Articles

A Reevaluation of Cancer Incidence Near the Three Mile Island Nuclear Plant: The Collision of Evidence and Assumptions

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Previous studies concluded that there was no evidence that the 1979 nuclear accident at Three Mile Island (TMI) affected cancer incidence in the surrounding area; however, there were logical and methodological problems in earlier reports that led us to reconsider data previously collected. A 10-mile area around TMI was divided into 69 study tracts, which were assigned radiation dose estimates based on radiation readings and models of atmospheric dispersion. Incident cancers from 1975 to 1985 were ascertained from hospital records and assigned to study tracts. Associations between accident doses and incidence rates of leukemia, lung cancer, and all cancer were assessed using relative dose estimates calculated by the earlier investigators. Adjustments were made for age, sex, socioeconomic characteristics, and preaccident variation in incidence. Considering a 2-year latency, the estimated percent increase per dose unit ± standard error was 0.020 ± 0.012 for all cancer, 0.082 ± 0.032 for lung cancer, and 0.116 ± 0.067 for leukemia. Adjustment for socioeconomic variables increased the estimates to 0.034 ± 0.013, 0.103 ± 0.035, and 0.139 ± 0.073 for all cancer, lung cancer, and leukemia, respectively. Associations were generally larger considering a 5-year latency, but were based on smaller numbers of cases. Results support the hypothesis that radiation doses are related to increased cancer incidence around TMI. The analysis avoids medical detection bias, but suffers from inaccurate dose classification; therefore, results may underestimate the magnitude of the association between radiation and cancer incidence. These associations would not be expected, based on previous estimates of near-background levels of radiation exposure following the accident. *Key words:* dose–response relationships, ecologic studies, environmental epidemiology, ionizing radiation, methodology, neoplasms, nuclear power. *Environ Health Perspect* 105:52–57 (1997)

The accident at the Three Mile Island (TMI) nuclear facility near Harrisburg, Pennsylvania, which began on 28 March 1979, resulted in environmental releases of ionizing radiation. A presidential commission expressed confidence that the maximum external radiation dose to a person in the general population was less than average annual background levels (about 1 mSv) and that no health effects would be detectable (*1*). Despite these assurances, public concerns about cancer and other health effects persisted, and the TMI Public Health Fund, created and governed by a court order, supported investigators from Columbia University to estimate doses to populations within the 10-mile area and collect information on incident cancers for the years 1975–1985. Analyses of associations between accident doses and cancer incidence were published in 1990 (*2*).

The Columbia investigators "tested *a priori* hypotheses that risks of specified cancers may have been raised by exposure to radiation emanating from the Three Mile Island nuclear power plant" (*2*). Primary hypotheses considered selected leukemias separately by age, childhood cancers, non-Hodgkin's lymphoma, and Hodgkin's disease. Among these endpoints, only non-Hodgkin's lymphoma showed a statistically significant (two-tailed, $p<0.05$) relationship with accident doses. All cancers and lung cancer were also significantly associated with accident doses. However, because of the lack of strong associations for childhood and highly radiosensitive cancers in their analysis, the possibility of uncontrolled confounding, and the estimates of low doses and short follow-up, the authors concluded that observed associations did not reflect an accident effect (*2,3*).

The assumption of Hatch et al. (*3*) that doses were too low to produce observable effects is supported by measurements of radioactivity in air, soil, animals, and food (*1,4*), but also follows from conditions under which doses for the cancer incidence study were estimated (*2*). Radiation doses were calculated under an order from the court governing the TMI Public Health Fund. This order prohibited "upper limit or worst case estimates of releases of radioactivity or population doses . . . [unless] such estimates would lead to a mathematical projection of less than 0.01 health effects" (*5*). The order also specified that "a technical analyst . . . designated by counsel for the Pools [nuclear industry insurers] concur on the nature and scope of the [dosimetry] projects" (*5*). Such legal restrictions suggest that investigators were not in a position to make an unencumbered critical evaluation of radioactive releases. These conditions raise doubts about the assumption that doses were of low magnitude and introduce circularity into the reasoning behind the previous conclusions that accident doses were too low to produce the associations previously reported (*2,3*).

Although the dosimetry model predictions used in the TMI study were shown to be consistent with limited thermoluminescent dosimeter readings at locations outside the boundary of the plant (*2*), important instruments were inoperable at the beginning

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of the accident (*6*): monitors were not disseminated beyond the immediate off-site area until days after the accident began, and there were large angular gaps in placement of dosimeters (*6,7*). Little dosimetric evidence was available for releases that occurred early in the accident and for releases that traveled in plumes with low dispersion (*6,7*). Low estimates of local doses were extrapolated from measurements of radioactive plumes from the accident at a distance of 375 km; however, those estimates were based on extensive assumptions about atmospheric mixing over great distances (*8*). In contrast, there were reports of erythema, hair loss, vomiting, and pet death near TMI at the time of the accident and of excess cancer deaths during 1979–1984 (*9,10*). In 1994–1995, cytogenetic analyses were conducted of 29 persons who lived near TMI and reported erythema, vomiting, diarrhea, and other symptoms at the time of the accident (*11,12*). Because 15 years had elapsed between the accident and the sampling, comparisons of temporal changes in ratios of unstable chromosomal aberrations (counts of dicentrics) to stable aberrations (translocations determined by the method of fluorescence *in situ* hybridization) were used to calibrate the dose estimated for TMI area residents. Ths calibration was based primarily on a group of Chernobyl emergency workers known as liquidators (*12*). Results of the measured ratio for the TMI sample obtained from the calibration curve produced dose estimates in the range of 600–900 mGy (*11,12*).

We present a reanalysis and reinterpretation of data on cancer incidence in relation to the accident at TMI for a number of reasons. First, there is a logical problem with testing a hypothesis that cannot be supported by evidence. Relative risks at the maximum accident dose estimate of 1 mSv cited by Hatch et al. (*2*) would be less than 1.005 according to National Academy of Science estimates of dose response (*13*). Although some research supports relative risk estimates an order of magnitude higher (*14–17*), relative risks would still not be detectable using epidemiological methods (*18*). Pool (*19*) noted that Hatch et al. "already believed that the very low levels of radioactivity released by the accident were unlikely to have a measurable effect on cancer rates." If the premise that maximum doses were no higher than average annual background levels is not open to question, then no positive association could be interpreted as evidence in support of the hypothesis that radiation from the accident led to increased cancer rates.

We take an alternative logical approach in which positive results can be interpretable. Uncertainties and assumptions about absolute dose levels are less problematic in epidemiological analyses of differences in cancer incidence. Such analyses are dependent on the relative classification of doses, as indicated by dispersion modeling, and the ability to rank the populations of small areas from lower to higher doses.

Our reanalysis also addresses methodological problems with the specification of primary hypotheses and analytical methods in the previous work. Analyses of one of the primary outcomes, childhood cancers, failed to consider birth cohorts. As a result, over time, increasing proportions of young children counted as exposed had not been conceived at the time of the accident, thus weakening the sensitivity of analyses of this primary outcome.

A second problem occurred with the primary method of confounder adjustment. Average socioeconomic characteristics of study tracts were used as proxies for unmeasured potential confounders, such as exposure to other carcinogens and susceptibility factors, that are associated with social inequalities (*2*). Socioeconomic measures are weak proxies for the complex characteristics related to cancer rates, and adjustment for confounders in aggregate studies of individual exposures does not necessarily reduce bias (*20*). A third problem occurred because data used to establish baseline incidence rates included a year for which Hatch et al. reported an undercount of incident cases that could bias reported associations (*3*). Finally, in interpreting their results, the authors did not consider the widely recognized difficulty of detecting exposure–disease associations in epidemiological studies that have poor information for classifying exposures.

Instead of specifying primary hypotheses regarding rare cancers with potentially short latency, we consider broad groups of cancers to be of primary interest because ionizing radiation affects most cancer types (*13*) and can play a role in late as well as early stages of the carcinogenic process (*21*). To control for the possibility that study tracts with higher accident doses already showed higher cancer rates before the accident, we use a regression model that includes incidence data for both preaccident and postaccident periods to adjust for preaccident differences in cancer incidence between study tracts. This method allows for control of unmeasured baseline characteristics, a technique that is not often possible in observational studies. For comparison with previous work, we also report analyses that use socioeconomic variables to control for preaccident associations. Additionally, our reanalysis avoids the problem of undercounted cancer cases in the preaccident period.

Materials and Methods

Data collection and measurement techniques were described previously (*2*). Briefly, an area within approximately 10 miles of TMI, including a population of approximately 160,000, was divided into 69 study tracts based on census block boundaries and meteorological considerations. Annual age and sex specific population counts for 1975–1985 were estimated from U.S. census data. Study tract population size varied between 500 and 9,400 and averaged about 2,300. Data on 1980 median family income, percent of high school graduates, and population density were also derived from census data. Incident cancer cases during 1975–1985 were enumerated by review of records from 19 local hospitals and 6 referral hospitals. Incident cases were assigned to study tracts according to their place of residence at the time of diagnosis (*2*). Information on place of residence at the time of the accident was not available.

Our reanalysis employs exactly the same dose estimates used in the original study (*2*). Estimates of gamma radiation doses from nighttime accident releases were assigned to each study tract based on data from radiation monitors within the plant and weather conditions. Although the authors cited estimates that the maximum dose for an individual (as opposed to the average for a study tract) was about 1 mSv, they recognized the uncertainty surrounding the absolute magnitude of doses. In calculating exposure and doses, there were several parameters related to the amount of radioactivity released, degree of dispersion, and length of exposure that made estimates of absolute exposure or dose highly uncertain. Due to this, exposure assessments (*2,6*) left these parameters unspecified and, instead, developed only relative dose estimates. It was determined that an estimate of the ratio of doses between two groups could be made with more certainty than estimates of the absolute dose for either group. Only these ratios, or relative doses, are used in this paper. Doses assigned to study tracts ranged from 0.0 to 1665.73 units.

Computerized data for the reanalyses. For each study tract, the TMI Public Health Fund provided the following: age, sex, and year-specific population size; an estimate of accident dose in relative units; values for percent high school graduates, median income, and population density; and age–sex specific counts for specific groups of cancers. Cancer counts were provided for each year and for time periods analyzed in the previous studies (*2,3*). Years were grouped as follows: 1975 through March 1979, April 1979–1985, 1981–1985, and 1975–1985 (n = 5,493).

Cancer counts for single years did not match counts for grouped years 1981–1985.

Examination of individual case records, also obtained from the TMI Public Health Fund, showed that the discrepancy was due to duplicate records and other inconsistencies. To avoid these data problems, a new file for 1981–1985 was created based on cancer counts summed from annual files.

Cancer incidence rates in 1975 were low because of an undercount of incident cancers during the time that hospital records were initially computerized (*3*). Inclusion of data for this year would lead to an upward bias in the comparison postaccident to preaccident incidence. To avoid this bias, as well as any bias that might result from differential under-ascertainment of cancer cases in areas with different estimated doses, we recalculated rates for the preaccident period by subtracting 1975 cases and populations from the preaccident period. Consequently, in analyses reported below, cancer incidence rates for the preaccident period are based on data for 1976 through March 1979.

Statistical methods. We used Poisson regression (*22*) to describe cancer incidence as a function of age and sex (20 categories), accident dose, time period (postaccident vs. preaccident), and interaction terms for time period with age, sex, and dose. The equation can be written as follows:

$$\ln \lambda(Z,w,x) = Z\alpha + \delta w + \phi x + (Zw)\varphi + \beta(wx) \text{ (Model 1).}$$

In model 1, the natural log of the incidence rate λ is considered in terms of a vector of indicator variables for age and sex (Z), a single indicator variable for the postaccident versus the preaccident time period (w), and radiation dose (x). A vector of parameters, α, is associated with the indicator variables for age and sex in the preaccident period; a parameter, δ, represents the overall change in cancer between the postaccident and preaccident time periods; a parameter, ϕ, represents the linear effect of dose in the preaccident period; a vector of parameter estimates, φ, represents differences in the influence of age and sex between the postaccident and preaccident time periods; and a parameter, β, represents the change in the association between dose and cancer incidence following the accident. The dose term, ϕ, which describes the association between accident doses and preaccident cancer incidence, is used to evaluate whether the baseline cancer incidence in study blocks was under the influence of unmeasured baseline risk factors correlated with the subsequent accident dose gradient. A null value for this regression coefficient would suggest the absence of any such baseline extraneous risk factors. The interaction parameter for dose and period, β, describes the incremental association of dose and cancer incidence after the accident, e.g., adjusted for the association prior to the accident. A null value for the interaction term means that the association between accident dose and cancer incidence is the same in preaccident and postaccident periods.

We created a second set of models, including linear terms for percent high school graduates, median income, and population density. We first examined the variation in cancer incidence across categories of each socioeconomic variable and noted that the assumption of linear relationships between each variable and cancer incidence appeared appropriate. Model 2 therefore adds a vector of terms (V) and linear parameter estimates for the effects of the three socioeconmic variables in the preaccident (γ) and postaccident periods (η) to Model 1:

$$\ln \lambda(Z,w,V,x) = Z\alpha + \delta w + \phi x + V\gamma + (wZ)\varphi + (wV)\eta + \beta(wx) \text{ (Model 2).}$$

Regression coefficients were derived by maximum likelihood procedures using the Generalized Linear Interactive Modelling (GLIM) statistical package (*23*). Although primary findings are presented using this multiplicative relative risk model, we also estimated the dose parameter on an additive relative risk scale to assess the sensitivity of the results to the model form. While a multiplicative relative risk model considers the incidence rate as an exponential function of dose [in simplified form, $\lambda(x) = e^{\beta x}$], an additive relative risk model considers the incidence rate as a function of the excess above the null value of the relative risk [$\lambda(x) = 1 + \beta x$]. The additive relative risk model has been widely used in studies of radiation and cancer (*24*). Additive relative risk coefficients were estimated using the AMFIT routine of the EPICURE statistical package (Hirosoft International, Seattle, WA) (*24*).

Adjusted associations between accident doses and cancer incidence are expressed as a percent, calculated as the regression coefficient for the dose–period interaction term times 100. Standard errors (SEs) of the regression coefficients from the multiplicative model can be multiplied by 1.645 to obtain 90% confidence limits. The change in deviance upon inclusion of the dose term in the model, which indicates the improvement in the fit of the model to the data, is also reported. The change in deviance may be evaluated using a chi-squared distribution with one degree of freedom. For comparison with previous findings, we present ratios of the estimated rate at an accident dose of 597 units compared to zero dose. Hatch et al. (*2*) reported ratios for this difference in dose because it corresponds to the difference between the median dose in the lowest and highest of four categories in their analysis.

Observed cases and ratios of observed to expected cases for each dose category are also presented. Observed counts are fractional because some cancer cases with rural addresses could not be assigned to one study tract with certainty and were apportioned by Hatch et al. (*2*) among adjacent potential tracts of residence according to the relative population sizes of the tracts. Expected counts for the 1981–1985 and 1984–1985 postaccident periods were calculated from the regression models by applying the coefficients for all variables in the model except the dose–time period interaction term to the age and sex specific person–year distribution of study tracts in each dose group during each postaccident period. Thus, the expected count represents the number of cancers that would have occurred after the accident if the study tracts in each dose group had the estimated incidence rates based on that dose group's preaccident incidence level and considering the overall age and sex specific changes in cancer after the accident. For Model 2, the expected count is also based on the socioeconomic level of the study tracts in each dose group. This method achieves internal or direct adjustment.

We analyzed data for all cancers, lung cancer, and leukemia. All cancer is of interest because ionizing radiation is a mutagen related to most, if not all, types of malignancies, because gamma doses were to the whole body, and because radiation-induced lowered immune responses can affect tumors at many sites within a few years of immunosuppression (*21*). Lung cancer is of interest because respiratory exposure to low- or non-penetrating beta or alpha radiation could have occurred from inhalation of radioactive plumes. Despite smaller numbers, we analyzed data for leukemia because it has been found to be particularly radiosensitive and has shown shorter latency periods in other studies (*13*). Other rarer cancers studied previously were not analyzed because the interaction of dose and time period, the primary effect of interest, requires adequate sample size (*25*).

Results

We first replicated Hatch et al.'s analyses (*2,26*), which adjust for age, sex, and socioeconomic variables separately for preaccident and postaccident years. Regression coefficients and SEs were identical, within rounding error, to those in an earlier report (*26*) (Table 1). There is a small positive association between accident dose and cancer incidence during the

Table 1. Comparison of associations of cancer incidence and accident dose by Hatch et al. (*2,26*) and reanalysis

	Hatch et al.	Reanalysis
Time period	Increase (%)[a] ± (SE)	Increase (%) ± SE
Preaccident		
1975–1979	0.004 ± 0.009	0.00442 ± 0.00949
Postaccident		
1981–1985	0.018 ± 0.007	0.01806 ± 0.00699
1984–1985	0.021 ± 0.011	0.02178 ± 0.01108

[a]Percent increase (on a log scale) in cancer rate per relative dose unit adjusted for age, sex, median income, percent high school graduates, and population density.

1975–1979 period, an association of about 0.018%/relative dose unit during the years 1981–1985, and a slightly stronger association (0.021%/unit) with incidence in the years 1984–1985.

Due to under-ascertainment of cancer incidence, further analyses excluded 1975. Counts for 1981–1985 were corrected using annual data. To quantify the impact of these modifications, estimates were recalculated for the time periods 1976–1979 and 1981–1985 as in Table 1. The preaccident association decreased to -0.013%/dose unit, and the association in 1981–1985 increased to 0.020% per unit.

Table 2 presents estimates of the association between all cancer incidence and accident doses adjusted for age, sex, and any preexisting association between cancer incidence and accident doses. Model 1 estimates are adjusted for the preaccident association but not socioeconomic variables, while Model 2 estimates include socioeconomic variables. The association between accident dose and cancer incidence in Model 1 is 0.020%/dose unit in 1981–1985. The association in the 1984–1985 period is 0.023%/unit. These estimates increase to 0.034 and 0.035%, respectively, upon inclusion of socioeconomic variables (Model 2).

Associations of accident dose with lung cancer incidence are larger, varying between about 0.08% and 0.10%/relative dose unit, depending on time period and adjustment for socioeconomic variables (Table 2). Based on Model 1, the ratio of the estimated lung cancer rate at a relative dose of 597 units to the estimated rate at zero dose is 1.85, and the rate ratio for the highest dose study tract, 1665.73, compared to zero, is 3.92 in 1981–1985. Associations of doses with 1976–1979 incidence were 0.002%/dose unit in Model 1 and -0.007%/dose unit in Model 2.

Associations of accident dose with leukemia (Table 2) are larger than those for all cancer and lung cancer; however, the SEs of these estimates are also larger, reflecting, in part, small numbers of cases. As in analyses of the other two outcomes, Model 2 estimates are slightly larger, and associations are larger in the 1984–1985 period than in the 1981–1985 period. In 1981–1985, the ratio of the estimated leukemia rate at a dose of 597 units to the estimated rate at zero dose is 2.0, and the rate ratio comparing the dose value for the tract with the highest dose to zero is 6.91 (Model 1). Prior to the accident, leukemia incidence was negatively associated with dose in both Model 1 (-0.086) and Model 2 (-0.107).

Table 3 presents observed numbers of cases and ratios of observed to expected cases by dose group for each cancer type. Ratios are based on expected numbers of cases calculated from the regression models using all variables except the estimate of the dose-related change in incidence following

Table 2. Association of cancer incidence and accident dose

	Model 1		Model 2	
Cancer type and time periods	Percent increase[a] ± SE	Change in deviance	Percent increase[b] ± SE	Change in deviance
All cancer				
1981–1985	0.020 ± 0.012	2.88	0.034 ± 0.013	6.88
1984–1985	0.023 ± 0.014	2.53	0.035 ± 0.015	5.15
Lung cancer				
1981–1985	0.082 ± 0.032	6.56	0.103 ± 0.035	8.51
1984–1985	0.084 ± 0.035	5.35	0.099 ± 0.039	6.09
Leukemia				
1981–1985	0.116 ± 0.067	2.85	0.139 ± 0.073	3.63
1984–1985	0.133 ± 0.077	2.74	0.147 ± 0.084	3.01

[a]Percent increase (log scale) in postaccident cancer rate per relative dose unit adjusted for age, sex, time period, the interaction of age, sex and period, and the association of doses with preaccident cancer rates. [b]Percent increase (log scale) in cancer rate per relative dose unit adjusted for variables in Model 1, median income, percent high school graduates, population density, and their interactions with time period.

Table 3. Observed cases[a] and ratio of observed to expected cases by dose group for all cancer, lung cancer, and leukemia in 1981–1985 and 1984–1985

	Relative dose group (population-weighted mean dose)								
Cancer type and time period	0 (0)	0–1 (0.005)	1–10 (5.2)	10–50 (28.1)	50–100 (65.3)	100–200 (128.1)	200–400 (268.6)	400–800 (496.1)	800–1666 (1304.1)
All cancer									
1981–1985 Obs	61.9	644.8	140.2	618.9	256.0	583.8	123.6	289.8	112.0
O/E[b]	0.65	0.97	1.12	0.99	1.10	1.03	1.47	1.09	1.23
O/E[c]	0.67	0.94	1.16	1.01	1.16	1.04	1.58	1.13	1.49
1984–1985 Obs	35.1	277.9	59.4	240.8	110.6	241.4	45.1	111.1	52.3
O/E[b]	0.89	1.01	1.15	0.93	1.15	1.04	1.28	1.01	1.41
O/E[c]	0.92	0.97	1.17	0.97	1.22	1.03	1.34	1.06	1.68
Lung cancer									
1981–1985 Obs	6.1	62.6	19.5	95.3	42.1	101.3	19.2	64.3	29.6
O/E[b]	0.43	0.68	1.05	1.07	1.22	1.26	1.66	1.69	2.34
O/E[c]	0.45	0.73	1.12	1.01	1.20	1.31	1.58	1.87	3.11
1984–1985 Obs	4.0	28.1	12.7	36.8	21.4	37.5	8.1	25.1	14.3
O/E[b]	0.66	0.72	1.60	0.97	1.45	1.10	1.62	1.56	2.66
O/E[c]	0.66	0.74	1.61	0.95	1.45	1.11	1.54	1.72	3.24
Leukemia									
1981–1985 Obs	1.4	18.6	2.2	18.4	4.1	15.8	4.6	7.0	3.0
O/E[b]	0.50	0.89	0.54	1.00	0.64	1.05	2.11	1.50	3.64
O/E[c]	0.48	0.89	0.52	1.00	0.63	1.11	2.36	1.69	4.84
1984–1985 Obs	0.4	7.6	1.0	11.0	0.0	6.0	0.0	3.0	2.0
O/E[b]	0.37	0.88	0.62	1.46	—[d]	0.99	—[e]	1.55	6.13
O/E[c]	0.42	0.89	0.71	1.46	—[d]	0.94	—[e]	1.62	7.92

Abbreviations: Obs, observed; O/E, observed to expected cases.
[a]Observed number are fractional because some rural residents were apportioned between possible study tracts of residence.
[b]Expected cases derived from Poisson models including age, sex, period, age and sex by period, and dose (Model 1; see text).
[c]Expected cases derived from Poisson models including Model 1 variables in addition to education, income, population density, and their interactions with period (Model 2; see text).
[d]2.62 expected, Model 1; 2.38 expected, Model 2.
[e]0.89 expected, Model 1; 1.97 expected, Model 2.

the accident. The null value of 1.0 indicates that the study tracts in a particular dose group have the average postaccident cancer incidence level for the entire 10-mile area. There are small numbers of cases and low observed/expected ratios in the zero dose group; however, the influence of data in that category on measures of association (Table 2) is tempered by large numbers in the next lowest category, 0–1, which has a population-weighted mean dose very close to zero (0.005; see Table 3). Ratios tend to increase with dose for each of the cancer types and time periods, with the trends being most consistent for lung cancer. The largest ratios occur for leukemia in the highest dose group, where the values vary between 3.64 and 7.92, depending on the time period and adjustment for socioeconomic variables. Adjustment for socioeconomic variables has the largest influence on ratios at the highest doses, where the number of expected cases in the postaccident period is smaller when taking socioeconomic variables into account.

Associations between accident dose and cancer incidence were also calculated using an additive relative risk model. Adjusted percent increases per dose unit (± SE) on an additive relative risk scale for 1981–1985 were 0.026 ± 0.014 for all cancer and 0.171 ± 0.033 for lung cancer. Deviance values for these models were 2.84 and 7.49, respectively. The small number of leukemia cases and the large increase in the ratio of observed to expected cases in the highest dose group (Table 3) produced an additive relative risk estimate for leukemia similar to the multiplicative estimate, but the additive estimate was sensitive to the convergence criterion for the likelihood estimation and showed poor correspondence with the observed/expected ratio in the highest dose group.

Discussion

Accident doses were positively associated with cancer incidence. Associations were largest for leukemia, intermediate for lung cancer, and smallest for all cancers combined; larger for longer than for shorter latency; and larger with adjustment for socioeconomic variables. Similar results were obtained using additive and multiplicative relative risk regression models. Larger associations for leukemia than for all cancers might be expected based on studies showing a higher radiosensitivity and shorter latency of leukemia than solid tumors (*13*).

Uncertainties regarding dose raise questions about the extent to which radioactive gases or particles with low or no penetration (alpha and beta radiation) accompanied the external penetrating (gamma) radiation exposures. Inhaled radionuclide contamination could differentially impact lung cancers, which show a clear dose-related increase in this study; however, the 6.75 year follow-up period is short for the observation of radiation-related lung cancer. Although stronger dose–response associations are often observed under latency assumptions of 10 or more years, some studies have found little evidence of latency effects for lung cancer (*17,27*), and elevated risks for uranium miners exposed to radon have been observed to begin 4–5 years since exposure (*28,29*). This is consistent with the potential of ionizing radiation to act at late as well as early stages in the carcinogenic process. At high doses, penetrating whole body irradiation causes immunosupression (*30*); lung cancer and other solid tumors have been observed to occur in excess within 1 to 5 years of immune suppression (*21*).

Results for lung cancer differ from those reported previously (*2*). Our estimate of the relative risk of lung cancer for an accident dose of 597 units, 1.85, is larger than the estimate of 1.3 by Hatch et al. (*2*) which is the only value in their paper that is described as adjusted for preaccident incidence (*2*). Regardless of adjustment for socioeconomic variables, we did not find lung cancer to be associated with accident dose in the preaccident period, as Hatch et al. reported (*2*). This difference in results is explained entirely by the exclusion in our analysis of data for 1975, the year with an undercount of incident cases.

Larger associations of accident dose with all cancer in models including socioeconomic variables were primarily due to the education variable, which was positively associated with accident dose. Education was also positively associated with all cancer incidence in the preaccident period. This adjustment could decrease bias if there were changes in postaccident incidence or detection, related to average education levels of study blocks, that were not controlled by adjustment for baseline incidence. For example, cancer detection may have been poorer prior to the accident in study areas with lower education than in areas with higher education. In that case, increases in detection after the accident could have been greater in study blocks with lower education levels, adjustment would be warranted, and the larger estimates of accident effect would be less biased. However, given concerns about ecological adjustment for confounding (*21*), we have emphasized the smaller estimates of the accident effect that are unadjusted for socioeconomic variables.

In studies of changing disease rates following a well-publicized event, heightened awareness of symptoms and surveillance by medical personnel can lead to increases in disease due to detection bias. However, if the relationship of accident dose to cancer increases was an artifact of changes in detection bias, changes in detection would have had to be coincident with plume paths from the accident. Because the dose estimates do not follow simple proximity or line-of-sight associations with TMI (*2*), in which case doses could have been associated with motivation to seek medical care for cancer symptoms more promptly, detection bias should not affect the analyses reported here. Furthermore, Hatch et al. (*3*) compared proportions of preaccident and postaccident cancers that were diagnosed at local, regional, and distant stages and found no consistent increases in early stage diagnoses.

Apart from the question of the accuracy of estimates of the magnitude of radiation exposures, poor classification of relative exposures within the 10-mile area detracts from the ability of the study to detect associations. Assignment of residence based on date of diagnosis, rather than following groups based on residence at time of the accident, leads to mixing of exposed and unexposed populations and dilution of incidence rate differences between dose groups. This bias would increase with time; however, even residence at time of the accident is only a proxy measure, because it does not account for time away from the home, location inside or outside, and other factors influencing individual radiation doses. Although the possibility of biases that would result in overestimation of effects cannot be excluded, the nature of the accident itself, and design of the original study suggest that measurement and data inadequacies, along with short follow-up, would be expected to result in underestimation of dose–effect associations.

This analysis shows that cancer incidence, specifically lung cancer and leukemia, increased more following the TMI accident in areas estimated to have been in the pathway of radioactive plumes than in other areas. The observation of a change in association is analytically powerful because it shows that the effect is temporally associated with the hypothesized causal event. Causal interpretation is further strengthened by the observation that the dose pattern resulting from plume travel is unlike many behavioral, occupational, and environmental exposures which are related in a complex biosocial process that makes them interdependent and potentially influenced by medical care and detection. Rather, higher and lower dose study tracts

are all within 10 miles of the source and differ in exposure only as a function of weather conditions at the time of the accident. In contrast to concerns about confounding and measurement errors that can lead to overestimation of effects in some types of epidemiological studies, these problems would lead to difficulties in detecting real effects and conservative underestimates of what would be found with better measurement and classification.

Hatch et al. (*2,3*) found some positive associations in their analyses of these data, but reasoned that the evidence did not suggest that the TMI accident affected cancer rates in the surrounding population. It is therefore interesting to note that situations in which positive results have been interpreted as negative due to a collision of evidence and assumptions have been reported previously (*31*). According to Rose (*32*), a participant in an inquiry into the relationship of childhood cancer to environmental exposures from the Sellafield, United Kingdom, nuclear facility,

> We were given information (which, it later transpired, was incorrect) of the total radioactive emissions from the plant, but the exposure levels of the children were a matter of speculation. The radiation experts on the committee calculated "best estimates" and they concluded, on theoretical grounds, that these could not have caused any major excess risk: "It couldn't have happened, so it didn't happen."

A major difference between our study and previous work is that we find support for continued surveillance of cancer and possibly other health effects in relation to the TMI accident, whereas previous authors have not suggested that further study is necessary (*2,3*). The potentially long lag between radiation exposure and cancer diagnosis suggests that studies of cancer incidence in the area should be continued past 1985.

Environmental and occupational radiation exposures from operating nuclear power plants, as well as from retired facilities and disposal sites, are of current concern, as is the role of nuclear power in overall energy policy. Public concerns about concealment of past radiation hazards have been increased by recent disclosures of environmental releases from government nuclear facilities and clinical human experimentation (*33–35*). Given the societal significance of the 1979 accident at TMI and the currency of debates around the safety of nuclear power, further critical examination of the human and environmental impacts of the accident at TMI is of great importance.

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