (24.1)	<.001
Gender			
Male	601 (23.0)	5,672 (23.9)	
Female	2,010 (77.0)	18,074 (76.1)	.32
Birthplace			
PA	1,450 (72.6)	6,841 (63.6)	<.001
Other US	451 (22.6)	3,446 (32.0)	<.001
Outside US	96 (4.8)	476 (4.4)	.44
Ethnicity/race			
White, non-Hispanic	2,420 (93.6)	21,245 (91.0)	<.001
Black, non-Hispanic	95 (3.7)	1,483 (6.4)	<.001
Hispanic	38 (1.5)	249 (1.1)	.06
Other	33 (1.3)	369 (1.6)	.23
Previous cancer			
No	2,351 (90.0)	21,332 (89.8)	
Yes (patient has had another primary)	260 (10.0)	2,424 (10.2)	.69
Alive at last contact			
Yes	2,279 (87.3)	20,095 (84.6)	
No	332 (12.7)	3,651 (15.4)	<.001
Follow-up (SD), d			
Mean follow-up (all)	508 (1,149)	565 (1,248)	.0167
Alive at last contact	1,512 (1,672)	1,725 (1859)	.0286
Not alive at last contact	362 (968)	354 (960)	.716
Thyroid cancer characteristics			
Focality			
Solitary tumor	556 (58.8)	5,214 (59.0)	
Multifocal tumor	389 (41.2)	3,621 (41.0)	.92
Tumor size			
<10 mm diameter	382 (39.6)	3087 (35.1)	.005
10–40 mm diameter	493 (51.1)	4805 (54.6)	.04
>40 mm diameter	89 (9.2)	914 (10.4)	.26
Histologic grade			
Well differentiated (grade I)	236 (65.7)	2,164 (56.6)	<.001
Moderately differentiated (grade II)	46 (12.8)	748 (19.6)	.002
Poorly differentiated (grade III)	32 (8.9)	368 (9.6)	.66
Undifferentiated (grade IV)	45 (12.5)	540 (14.1)	.40
Histology			
Papillary	2,201 (84.3)	18,908 (79.6)	<.001
Follicular	150 (5.7)	1,921 (8.1)	<.001
Oxyphilic adenocarcima	95 (3.6)	884 (3.7)	.83
Lymphoma	43 (1.6)	534 (2.2)	.05
Medullary	20 (0.8)	229 (1.0)	.32
Anaplastic	17 (0.7)	225 (1.0)	.13
Other	85 (3.3)	1,045 (4.4)	.006
SEER Program summary stage			
In situ	3 (0.1)	61 (0.3)	.21*
Local	1977 (78.9)	16781 (72.9)	<.001
Regional	433 (17.3)	4953 (21.5)	<.001

(*Continued*)

TABLE I.
(*Continued*).

Patient Demographics	TMI Area, No. (%), n = 2,611	Rest of PA, No. (%), n = 23,746	*P* Value
Distant	94 (3.7)	1224 (5.3)	<.001
Treatment characteristics			
Surgery type			
Lobectomy/isthmectomy	331 (21.2)	2,585 (19.1)	.04
Lobe removal	15 (1.0)	139 (1.0)	.81
Thyroidectomy	1,194 (76.5)	10,621 (78.4)	.09
Surgery, not specified	31 (1.3)	201 (1.5)	.14
Scheduled chemotherapy			
Yes	15 (1.0)	231 (1.8)	
No	1,446 (99.0)	12,956 (98.2)	.04
Scheduled radiation therapy			
Yes	623 (51.2)	5,627 (50.0)	
No	594 (48.8)	5,628 (50.0)	.43
Type of radiation therapy			
Beam	32 (5.1)	300 (5.3)	.84
Radiation implants	6 (1.0)	121 (2.2)	.05*
Radioisotopes	574 (92.1)	5,133 (91.2)	.44
Other/not specified	11 (1.8)	73 (1.3)	.36*

*Fisher exact test used.
TMI = Three Mile Island, PA = Pennsylvania, US = United States; SD = standard deviation; SEER = Surveillance, Epidemiology, and End Results.

To further evaluate the significance of the proportion alive at last contact, data on mean follow-up were evaluated. Patients in the local region were followed for an average of 508 days (~17 months), with follow-up ranging from 0 days to 8,153 days (~271 months), with a standard deviation of 1,149 days (~38 months). The rest of Pennsylvania was followed for an average of 565 days (~19 months) with a range from 0 days to 8,875 days (~296 months), with a standard deviation of 1,248 days (~41.6 months). Assuming unequal variances, the *P* value of the two populations being different is .0167. The mean follow-up among those not alive at last contact was 1,512 days in the TMI group and 1,725 days in the rest of Pennsylvania ($P = .0286$). The mean follow-up among those alive at last contact was 362 days in the TMI group and 354 days in the rest of Pennsylvania ($P = .716$).

The cancer characteristics among the TMI cohort shows a higher rate of grade 1 cases (65.7% vs. 56.6%, $P < .001$), lower rate of grade 2 cases (12.8% vs. 19.6%, $P < .001$), higher rate of <10-mm tumor sizes (39.6% vs. 35.1%, $P = .005$), higher rate of papillary cancer (84.3% vs. 79.6%, $P < .001$), lower rate of follicular cancer (5.7% vs. 8.1%, $P < .001$), and a lower rate of regional cancers (17.3% vs. 21.5%, $P < .001$).

The comparison in trends (Table II) suggest a significant difference between TMI and the rest of the state from 1985 through 1996 to 1997 through 2008 for those born in PA (relative risk: 9 vs 0.8, $P = .001$). There is no evidence of a statistically significant difference in the relative risk between TMI and state with regard to grade, histology, or SEER summary stage.

Table III and Figure 1 show age-adjusted rates for thyroid cancer cases per 100,000. PA rates in the mid-1980s were well below the United States (−31.1% in 1985). But the gap narrowed steadily until PA exceeded the United States for the first time in 1997. The gap between state and nation grew quickly until it reached +37.1% higher in PA in 2001, where it has tended to remain since. Additionally, the number of thyroid cases diagnosed in Pennsylvania residents has soared from 1985 to 2008, with no signs of a leveling off or decline in the future. Descriptively, the thyroid cancer incidence for the TMI area counties parallels the state rates, though they are higher than the norm since 1992 for all but 2 years.

The crude and age-adjusted rates for the TMI area and the other 64 counties in Pennsylvania for deaths occurring 1979 to 2007 were calculated. The number of thyroid cancer deaths in the TMI area from 1985 to 2007 was 163. In the rest of Pennsylvania, 1,771 deaths were attributed to thyroid cancer. The local age-adjusted death rate (0.527 per 100,000) is slightly (+8.0%) greater than the rest of Pennsylvania (0.488 per 100,000). The lower (−1.6%) TMI crude rate suggests that crude thyroid cancer rates may differ from age-adjusted rates. The number of deaths from thyroid cancer (163) from 1985 to 2007 is well below the number of deaths in persons diagnosed with thyroid cancer from 1985 to 2008 (332), suggesting that the death rate is closer to 4% to 5% rather than the 12.7% observed in the PCR, and that most decedents in the registry's files died from other conditions. This is also true for the rest of Pennsylvania, with 1,771 deaths attributed to thyroid cancer in the CDC and 3,651 not alive at last contact in the PCR database.

DISCUSSION

Analysis of the cancer registry data revealed that the thyroid cancer cases from the area surrounding TMI

TABLE II.
Comparison of Selected Cancer Registry Trends Between Three Mile Island and Other Pennsylvania Counties.

	TMI, No. (%)		Rest of PA, No. (%)		Relative Risk (1997–2008/1985–1996)		
	1985–1996	1997–2008	1985–1996	1997–2008	TMI	Rest of PA	*P* Value*
Birthplace							
PA	396 (75.5)	1,054 (71.5)	2,850 (70.1)	3,991 (59.6)	0.9	0.8	.001
Other US	104 (19.9)	347 (23.5)	1,058 (26.0)	2,388 (35.7)	1.2	1.4	.17
Outside US	23 (4.4)	73 (5.0)	160 (3.9)	316 (4.7)	1.1	1.2	.80
Grade							
1	67 (56.8)	169 (70.1)	715 (53.1)	1,449 (58.6)	1.2	1.1	.22
2	15 (12.7)	31 (12.9)	262 (19.5)	486 (19.6)	1.0	1.0	.99
3	14 (11.9)	18 (7.5)	154 (11.4)	214 (8.6)	0.6	0.7	.61
4	22 (18.6)	23 (9.5)	215 (16.0)	325 (13.1)	0.5	0.8	.10
Histology							
Anaplastic	6 (0.9)	11 (0.6)	82 (1.3)	143 (0.8)	0.7	0.6	.88
Follicular	64 (10.0)	86 (4.4)	842 (13.1)	1,079 (6.2)	0.4	0.5	.60
Lymphoma	23 (3.6)	20 (1.0)	252 (3.9)	282 (1.6)	0.3	0.4	.22
Medullar	0 (0.0)	20 (1.0)	0 (0.0)	229 (1.3)	—	—	—
Other	51 (7.9)	34 (1.7)	545 (8.5)	500 (2.9)	0.2	0.3	.04
Oxyphilic adenocarcinoma	17 (2.6)	78 (4.0)	181 (2.8)	703 (4.0)	1.5	1.4	.90
Papillary	482 (75.0)	1,719 (87.3)	4,547 (70.5)	14,361 (83.0)	1.2	1.2	.69
SEER summary stage							
In situ	2 (0.3)	1 (0.1)	50 (0.8)	11 (0.1)	0.3	0.1	.60
Local	451 (74.4)	1,526 (80.3)	4,067 (66.1)	12,714 (75.4)	1.1	1.1	.05
Regional	116 (19.1)	317 (16.7)	1,490 (24.2)	3,463 (20.5)	0.9	0.8	.79
Distant	37 (6.1)	57 (3.0)	548 (8.9)	676 (4.00)	0.5	0.4	.68

*P values are from a likelihood ratio test for homogeneity of relative risk using log-binomial regression.
TMI = Three Mile Island, PA = Pennsylvania; US = United States; SEER = Surveillance, Epidemiology, and End Results.

appear to be less advanced and less aggressive at presentation. Statistically significant differences were noted between the two populations with regard to age, race, tumor size and grade, and SEER staging. Of note, a higher statistically significant proportion of thyroid carcinomas were PTC in the TMI cohort, and fewer were follicular carcinomas. Additionally, evaluating the aggregate three-county incidence rates from 1985 to 2008 in comparison to the rest of Pennsylvania revealed periods of increased incidence between 1993 to 2000 and 2002 to 2006. The demographics of the thyroid cancer population surrounding TMI relative to the rest of Pennsylvania were not statistically significant aside from racial disparities that are consistent with differences in racial distribution among the healthy population. A higher proportion of the TMI cohort was born in Pennsylvania as compared to the other cohort. Although a statistically significant difference in mortality was noted between the TMI population and the rest of Pennsylvania, given the discrepancy between deaths in the cohort and deaths in the cohort due to thyroid cancer, this finding is likely confounded by other causes of mortality. Differences in mean follow-up between the TMI population and the rest of Pennsylvania approached statistical significance, especially among the subgroup that was not alive at follow-up. However, it should be noted that the last follow-up for those not alive at follow-up is their recorded date of death. This may suggest that the deceased patients in the TMI cohort had more aggressive disease given the shorter follow-up, although the difference was not statistically significant under our stricter criteria ($P < .005$), and the other data do not support this claim.

Interestingly, previous research has commented that an increase in the incidence of cancer immediately after the TMI incident could be attributed to an increased sensitivity in the population to be examined.[5] It is possible that the diagnosis of thyroid cancer at an earlier stage is a result of this increased vigilance. However, with almost 30 years since the event, it is possible that increased vigilance may not completely explain this difference. Our data are consistent with Levin's, which showed increased incidence in the TMI area (specifically Lancaster and York counties) from 1993 to 2000.[7] With the more up-to-date data, we saw that the increased incidence continues from 2002 to 2006. Relative to the rest of the country, Pennsylvania as a whole demonstrates a higher incidence of thyroid cancer since 1997.

In our study, the thyroid cancer diagnosed among the TMI cohort appears to be less aggressive, with a higher proportion of the reported cancers being well differentiated and without regional spread. This is in contrast to the cohorts exposed to Chernobyl, Hiroshima, and Nagasaki, where the thyroid carcinoma is often aggressive, with a propensity for metastasis and recurrence.[1,10] The Chernobyl population has also demonstrated a significant propensity for children to

TABLE III.
Adjusted (2000 Standard) Thyroid Cancer Incidence Rates Per 100,000.

Year	TMI rate	Rest of PA rate	All of PA rate	US rate	PA vs US
1985	3.65	3.53	3.54	5.13	−31.07
1986	4.11	3.85	3.87	5.32	−27.18
1987	3.03	4.34	4.23	5.05	−16.15
1988	3.29	4.02	3.96	4.94	−19.80
1989	4.07	4.29	4.28	5.36	−20.24
1990	4.83	4.62	4.63	5.5	−15.80
1991	4.97	4.81	4.82	5.49	−12.18
1992	5.26	5.18	5.19	5.87	−11.63
1993	6.13	5.44	5.50	5.65	−2.61
1994	6.79	4.86	5.03	6.08	−17.22
1995	8.54	5.78	6.01	6.22	−3.33
1996	8.09	6.35	6.51	6.51	−0.05
1997	9.17	6.78	6.99	6.78	3.04
1998	9.83	7.74	7.93	6.98	13.54
1999	11.16	8.14	8.40	7.35	14.23
2000	10.45	10.21	10.23	7.61	34.44
2001	11.34	11.37	11.37	8.29	37.12
2002	15.42	12.06	12.36	9.22	34.04
2003	16.25	12.47	12.82	9.64	32.96
2004	15.62	13.15	13.38	10.1	32.48
2005	16.14	13.70	13.93	10.91	27.65
2006	17.75	15.10	15.35	11.29	35.99
2007	16.69	16.77	16.75	12.34	35.77
2008	16.92	18.72	18.54	13.22	40.28

TMI = Three Mile Island, PA = Pennsylvania, US = United States

develop thyroid carcinoma in a dose-dependent fashion.[11] Our data do not suggest this, with no statistically significant difference noted between the TMI population and the rest of the state in the youngest cohort (0–39 years). An analysis of the TMI tumor registry by Han et al. also failed to show any cases of thyroid neoplasm in individuals under 18 years old.[12]

Previous studies have evaluated the impact of incidental ionizing radiation exposure on thyroid cancer characteristics. Seaberg et al. studied patients with thyroid cancer who had been previously exposed to radiation and found a higher incidence of extrathyroidal spread, distant metastases, and mortality from disease.[13] On the other hand, Furlan and Rosen compared thyroid cancer patients with previous radiation exposure to those without previous exposure and found those with radiation exposure had evidence of smaller tumor size and often had incidental microcarcinomas.[14] Although our data do not elucidate the presence or absence of microcarcinomas, they do show the TMI cohort to have smaller neoplasms as compared to the general population.

With iatrogenic radiation exposure populations, PTC is more commonly seen among thyroid carcinomas in the population. Among atomic bomb survivors from Hiroshima and Nagasaki, researchers found that most thyroid carcinogenesis was dose-related to the amount of gamma radiation received. Similarly, certain mutations conferred greater latency before presentation.[1,2,15] In the TMI cohort, no similar association or causality has been determined between the history of radiation exposure from TMI and the presentation of thyroid carcinoma.[7,12] Our results do note a statistically significant higher proportion of PTC among the TMI cohort as compared to the surrounding Pennsylvania counties, yet this does not show causality.

In comparison to other reported releases of radioactive gasses, TMI involved a much lower total volume of gas released, and also released more xenon and krypton with very low amounts of iodine isotopes. As estimated by the Nuclear Regulatory Commission, the total radiation effect to an individual during the TMI incident approximated 1.4 mrem (where 1 rem is the biological effect of 1 rad of gamma radiation exposure). For comparison, the average dose in the TMI area received from background radiation in 1 year is approximately 116 mrem.[5] However, despite these low estimates, cohort studies involving the TMI population and the established tumor registry have shown a higher relative risk of leukemia, and cancers of the bronchus, trachea, and lung as compared to the general population. Within the tumor registry, only eight cases of thyroid carcinoma were noted.[12]

Many studies have evaluated the effects of low-dose radiation exposure and the association with thyroid carcinogenesis. Sklar et al. specifically evaluated the risk of thyroid disorders in patients receiving low dose radiation therapy for Hodgkin's disease, and found a more than 18-fold increased relative risk among those who received therapy as compared to the general population.[3] The National Research Council (NRC) published a review in 2006 evaluating the risks associated with low-dose ionizing radiation. The study described an established dose-dependent relationship between ionizing radiation and thyroid cancer, most pronounced in children under 15 years of age, citing studies regarding Chernobyl and medical treatment of childhood cancers as well as benign diseases. In contrast, the NRC found little information quantifying the risks of carcinoma from ^{131}I exposure for

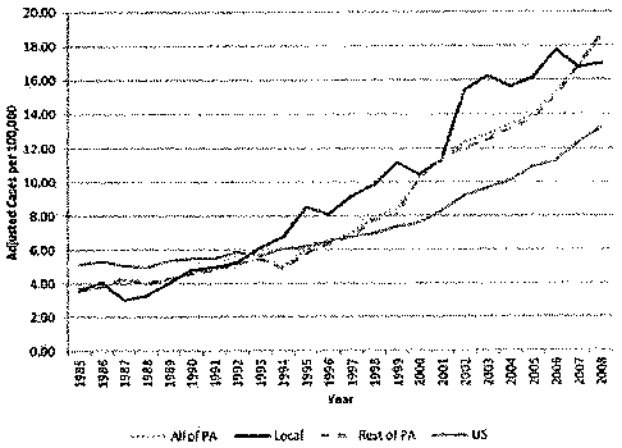

Fig. 1. The graph charts the rise in incidence of thyroid cancer in the United States, Pennsylvania (PA), the Three Mile Island (TMI) region, and the rest of Pennsylvania excluding the TMI region.

the treatment of benign disease, although the large studies reviewed showed no significant increased incidence of thyroid neoplasm.[16] Berrington de Gonzalez et al. modeled the radiation dosage to the thyroid in people undergoing computed tomography (CT) and estimated 1,000 thyroid neoplasms in the future to be related to CT scans performed in 2007 in United States.[17]

The mechanism of carcinogenesis from radiation has multiple theories. Ionizing radiation in particular is thought to cause injury to cellular DNA via the creation of free radicals and ions in the body. ^{131}I is a radioactive isotope of iodine that has preferential uptake by the thyroid that decays and releases ionizing radiation. As stated before, the majority of gasses released in the TMI incident were xenon and krypton, specifically the isotopes xenon-133 and krypton-85. This isotope of xenon releases both beta (99.3% of the time) and gamma (36.5% of the time) radiation and has a half-life of 5.3 days. Although gamma radiation can penetrate deeply, beta rays are not very penetrating and do not usually pose a significant health hazard. Krypton-85 has a half-life of 10.8 years, and decays more than 100% of the time via release of a beta particle and only releases gamma rays 0.43% of the time. In contrast, ^{131}I has a half-life of 8.02 days and releases beta particles 89% of the time and gamma particles 81% of the time. Although it also decays with beta particle release, because the iodine has a preferential uptake in the thyroid, the beta decay also directly affects this adjacent tissue. This can help demonstrate the difference in thyroid cancer characteristics between Chernobyl and TMI, as the higher release of ^{131}I in Chernobyl would be directly related to increased uptake and radiation absorbed by the thyroid.

There are several limitations to this study. First, the data are from an historical data source, and thus have inherent biases from the study being performed retrospectively. Additionally, the PCR only collected data from 1985, thus missing possible differences between the TMI and Pennsylvania population that occurred in the years immediately after the TMI incident. A retrospective study by Berkheiser evaluated thyroid cancer incidence from 1974 to 1984 at a community hospital in Dauphin county and did not elicit any differences between the incidence or histology at the hospital and published reports from other metropolitan or community hospital settings.[18]

The PCR also includes individuals who were not part of the population initially exposed to TMI but now live in the Dauphin, Lancaster, or York counties. However, there is no information to suggest that the population migratory patterns between the TMI area and surrounding areas yielded significant egress or ingress. Of note, our data suggest that the TMI cohort is less migratory, with a larger proportion having been born in Pennsylvania. Still, this limitation of the PCR may underestimate the significance of certain differences between the TMI population and the surrounding Pennsylvania population.

CONCLUSION

In contrast to the belief that the population around TMI and exposed to TMI has a higher rate of aggressive thyroid cancer, the characteristics of the thyroid cancer in the TMI population appeared less aggressive and less advanced. The pathology is more likely to be PTC and less likely to be follicular cell when compared to the rest of Pennsylvania. Evaluating incidence rates from the PCR does show an increased incidence in the TMI area as compared to the rest of Pennsylvania consistent with previous studies, yet this difference does not appear to be statistically significant. Although low-dose radiation has been linked to increased thyroid cancer incidence in children, our data do not support a similar link among the TMI cohort. Further research can help determine whether histological differences, if any, exist between thyroid cancers in the TMI region compared to the rest of Pennsylvania. Additional staining for mutations such as BRAF or rearranged in transformation/PTC may reveal differences in the TMI cohort and surrounding population.

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BIBLIOGRAPHY

1. Nikiforov YE. Radiation-induced thyroid cancer: what we have learned from chernobyl. *Endocr Pathol* 2006;17:307–317.
2. Nakachi K, Hayashi T, Hamatani K, Eguchi H, Kusunoki Y. Sixty years of follow-up of Hiroshima and Nagasaki survivors: current progress in molecular epidemiology studies. *Mutat Res* 2008;659:109–117.
3. Sklar C, Whitton J, Mertens A, et al. Abnormalities of the thyroid in survivors of Hodgkin's disease: data from the Childhood Cancer Survivor Study. *J Clin Endocrinol Metab* 2000;85:3227–3232.
4. De Jong SA, Demeter JG, Jarosz H, Lawrence AM, Paloyan E. Thyroid carcinoma and hyperparathyroidism after radiation therapy for adolescent acne vulgaris. *Surgery* 1991;110:691–695.
5. United States. Nuclear Regulatory Commission. Special Inquiry Group. *Three Mile Island: a report to the Commissioners and to the public*. Washington, DC: Nuclear Regulatory Commission, Special Inquiry Group; 1980.
6. Goldhaber MK, Tokuhata GK, Digon E, et al. The Three Mile Island Population Registry. *Public Health Rep* 1983;98:603–609.
7. Levin RJ. Incidence of thyroid cancer in residents surrounding the Three Mile Island nuclear facility. *Laryngoscope* 2008;118:618–628.
8. Jablon S, Hrubec Z, Boice JD Jr. Cancer in populations living near nuclear facilities. A survey of mortality nationwide and incidence in two states. *JAMA* 1991;265:1403–1408.
9. Talbott EO, Youk AO, McHugh KP, et al. Mortality among the residents of the Three Mile Island accident area: 1979-1992. *Environ Health Perspect* 2000;108:545–552.
10. Pacini F, Vorontsova T, Demidchik EP, et al. Post-Chernobyl thyroid carcinoma in Belarus children and adolescents: comparison with naturally occurring thyroid carcinoma in Italy and France. *J Clin Endocrinol Metab* 1997;82:3563–3569.
11. Ermak G, Figge JJ, Kartel NA, Davies KJA. Genetic aberrations in Chernobyl-related thyroid cancers: implications for possible future nuclear accidents or nuclear attacks. *IUBMB Life* 2005;55:637–641.
12. Han YY, Youk AO, Sasser H, Talbott EO. Cancer incidence among residents of the Three Mile Island accident area: 1982-1995. *Environ Res* 2011;111:1230–1235.
13. Seaberg RM, Eski S, Freeman JL. Influence of previous radiation exposure on pathologic features and clinical outcome in patients with thyroid cancer. *Arch Otolaryngol Head Neck Surg* 2009;135:353–359.
14. Furlan JC, Rosen IB. Prognostic relevance of previous exposure to ionizing radiation in well-differentiated thyroid cancer. *Langenbecks Arch Surg* 2004;389:198–203.
15. Hamatani K, Eguchi H, Ito R, et al. RET/PTC rearrangements preferentially occurred in papillary thyroid cancer among atomic bomb survivors exposed to high radiation dose. *Cancer Res* 2008;68:7176–7182.
16. National Research Council (U.S.). *Committee to Assess Health Risks from Exposure to Low Level of Ionizing Radiation. Health risks from exposure to low levels of ionizing radiation: BEIR VII Phase 2*. Washington, DC: National Academies Press; 2006.
17. Berrington de Gonzalez A, Mahesh M, Kim KP, et al. Projected cancer risks from computed tomographic scans performed in the United States in 2007. *Arch Intern Med* 2009;169:2071–2077.
18. Berkheiser SW. Thyroid cancer and TMI. *Pa Med* 1985;88:50–51.