On 28 March 1979, an accident at Three Mile Island (TMI) nuclear power plant in Pennsylvania produced the release of small quantities of xenon and iodine radioisotopes into the environment. Based on residential proximity and travel into and out of a 5-mile area during the 10 days after the accident, scientists estimated maximum and likely whole-body gamma exposures for each individual. The estimated average likely and maximum gamma doses were 0.09 mSv or 9 mrem and 0.25 mSv or 25 mrem, respectively. The range of likely gamma exposure was estimated to be 1–170 mrem. The average annual effective dose from natural background radiation in the United States is estimated to be approximately 3 mSv (300 mrem) [Committee on the Biological Effects of Ionizing Radiation (BEIR V) 1990]. These exposures were therefore considered minimal.

However, in the late 1970s and 1980s, several investigators reported an increased cancer risk, primarily leukemia, among persons exposed to fallout from nuclear weapons testing (BEIR V 1990). Estimates of the doses were reported to be sufficiently low so that “no detectable increase in risks would have been predicted on the basis of cancer risk estimates from high dose studies” (BEIR V 1990). A possible exception to this would be the dose to the thyroid in some individuals. These studies included residents of Utah and neighboring states downwind of the Nevada test site as well as veterans who participated in the test (Dalager et al. 2000; Rallison et al. 1990).

Because the long-term effects from exposure to low-dose exposure remain a concern, public health officials immediately began to assess whether the brief exposure to low-level radiation emitted from TMI would pose any health risks to the individuals residing near the facility. The Pennsylvania Department of Health (PADOH) created the TMI Population Registry, which was a compilation of individual sociodemographic, medical, occupational, and behavioral information. Over 93% of the population residing within the 5-mile radius of TMI was interviewed and included in this registry.

Four large-scale health end point studies have focused on residents living near the TMI facility. Two investigations (Hatch et al. 1991; Ramaswamy et al. 1991) focused on hospital- or registry-based cancer incidence among residents living within either 5 or 10 miles of the TMI nuclear plant and were carried out during a 6-year interval subsequent to the accident. The remaining two studies (Ramaswamy et al. 1989; Talbott et al. 2000a) assessed the mortality experiences of the residents living within 5 miles of the TMI facility with 6 and 13 years of follow-up, respectively.

In 1985, investigators at Columbia University (Hatch et al. 1991) initiated a study to ascertain cancer cases (based on hospital records) that occurred before and after the TMI accident. The cohort included individuals who resided within a 10-mile radius of the greater TMI area (1979–1985) and included nearly 160,000 persons. The study area was divided into 69 study tracts, and cancer cases within each tract were ascertained for the 1975–1985 period. Cancer rates were adjusted for population density, income, and education, but analyses were limited because no personal risk factor information was collected. For accident emissions, the researchers found no definite effects of exposure on the cancer types and population subgroups considered. No association was seen for leukemia in adults or for childhood cancers. However, elevated risks were noted for non-Hodgkin’s lymphoma relative to accident emissions [odds ratio (OR) = 2.0; 95% confidence interval (CI), 1.2–3.5] as well as for lung cancer (OR = 1.75; 95% CI, 1.47–2.08). Background gamma radiation also showed a slight increase in risk for lung cancer with an OR of 1.1 (95% CI, 0.9–1.4).

In a reanalysis of the Columbia University study, Wing et al. (1997) considered Poisson regression models (for all cancers, lung cancers, and leukemia) to describe the relationship between cancer incidence and accident dose. Models were adjusted for age, sex, time period (preaccident, postaccident), and socioeconomic status. Wing et al. (1997) noted large percent increases in postaccident cancer rates per relative accident dose for all three sites considered (all cancer = 2%, lung cancer = 8.2%, and leukemia = 11.6%). Percent increases were

On 28 March 1979, an accident at Three Mile Island (TMI) nuclear power plant (1979) prompted the Pennsylvania Department of Health to initiate a cohort mortality study in the TMI accident area. This study is significant because of the long follow-up (1979–1998), large cohort size (32,135), and evidence from earlier reports indicating increased cancer risks. Standardized mortality ratios (SMRs) were calculated to assess the mortality experience of the cohort compared with a local population. Relative risk (RR) regression modeling was performed to assess cause-specific mortality associated with radiation-related exposure variables after adjustment for individual smoking and lifestyle factors. Overall cancer mortality in this cohort was similar to the local population. RR modeling showed neither maximum gamma nor likely gamma exposure was a significant predictor of all malignant neoplasms; bronchus, trachea, and lung; or heart disease mortality after adjusting for known confounders. The RR estimates for maximum gamma exposure (≥ 8, 8–19, 20–34, ≥ 35 mrem) in relation to all lymphatic and hematopoietic tissue (LHT) are significantly elevated (RRs = 1.00, 1.16, 2.54, 2.45, respectively) for males and are suggestive of a potential dose–response relationship, although the test for trend was not significant. An upward trend of RRs and SMRs for levels of maximum gamma exposure in relation to breast cancer in females (RRs = 1.00, 1.08, 1.13, 1.31; SMRs = 104.2, 113.2, 117.9) was also noted. Although the surveillance within the TMI cohort provides no consistent evidence that radioactivity released during the nuclear accident has had a significant impact on the overall mortality experience of these residents, several elevations persist, and certain potential dose–response relationships cannot be definitively excluded. Key words: dose–response relationship, epidemiology, ionizing radiation, mortality, neoplasms, nuclear reactors. Environ Health Perspect 111:341–348 (2003). doi:10.1289/ehp.5662 available via http://dx.doi.org/ [Online 30 October 2002]
larger in the models adjusting for socioeconomic status (all cancer = 3.4%, lung = 10.3%, leukemia = 13.9%). The reanalysis also demonstrated an apparent relationship of increased cancer rates across increasing levels of dose, with the trend being most consistent for lung cancer.

The PADoH cancer incidence study gathered information using the original cohort of 35,946 individuals living within a 5-mile radius and enrolled in the TMI Registry shortly after the accident (Ramaswamy et al. 1991). The cohort was followed annually from 1982 to 1988 to determine vital status. Cancer diagnoses were also determined using the newly formed Pennsylvania Cancer Registry (PCR), which commenced operation in 1982. Although vital status can be tracked nationally, cancer registry information is complete only for those who remain within Pennsylvania. Age/sex-adjusted incidence rates for the cohort were compared with corresponding Surveillance, Epidemiology, and End Results (SEER) Program data (National Cancer Institute, Bethesda, MD) and with data for Pennsylvania. Standardized incidence ratios indicated that the 6-year cancer incidence among those exposed to radiation and psychological stress from the accident was not significantly different from the control populations. It was also noted that cancer incidence was not related to the level of accident radiation exposure.

The first mortality study was conducted by the PADoH and used the extensive Pennsylvania Cancer Registry information described above to report on 6 years of mortality follow-up for the 1979–1985 period (Ramaswamy et al. 1989). Age-adjusted standardized mortality ratios (SMRs) were calculated using Pennsylvania death rates (not including the Philadelphia region) in the computation of expected deaths. Multiple regression analyses were performed to determine the probabilities of death from all causes, noncancer causes, and cancer (dependent variables) in relation to radiation dose estimates during the 10 days after the accident. The regression modeling showed that neither estimated maximum nor likely whole-body gamma doses was associated with all causes, noncancer, or total cancer mortality when controlling for confounding factors, including age, sex, race, pre-TMI thyroid disease, pre-TMI cancer diagnosis, pre-TMI radiation treatment, and occupational radiation exposure.

The University of Pittsburgh, in collaboration with the PADoH, conducted the second mortality assessment (Talbott et al. 2000a). This study reported on the 13-year mortality experience of 32,135 members of the TMI cohort (formerly known as the University of Pittsburgh/PADoH cohort) for the 1979–1992 period. Analyses of SMRs using a local comparison population and relative risk (RR) regression modeling were performed to assess overall mortality and specific cancer risks by confounding factors and radiation-related exposure variables. Total mortality was significantly elevated for both white men and women (SMR = 109 and 118, respectively), but overall cancer mortality was similar when compared with the local population (SMR = 100, males; SMR = 101, females). In the RR modeling, there was a significant effect for all lymphatic and hematopoietic tissue (LHT) in males in relation to natural background exposure (p = 0.04). A significant linear trend for female breast cancer risk in relation to increasing levels of TMI-related likely gamma exposure (p = 0.02) was also noted.

Controversy remains surrounding the health effects of low-level radiation (Crawford and Wilson 1996; Crump et al. 1976). To date, no other study has followed prospectively a nonoccupationally exposed cohort of this magnitude. This study was considered noteworthy, as it included a relatively long period of follow-up in a large cohort, and because several earlier reports on the cohort indicated increased cancer risk. Given that most radiosensitive tumors have long latencies (20–30 years), continued follow-up of this cohort was recommended (Talbott et al. 2000a). Additionally, individual exposures were not known but estimated. Several other researchers have indicated that the exposures may have been several orders of magnitude larger than originally estimated (Hatch et al. 1991; Wing and Richardson 2000). The likely gamma whole-body exposures were potentially from 1 to 170 mrem during and shortly after the accident. With the backdrop of this debate and continuing concern over accidental releases to the community, a hard end point prospective mortality study is one of the primary methods to determine true risk to the population. We report here on nearly 20 years of follow-up of the overall and cause-specific mortality of the TMI cohort.

Methods

Study population. The TMI cohort consisted of 32,135 individuals who were initially enrolled in the 1979 TMI census and who met certain inclusion criteria as defined previously (Talbott et al. 2000a). Data collected included individual information on education, occupation, smoking status, residential history, medical history, previous radiation exposure (treatment or occupational), and daily travel in and out of the area during the 10 days after the accident (Goldhaber et al. 1983). The mean age at the time of census registration was 32.9 years compared with a mean age in 1998 of 49.2 years. Approximately 97% of the cohort was white, and 2.8% of the cohort was considered to be of other race. Because of the small percentage of minorities in the TMI cohort (n = 888), all analyses presented are based on white cohort members (n = 31,246) only.

Cohort tracing. The vital status of the TMI cohort was assessed using the TMI Population Registry, the PADoH death certificate files, and the National Death Index (NDI). To maintain the follow-up of the registry, the PADoH, along with the U.S. Postal Service, annually obtained the current addresses of persons in the registry. Names and addresses of all persons in the registry ≥ 16 years of age were sent to the local post office for address verification and update. The registry was updated yearly for address confirmation through 31 December 1996.

The mortality status for the TMI cohort was updated annually through 31 December 1998 by the PADoH. The TMI Population Registry was matched yearly against the death certificate files maintained by the PADoH to identify those TMI cohort members who were previously identified as being deceased within Pennsylvania. The PADoH used the NDI-Plus file maintained by the National Center for Health Statistics for those TMI cohort members who were not identified as deceased solely using the PADoH death certificate files. Because follow-up of the TMI Population Registry was only complete through 31 December 1996, confirmation of alive status could only be verified through that date. Death confirmation was complete through 31 December 1998.

Using this protocol, the PADoH identified 5,516 total deaths in white males and females in the TMI cohort as of 31 December 1998 and determined a cause of death for 5,464 (99.1%), as shown in Table 1. A total of 1,657 deaths were added to the 3,859 deaths identified in the 1992 update. Only 529 individuals were lost to follow-up. All underlying causes of death were coded according using the International Classification of Diseases and Causes of Death revision in effect at time of death.

Exposure estimates. Estimated radiation levels the day of the accident. The individual dose estimates used in this study were modeled by Gur et al. (1983) using the location of

| Table 1. Distribution of Three Mile Island cohort by vital status and sex as of 31 December 1998. |
|-----------------------------------------------|------------------|------------------|
| Vital status                              | Male | Female | Total |
| Alive                                      | 12,516 | 12,985 | 25,501 |
| Deceased                                  | 2,778  | 2,738  | 5,516  |
| Known cause of death                      | 2,752  | 2,712  | 5,464  |
| Unknown cause of death                     | 26     | 26     | 52     |
| Total                                     | 15,538 | 15,707 | 31,246 |

*After 31 December 1996, those not identified as deceased are assumed to be alive.*
residence in relation to TMI (distance and direction) and data on movements in and out of the area during the 10 days after the accident. The inclusion of migration factors creates a more sensitive measure of individual dose than does an exposure assignment based on study tracts as used in other TMI studies (Gur et al. 1983; Talbott et al. 2000b). This information was used along with estimated time-dependent dose distributions to assign likely and maximum dose estimates to those living within a 5-mile radius of TMI (Gur et al. 1983) and was similar to methods developed by Woodard (1979).

Estimated maximum and likely whole-body gamma radiation doses for the TMI cohort are presented in Figures 1 and 2, respectively. The average maximum gamma dose was 24.6 mrem (0.25 mSv) per individual, with approximately 18% of the TMI cohort exposed to over 40 mrem (0.4 mSv) maximum gamma radiation (approximately three chest X-rays). The average likely gamma radiation dose was 10.4 mrem (0.10 mSv), with approximately 13% of the cohort exposed to over 20 mrem (0.20 mSv). Less than 2.1% of the cohort received the highest levels of estimated maximum or likely gamma radiation (Talbott et al. 2000a).

Natural background radiation exposure prior to the TMI accident. Natural environmental background exposure estimates (not including TMI radioactivity releases) were also assigned based on a direct measurements recorded with a scintillation detector and associated instrumentation from a 1976 airborne radon survey (EG&G Inc. 1997). Quartiles of natural background radiation exposure defined as low [5.7–7.2 microrads per hour (µR/hr)], low/medium (7.3–7.9 µR/hr), medium/high (8.0–8.7 µR/hr), and high (8.8–10.5 µR/hr) were originally assigned to individuals residing within a 10-mile radius of TMI for the analysis by Hatch et al. (1991; Hatch and Susser 1990).

Even though background exposure estimates are more ecological in nature, based on area and not individuals, this information was included in the analysis because of the findings of increased lung cancer based on background radiation in a previous report on the TMI cohort (Hatch et al. 1991). Quartiles of exposure were applied to the TMI cohort residing within a 5-mile radius of TMI, using ZIP code of residence (Talbott et al. 2000a).

Natural background radiation doses for the TMI cohort are presented in Figure 3. The highest quartile (8.8–10.5 µR/hr) lies largely outside of the 5-mile radius of the TMI cohort and is not presented (Talbott et al. 2000a). Over three quarters of the individuals within the cohort resided in the lowest exposure areas (32.1% and 44.5% were exposed to low and low/medium doses, respectively).

Statistical analyses. Standard mortality rates. The total and cause-specific mortality experiences of the TMI cohort were examined for the period of 28 March 1979–31 December 1998 using the modified life table technique of the Occupational Cohort Mortality Analysis Program (OCMAP-PLUS) (Marsh et al. 1998). Expected counts of deaths were computed using three counties surrounding the TMI study area (defined as an aggregate of Dauphin, Lancaster, and York counties). The standard mortality rates were also obtained from the Mortality and Population Data System maintained at the University of Pittsburgh (Marsh et al. 2000). The mortality experience for white males and females was also examined by time period (1979–1984, 1985–1989, 1990–1994, and 1995–1998) and age groups (< 15, 15–34, 35–49, 50–69, ≥ 70) and compared with the three-county aggregate.

Excess and deficit mortalities were expressed as SMRs. Statistically significant deviations of the SMR below and above 100, indicating deficit and excess mortality risks, respectively, were identified using Poisson probabilities. No formal probability adjustments were made for the multiple statistical comparisons performed.

Relative risk regression. All RR regression models were based on white cohort members who were ≥ 18 years of age on the day of the accident. This restriction was based on the absence of data on nonwhites in the population and the lack of confounder information in children under the age of 18 years.

RR regression was used to investigate the dependence of the internal cohort rates on the radiation exposure variables for six outcomes of interest including all malignant neoplasms (MN); cancer of the bronchus, trachea, and lung (BTL); cancer of the breast (females only); cancer of LHT; cancer of the central nervous system (CNS); and all heart disease. The four cancer sites were chosen because of their radiosensitive nature (BEIR V 1990). Chronic lymphocytic leukemia and Hodgkin’s disease were excluded from further analysis in the all LHT cancer grouping, as they have rarely been linked to radiation exposure (Ron 1998). These outcomes were analyzed on combinations of the three exposure-related variables and the potential confounding factors.

Natural background radiation was considered as an individual predictor variable as well as a confounding variable in the maximum and likely models.

The RR modeling was performed separately for each of the six time-to-event outcomes, using risk sets constructed from the cohort data file with age as the primary time dimension. A risk set consisted of a “case” (cause-specific outcome) and all other cohort members who were alive and at risk at the age that the case died. To adjust for birth cohort effects, the risk sets were restricted to include only individuals born within 2 years of the corresponding case. The risk sets were constructed using the RISK-SET module of OCMAP-PLUS software (Marsh et al. 1998).

Multiplicative RR models of the form \( \lambda(t) = \lambda_0(t) \exp(x(t)\beta) \) were fit to the internal cohort rates. Mathematical details of the models are given elsewhere (Breslow and Day 1987; Cox 1972, 1975). The conditional logistic regression program in STATA (STATA Corp. 2001) was used to estimate \( \beta \) from the explicitly constructed risk sets.

The potential confounders considered included smoking (never, ever), education at the time of the accident (< 12 years, ≥ 12 years), and natural background radiation (low, low/medium, medium/high). Most of these variables were shown to be related not only to outcome but to the exposures of interest. All models are shown both with and without adjustment for these factors. The radiation-related exposure variables included estimated maximum and likely gamma exposure during

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**Figure 1.** Estimated maximum gamma exposure among TMI residents.

**Figure 2.** Estimated likely gamma exposure among TMI residents.

**Figure 3.** Natural background radiation exposure among TMI residents.
the 10 days after the accident (0–7, 8–20, 21–34, ≥ 35 mrem; 0–2, 3–7, 8–15, ≥ 16 mrem, respectively), and natural background exposure (low, low/medium, and medium/high). The lowest category of each risk factor was used as baseline for the estimated RR and always has a RR value of 1.00. Individual RR estimates were statistically significant if their 95% CIs did not include 1.00. Potential confounders were screened by identifying variables that were individually significant before adding to a model as an adjustment factor. The statistical significance of each main effect was assessed with a likelihood ratio statistic. All tests were done at the 0.05 significance level; no adjustment was made for multiple comparisons.

For the quantitative exposure variables that exhibited a monotonic increasing or decreasing pattern in the parameter estimates, a test for linear trend (based on equally spaced scores) was conducted.

**Results**

**General mortality patterns.** Table 2 presents the distribution of observed and expected deaths and SMRs for selected causes of death by sex. The SMRs are calculated for white males and white females for the entire TMI cohort for the follow-up period 1979–1998 using the three-county comparison group. Over a half-million person-years were accrued by the white males and females of this cohort (white males: 278,695; white females: 282,368).

A total of 2,778 white male deaths were observed, which resulted in statistically significant elevated mortality when compared with the three-county area (SMR = 108.0). There were also significant elevations in deaths from cancer of the respiratory system (SMR = 114.8), cancer of the BTL (SMR = 117.3), all heart disease (SMR = 110.9), and nonmalignant respiratory disease (SMR = 114.6). Other elevations included all MN (SMR = 103.7), breast cancer (SMR = 236.3), leukemia (SMR = 127.4), and all external causes (SMR = 103.4), but none were statistically significant. One new death due to thyroid disease was observed in this update, resulting in an SMR of 48.6.

A total of 2,738 white females deaths led to an all-cause SMR of 116.7, which was statistically significant (Table 2). Mortality due to all heart disease (SMR = 126.7) and nonmalignant respiratory disease (SMR = 132.8) was statistically significantly elevated when compared with the local county comparison. Non–statistically significant elevations were noted for deaths due to cancer of the CNS (SMR = 107.1), breast cancer (SMR = 105.8), leukemia (SMR = 110.8), all LHT (SMR = 122.2), other lymphopoietic cancer (SMR = 123.0), and all external causes (SMR = 106.0). Mortality due to all MN was essentially the same as observed in the three-county area (SMR = 99.8). There were no deaths from thyroid cancer.

Although not shown, a three-county comparison was carried out for white males and white females for age groups < 15, 15–34, 35–49, 50–69, and ≥ 70 years. These results were essentially the same as observed in the three-county area (SMR = 99.8). There were no deaths from thyroid cancer.
were no differences in the all-MN rate among men of any age. In the < 15-year age group, a total of two malignancies were noted over the 20-year period. The SMR was not statistically significant for either males or females in this age group (SMR = 70 and 135 for males and females, respectively). There was one death from Burkett’s lymphoma among males and one death in females from CNS (brain cancer).

For those who were < 18 years of age at the time of the accident, there was a total of 10 deaths from cancer over the 20-year period. Among males, these deaths were from cancer of the BTL, Burkett’s lymphoma, acute lymphoid leukemia, connective tissue cancer, and Hodgkin’s disease. Among females < 18 years of age at the time of the accident, the five cancer deaths included bronchus/lung, brain, ovary, Hodgkin’s disease, and acute myeloid leukemia. The only age-specific cancer site found to be significant was LHT cancer in white females in the 50–69 year age group (SMR = 157.5; p < 0.05). This SMR was based on 28 observed and 17.78 expected cases.

Mortality trends by time period. Tables 3 and 4 present SMRs for mortality trends by time period (all ages) for white males and females in the cohort. There was a significant elevation in all-cause mortality for white males for the earliest time period only, 1979–1984 (SMR = 113.2; p < 0.01). There was also an increase among males for BTL cancer (SMR = 135.3; p < 0.01) for the 1995–1998 period. As shown in Table 4, among white females, the all-cause SMR was elevated for all time intervals (1979–1998). There was also an increase in SMRs in the all heart disease category for the 1979–1994 period only. Additionally, the SMR for LHT was significantly increased in white females in the 1985–1989 period (SMR = 162.8, p < 0.05).

Mortality patterns by exposure variables. Natural background radiation. Tables 5–7 show sex-specific SMRs for natural background exposure. For males in the low and low/medium exposure groups, all-cause mortality was significantly elevated (SMRs = 107.6 and 106.4, respectively). Among white males in the medium/high background group, statistically significant increases were noted for all-cause mortality (SMR = 109.4), cancer of the BTL (SMR = 154.6), and all heart disease (SMR = 116.7). SMRs for all MN were elevated and exhibited an upward trend for increasing levels of background (SMRs = 100.9, 101.6, 112.2); however, none of the individual SMRs were statistically significant.

For white females, SMRs in the low/medium and medium/high background exposure groups were significantly elevated for overall mortality (SMRs = 124.3 and 125.3, p < 0.01). For white females in the low/medium and high exposure categories, statistically significant elevations were seen for all heart disease (SMRs = 140.0 and 137.1, respectively). For the low/medium background group, all LHT cancer showed a statistically significant increase (SMR = 160.3).

Maximum gamma. Sex-specific SMRs for the five cause-specific outcomes of interest are shown in Tables 5–7 for levels of maximum gamma exposure during the 10 days after the accident. The estimated levels were grouped by quartiles of exposure (< 8, 8–20, 21–34, > 35 mrem).

For all-cause mortality, the lowest maximum gamma exposure level (< 8 mrem) exhibited a statistically significant SMR of 120.3 in white males (Table 5). Although other levels were elevated, none were statistically significant, and no trend was noted with increasing levels of exposure. Also in Table 5, white males in the lowest maximum gamma category (< 8 mrem) showed a statistically significant increase in cancer of BTL (SMR = 148.4), as well as a statistically significant elevation in all heart disease (SMR = 132.1). In Table 6, all-cause mortality for white females was statistically significantly elevated for the lowest maximum gamma exposure level (SMR = 139.6) and for the highest level (SMR = 117.5). All levels of maximum gamma exposure were elevated for all-cause mortality.
Table 7. SMRs* for breast cancer in white females, PADOH TMI cohort, 1979–1998.

| Background radiation | Risk factor | OBS | SMR | 95% CI  |
|----------------------|-------------|-----|-----|---------|
| Low                  | Breast cancer | 50  | 120.9 | 89.7–159.4 |
| Low/medium           |              | 44  | 97.5  | 70.8–130.9 |
| Medium/high          |              | 21  | 94.9  | 58.7–145.0 |
| Maximum gamma        | < 8 mrem     | 22  | 87.9  | 55.1–133.1 |
|                      | 8–19 mrem    | 33  | 104.2 | 71.7–146.3 |
|                      | 20–34 mrem   | 30  | 113.2 | 76.4–161.6 |
|                      | ≥ 35 mrem    | 30  | 117.9 | 79.6–168.4 |

Table 8. Summary of RR regression modeling* in white males ≥ 18 years of age, 1979–1998.

| Cause of death | Background RR (95% CI) | Maximum gamma (mrem) RR (95% CI) | Likely gamma (mrem) RR (95% CI) | p-value |
|----------------|------------------------|-----------------------------------|-----------------------------------|---------|
| All MN (OBS = 648) | 1.00 1.01 (0.94–1.11) 1.12 (0.91–1.33) | 1.00 2.46 (2.18–2.82) 2.54 (1.70–3.82) | 1.00 1.01 (0.87–1.16) 1.06 (0.84–1.34) | < 0.0001 |
| All MN* (OBS = 648) | 1.00 1.00 (0.93–1.08) 1.08 (0.96–1.21) | 1.00 1.50 (1.22–1.84) 1.64 (1.29–2.06) | 1.00 0.89 (0.74–1.06) 0.98 (0.78–1.24) | = 0.39 |
| BTL (OBS = 235) | 1.00 0.92 (0.86–0.98) 1.38 (1.08–1.79) | 1.00 1.01 (0.92–1.11) 1.27 (1.03–1.57) | 1.00 0.90 (0.78–1.03) 0.91 (0.78–1.09) | = 0.26 |
| BTL* (OBS = 235) | 1.00 0.90 (0.85–0.96) 1.29 (1.08–1.54) | 1.00 0.88 (0.79–0.97) 0.96 (0.84–1.10) | 1.00 0.89 (0.78–1.02) 0.96 (0.82–1.13) | = 0.30 |
| All LHT (OBS = 53) | 1.00 1.72 (1.51–2.13) 1.43 (1.18–1.72) | 1.00 1.19 (1.06–1.34) 1.34 (1.11–1.62) | 1.00 0.95 (0.82–1.10) 0.97 (0.83–1.14) | = 0.09 |
| All LHT (OBS = 11) | 1.00 0.71 (0.63–0.79) 0.89 (0.75–1.06) | 1.00 1.02 (0.89–1.16) 1.12 (0.97–1.29) | 1.00 0.88 (0.75–1.03) 0.89 (0.74–1.06) | = 0.03 |

Table 9. Summary of RR regression modeling* in white females ≥ 18 years of age, 1979–1998.

| Cause of death | Background RR (95% CI) | Maximum gamma (mrem) RR (95% CI) | Likely gamma (mrem) RR (95% CI) | p-value |
|----------------|------------------------|-----------------------------------|-----------------------------------|---------|
| All MN (OBS = 558) | 1.00 1.12 (0.99–1.26) 1.08 (0.94–1.23) | 1.00 1.01 (0.87–1.16) 1.01 (0.87–1.16) | 1.00 1.00 (0.86–1.14) 1.00 (0.86–1.14) | < 0.0001 |
| All MN* (OBS = 558) | 1.00 1.11 (0.98–1.25) 1.08 (0.95–1.21) | 1.00 1.08 (0.94–1.24) 1.09 (0.94–1.25) | 1.00 1.00 (0.86–1.16) 1.00 (0.86–1.16) | = 0.34 |
| BTL (OBS = 64) | 1.00 0.82 (0.75–0.89) 1.07 (0.90–1.26) | 1.00 1.07 (0.90–1.25) 1.13 (0.95–1.34) | 1.00 0.95 (0.82–1.10) 0.97 (0.83–1.14) | < 0.0001 |
| All LHT (OBS = 71) | 1.00 2.26 (1.26–4.13) 2.12 (1.06–4.22) | 1.00 1.07 (0.66–1.77) 1.16 (0.69–1.92) | 1.00 0.92 (0.74–1.13) 0.93 (0.74–1.13) | < 0.0001 |
| All LHT* (OBS = 71) | 1.00 0.89 (0.73–1.07) 0.96 (0.72–1.32) | 1.00 1.08 (0.91–1.30) 1.18 (0.91–1.54) | 1.00 0.92 (0.74–1.13) 0.93 (0.74–1.13) | < 0.0001 |

For white females in the lowest maximum gamma exposure category (≥ 35 mrem), there was a statistically significant elevation (SMR = 122.8) for all heart disease. For white females in Table 7, there was an increasing trend in SMRs for breast cancer across levels of increasing exposure to maximum gamma, although none of the individual SMRs were statistically significant (SMRs = 87.9, 104.2, 113.2, 117.9).

Likely gamma. Also shown in Tables 5–7 are the sex-specific SMRs for quartiles of likely gamma exposure during the 10 days after the accident (< 3, 3–7, 7–15, ≥ 16 mrem). For the lowest level of likely gamma exposure, all-cause mortality was statistically significantly increased (SMR = 118.5) for white males. Cancer of the BTL (SMR = 143.3) and all heart disease (SMR = 123.5) were both statistically significantly elevated for the lowest level of likely gamma exposure. In the highest likely gamma exposure group (≥ 16 mrem), all-cause mortality was slightly increased and statistically significant (SMR = 108.1). No elevations were noted for CNS cancers in white males.

For white females in the lowest likely gamma exposure category, all causes of death (SMR = 139.7) and all heart disease categories were significantly elevated (SMR = 171.1). For white females in the highest likely gamma exposure category (≥ 16 mrem), statistically significant increases were also noted for all causes of death (SMR = 118.6) as well as all heart disease (SMR = 122.3).

Relative risk regression. Tables 8 and 9 show the results from the RR regression modeling for white males and white females, respectively. Shown for each cause of interest is the estimated RR and associated 95% CI, along with a global p-value and a trend p-value where appropriate. If the confounder (smoking and education) was a significant predictor of risk, multivariate models were fit adjusting for the level of background radiation exposure.

As shown in Table 8, even though background exposure was not a significant predictor of male cancer risk, the RR were slightly elevated (RRs = 1.00, 1.01, 1.12, respectively).

OBS, observed.

*Adjusted by age. **Compared with Pennsylvania three-county comparisons.

# models for max and likely gamma were adjusted for background. Model adjusted by smoking status and educational level. Model adjusted by smoking status. Exact models used due to small numbers of observed deaths.

OBS, observed.

*Risk sets were adjusted to include only individuals born within 2 years of the corresponding case. **Models for max and likely gamma were adjusted for background. Model adjusted by smoking status. Exact models used due to small numbers of observed deaths.

OBS, observed.
Neither maximum gamma nor likely gamma exposures were significant predictors of cancer risk, with most RRs < 1. No significant associations were noted when models for all MN were controlled for both education and smoking. Controlling maximum and likely gamma models for education, smoking, and background radiation did not alter the results. Smoking, education, and background radiation were individual significant predictors of risk for male BTL cancer; after adjustment for these factors, neither maximum nor likely gamma radiation levels were significant predictors of male BTL cancer, as seen in Table 8.

The RR models for all cancer of the LHT in males show no significant potential confounders. Only the model for maximum gamma exposure was statistically significant ($p = 0.05$). The RRs for maximum gamma exposure were elevated, with the suggestion of an increasing trend (RRs = 1.00, 1.16, 2.54, 2.45). However, the trend was nonmonotonic and not statistically significant. The RR models for cancer of the CNS in males were fit using the exact logistic regression module in LogXact because of the small number of cases (Cytel Software 1996). None of the variables were statistically significant predictors of risk, and the CIs on the individual estimates were extremely wide because of data sparseness.

The heart disease RRs for maximum gamma exposures were reduced in males (RRs = 1.00, 0.83, 0.81, 0.85; $p = 0.06$). Because both smoking and education were significant predictors of heart disease ($p < 0.001$), a model for maximum gamma exposure was fit controlling for both factors. After adjustment for these confounders as well as for natural background radiation, maximum gamma radiation was a significant predictor of heart disease in males, although the RRs were still reduced.

As shown in Table 9, the results for all MN for females reveal no statistically significant predictors after control for smoking. The results for cancer of the BTL for females show that smoking was a significant predictor (data not shown). None of the radiation exposure variables were significant. For the LHT models in females, background radiation was a statistically significant predictor of risk ($p = 0.02$). Data sparseness problems ($n = 13$) also existed with the modeling of cancer of the CNS in females. Maximum and likely gamma were not significant predictors of risk for cancer of the CNS, whereas background radiation was of borderline significance ($p = 0.06$).

There were no exposure variables or confounders that were statistically significant for female cancer of the breast. There were elevated RRs for both maximum gamma exposure and likely gamma exposure. In addition, maximum gamma exhibited a non–statistically significant increasing trend with level of exposure (RRs = 1.00, 1.08, 1.13, 1.31) for female cancer of the breast. Maximum and likely gamma exposures both exhibited a statistically significant negative association with all heart disease. These relationships remained statistically significant and negative after additional control for education, smoking, and background ($p = 0.001$).

**Discussion**

This mortality study of the residents living within a 5-mile radius of the TMI facility covers nearly 20 years of follow-up (1979–1998). In this latest update of the TMI cohort, total mortality was significantly elevated for men and women (SMRs = 108.0 and 116.7, respectively) when compared with a local population. The majority of this increase could be attributed to deaths from heart disease, which accounted for 39.9% of the total deaths.

The literature remains controversial with regard to natural background radiation and cancer risk (Archer 1987; Wang et al. 1990). Although the TMI area borders the Reading Prong, an area of granitic rock with higher levels of natural background radiation, the differential in background gamma levels between the low and the medium/high natural background exposure categories is small within the study area, covering a 5-mile radius (Reimer and Gundersen 1989). In contrast to our earlier study (Talbott et al. 2000a), there was no significant effect for all LHT cancers in males in relation to natural background radiation. In females, background radiation was a significant predictor of LHT risk and remained statistically significant after controlling for education ($p = 0.02$). Also noted was an elevation in SMR for LHT among white females 50–69 years of age for the 20-year study period as well as for the overall age group of female whites in the 1985–1989 period ($p < 0.05$). Both Hatch et al. (1991) and our earlier investigation (Talbott et al. 2000a) reported a borderline significant increasing trend in lung cancer risk with increasing natural background radiation in males. This trend was no longer apparent after adjustment for smoking history in the current study.

In the previous study, a nonsignificant elevation in risk was noted for LHT in males in relation to maximum gamma exposure (RRs = 1.00, 1.55, 3.40, 2.71; $p = 0.12$). In the present update, the LHT-maximum gamma exposure RRs are significantly elevated (RRs = 1.00, 1.16, 2.54, 2.45; $p = 0.05$) and indicate a potential dose–response relationship. No such relationship was noted for likely gamma exposure.

Although no overall significant effect of likely gamma exposure to the risk of female breast cancer was noted in our previous study (Talbott et al. 2000a), there was a significant linear trend in the RRs for increasing levels of likely gamma exposure (RR = 1.76, 1.76, and 2.42). In the current investigation, the trend with increasing levels of likely gamma exposure was no longer apparent (RRs = 1.79, 1.45, 1.93), although the RRs remain elevated. Also seen was an upward trend with increasing levels of maximum gamma (RRs = 1.08, 1.13, 1.31; SMRs = 104.2, 113.2, 117.9). As noted previously, several investigations have demonstrated the relationship of ionizing radiation and breast cancer risk (Boice 1996; Darby et al. 1985; Mackenzie 1965; Miller et al. 1989), but all of these studies reflect considerably higher doses of radiation than those estimated in the present study.

Modan et al. (1974), Reftoff et al. (1975), and Harley et al. (1976) studied the relationship of thyroid cancer and CNS tumors with irradiation during childhood for tinea capitis. In the present study of the TMI cohort, we noted only one death from thyroid cancer and a total of nine incident cases of thyroid cancer (reported to the cancer registry through 1996). Moreover, a summary of RR regression modeling for males and females for CNS revealed little in the way of relationships with background, maximum, or likely gamma radiation.

The current mortality follow-up of the TMI cohort has important strengths. With a very long and comprehensive follow-up, the vital status was ascertained for 98.3% of the individuals in the cohort. The 31,246 members of this cohort contributed over a half-million person-years of follow-up, and this large size ensured adequate numbers of events in most disease-specific categories.

Several limitations should also be noted. Small numbers of CNS deaths limited the analyses of this disease-specific category. Data on important confounders (cigarette smoking and education) for individuals < 18 years of age at the time of the accident were lacking. Information was not available from the cohort on possible exposure prior to the TMI incident to high-dose medical X-rays in the 1970s and 1980s, a potential confounder (Peterson et al. 1993). Thyroid cancer incidence is a sensitive indicator of radiation exposure; however, mortality from thyroid cancer, depending on cell type, is relatively low (< 10%), rendering it a poor indicator of exposure. In addition, standardized incidence ratios for the TMI population could not be examined because the completeness of the registry with regard to individuals who may have chosen to leave the area is in question. As there is no national cancer registry, those from the cohort who may have left Pennsylvania would be lost to follow-up, resulting in incomplete ascertainment of cancers. Conversely, for deaths, the NDI-Plus system, supported by the National Center for Health Statistics, provides a national mortality database, making it possible to track individuals with names, social security numbers, and dates.
of birth with a 98% accuracy. Finally, no attempt was made to adjust for the multiple statistical comparisons made in the study.

On balance, the strengths of this study outweigh the weaknesses. Most importantly, the acknowledged limitations do not diminish the findings of this update for white males and females > 18 years of age at the time of the accident, and the overall strengths of the study add to the credibility of the findings in this long-term follow-up.

To help elucidate the mortality experience of this cohort, future research should be directed in four areas:

- The acquisition of personal lifestyle and medical history updates not included in the mortality follow-up. This would include a re-interview of a subset of the population regarding smoking and alcohol consumption, occupational history since the accident, and educational attainment, as well as specific risk factors for each of the cancer sites.

- Continued monitoring of the childhood cohort of TMI. The number of events for the childhood population is small and precludes any analysis.

- Additional investigation of natural background radiation as it relates to the cancer rates in this population. The data used in the analysis of natural background radiation were ecological in nature (i.e., area averages were applied to individuals in the database, as individual dose estimates were not computed). Verification of an exposure gradient within this area on an individual exposure basis would be important to determine if slight increases in SMRs for lymphatic and hematopoietic cancers are due to confounding factors or misclassification bias because of incorrect exposure measures related to the ecological assignment of background radiation levels.

- Continued acquisition of mortality follow-up for the population past the current end date of 31 December 1998. This continued follow-up would be valuable for cancers of longer latency such as lung, thyroid, and possibly cancers of the CNS.

In conclusion, the mortality surveillance of this cohort, with a total of almost 20 years of follow-up, provides no consistent evidence that radioactivity released during the TMI accident (estimated maximum and likely gamma exposure) has had a significant impact on the mortality experience of this cohort through 1998. Slight increases in overall mortality and overall cancer mortality persist. The findings of increased risk of LHT for males for maximum gamma exposure and in females for background gamma are of interest and merit continued surveillance to determine if the trend continues. With the exception of breast cancer risk and all lymphatic and hematopoietic tissue (LHT) and maximum gamma exposure, no apparent trends were seen with any of the radiation exposure variables. The slight trend for female breast cancer and likely gamma exposure seen in the earlier update is no longer evident.

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