RADIATION RESEARCH **112,** 381–390 (1987)

Altitude, Radiation, and Mortality from Cancer and Heart Disease

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WEINBERG, C. R., BROWN, K. G. AND HOEL, D. G. Altitude, Radiation, and Mortality from Cancer and Heart Disease. *Radiat. Res.* **112,** 381–390 (1987).

The variation in background radiation levels is an important source of information for estimating human risks associated with low-level exposure to ionizing radiation. Several studies conducted in the United States, correlating mortality rates for cancer with estimated background radiation levels, found an unexpected inverse relationship. Such results have been interpreted as suggesting that low levels of ionizing radiation may actually confer some benefit. An environmental factor strongly correlated with background radiation is altitude. Since there are important physiological adaptations associated with breathing thinner air, such changes may themselves influence risk. We therefore fit models that simultaneously incorporated altitude and background radiation as predictors of mortality. The negative correlations with background radiation seen for mortality from arteriosclerotic heart disease and cancers of the lung, the intestine, and the breast disappeared or became positive once altitude was included in the models. By contrast, the significant negative correlations with altitude persisted with adjustment for radiation. Interpretation of these results is problematic, but recent evidence implicating reactive forms of oxygen in carcinogenesis and atherosclerosis may be relevant. We conclude that the cancer correlational studies carried out in the United States using vital statistics data do not in themselves demonstrate a lack of carcinogenic effect of low radiation levels, and that reduced oxygen pressure of inspired air may be protective against certain causes of death.

INTRODUCTION

Observational, "ecological" studies involving large populations offer the only practical approach to studying effects on humans of chronic exposure to very low levels of ionizing radiation. Such studies have generally reported either no effect (*1–4*), in

0033-7587/87 $3.00

the case of leukemia, or an apparent protective effect of radiation, in that negative correlations between background radiation levels and mortality from certain cancers are found (*1, 5, 6*).

These unexpected negative correlations have been interpreted (*6–8*) as suggesting that low doses of radiation are beneficial, perhaps by stimulating natural defense and repair mechanisms. This kind of phenomenon, where a harmful exposure becomes helpful at low doses, has been termed "hormesis" (*9*). A reversal in the dose–response curve at low doses would have obvious implications for the problem of low dose extrapolation, and thus the claim of hormesis for ionizing radiation has provoked interest and controversy.

An environmental factor strongly related to background radiation is altitude. This is because the flux of cosmic radiation increases as atmospheric shielding thins with increasing altitude. While high altitude residents are exposed to higher levels of background radiation, the air they breathe is also different. The reduced availability of oxygen at higher altitudes stimulates a remarkable variety of physiological adaptations (*10, 11*). The apparent negative correlations between mortality and background radiation might thus be due to confounding with physiologic effects of other factors related to altitude. We therefore investigated models for mortality that simultaneously incorporated both altitude and background radiation.

MATERIALS AND METHODS

All cities listed in the United States Metropolitan Mortality report for 1959–1961 (*12*) with altitude higher than 900 feet were identified. Other cities at lower altitudes were added to make a total of 80 cities with a range of altitude and background radiation adequate for study. Selection was unsystematic, with the only requirement being availability of population-weighted altitude and radiation estimates (*13*). Salt Lake City was excluded because its size would give it strong influence on the regressions and because its population was already known to have low mortality, most likely for idiosyncratic reasons related to the prevailing Mormon lifestyle. All selected metropolitan areas had population exceeding 58,000, the median population being 130,000. Population data were based on the 1960 census for white males and females.

Eight causes of death were studied, as categorized according to the International Statistical Classification of Diseases, Injuries, and Causes of Death (ISC, World Health Organization, Geneva, 1957): arteriosclerotic heart disease (ISC 420), nonarteriosclerotic heart disease (ISC 410–416, 421, 422, 430–434, 440–443), cancer of the trachea, bronchus, and lung (ISC 162–163), stomach cancer (ISC 151), cancer of the small or large intestine (ISC 152–153.8), female breast cancer (ISC 170), multiple myeloma (ICD 203 except 203.1), and leukemia (ISC 204). Age-adjusted mortality rates (direct method) for causes other than multiple myeloma were available from the United States Metropolitan Mortality report for 1959–1961 (*12*). Rates for multiple myeloma had to be computed by taking population-weighted averages of rates for counties within the respective SMSA regions, using the 1960–1969 rates from U.S. Cancer Mortality Rates and Trends 1950–1979 (*14*).

Sex- and cause-specific mortality rates (as deaths per 100,000) for whites were regressed against predictors including radiation and altitude, with adjustment for population and percentage foreign-born. The latter covariates were presumed to serve as rough surrogates for industrialization/urbanization and ethnicity. Background radiation levels in millirems per year were taken from the work of Oakley (*13*), partitioned into three sources: cosmic neutron, cosmic nonneutron, and terrestrial. The data can be made available to the reader upon request. Since there is reason to suspect that high-LET forms of radiation like neutrons have an enhanced relative biological effect at low doses (*15*), we analyzed the data with total background radiation and also with neutron and nonneutron components entered separately.

The linear regressions were weighted by the method of Pocock *et al.* (*16*), which partitions the variance into a component due to binomial variability and a component due to city-to-city variability, i.e., the aggregate of all factors not included in the model. The binomial component is a simple function of the city-

TABLE I

Adjusted Coefficients (Standard Error) for Selected Models[a]

Cause of death	*Sex*	*Total radiation (mrems)*	*Total radiation*	*Altitude (1000s ft)*	*Neutron radiation*	*Nonneutron radiation*	*Altitude*
Arteriosclerotic heart disease	M	−1.23***	−0.23	−15.0**	+27.2*	—	−74.1**
		(0.34)	(0.50)	(5.8)	(13.0)		(27.4)
	F	−0.44*	+0.42	−13.0***	+20.3**	—	−51.9**
		(0.21)	(0.30)	(3.5)	(7.8)		(16.5)
Lung cancer	M	−0.20***	−0.04	−2.4**	+2.8	—	−8.8*
		(0.04)	(0.06)	(0.78)	(1.7)		(3.7)
	F	—	—	−0.3*	—	—	−0.3*
				(0.13)			(0.13)
Intestinal cancer	M	−0.07*	+0.01	−1.3**	—	—	−1.1***
		(0.03)	(0.04)	(0.46)			(0.30)
	F	−0.04*	+0.04	−1.2**	+1.7*	—	−4.5**
		(0.02)	(0.03)	(0.37)	(0.81)		(1.7)
Breast cancer	F	−0.01	+0.72*	−1.4**	+2.0*	+0.06	−5.3**
		(0.02)	(0.32)	(0.44)	(0.97)	(0.03)	(2.0)
Leukemia	M	−0.01	−0.00	−0.14	+1.1*	—	−2.4*
		(0.01)	(0.02)	(0.23)	(0.50)		(1.1)

[a] A quality factor of 8 is assumed for neutron radiation.

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.001$.

specific mortality rate and the population size, while the extrabinomial component allows the underlying binomial rates to vary randomly (following a 0-mean Gaussian distribution) among cities after predictor variables have been taken into account. Significance levels cited are based on ratios of estimated coefficients to their estimated standard errors, and *P* values reported are two-sided in all cases.

Since oxygen pressure of inspired air is a (nonlinear) function of altitude, one might wish to consider oxygen pressure in place of altitude in the regression models. Unfortunately, the relationship between altitude and oxygen pressure is almost perfectly linear over the range of altitudes included in our sample ($r > 0.999$). Thus linear models that incorporate altitude are statistically indistinguishable from those that incorporate oxygen. Somewhat arbitrarily then, the results will be described in terms of altitude rather than oxygen pressure.

RESULTS

Neither altitude nor radiation appeared to be related to mortality from stomach cancer or nonarteriosclerotic heart disease. The same was true for multiple myeloma, although in this case the extrabinomial variance was very low for both males (0.1) and females (0.0), suggesting there may be little or no variation to be explained by environmental factors.

Results for the other causes of death are summarized in Table I. Unadjusted correlations between total background radiation and mortality were all negative, and this was highly statistically significant for lung cancer and arteriosclerotic heart disease.

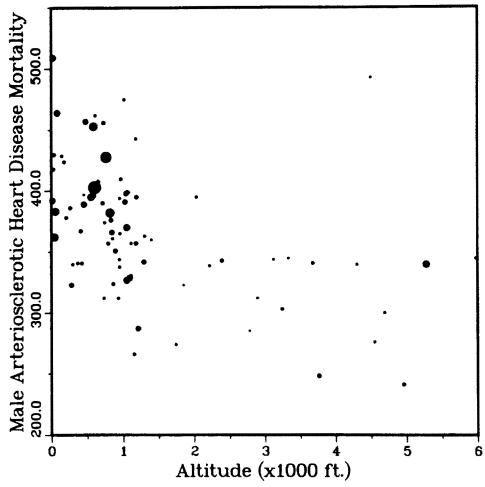

FIG. 1. Age-adjusted male arteriosclerotic heart disease mortality per 100,000, plotted against altitude in thousands of feet, for 80 U.S. cities. The dot area is proportional to the population size, so that the larger cities, weighted according to their population size in the analysis, will be given commensurate prominence to the eye.

However, mortality was also negatively related to altitude. As an example, the mortality from arteriosclerotic heart disease for males is plotted against altitude in Fig. 1. When altitude was included in the models the coefficient for radiation became positive or indistinguishable from 0 in every case, while the altitude coefficient remained significantly negative, even with adjustment for radiation, except in the case of leukemia. When background radiation was partitioned into neutron and nonneutron components, the coefficient for neutron radiation was in most cases significantly positive, while that for nonneutron radiation was indistinguishable from 0, except in the case of breast cancer, where it, too, was positive.

Examination of standardized residuals from these models revealed no evidence of spatial correlation, that is, there was overall no tendency for cities close together to have more similar deviations from the model than cities far apart. Thus independence among cities, as needed in the analysis, appears to have been a reasonable assumption.

We estimated the extent to which the extrabinomial variability that remained after adjustment for confounders could be accounted for by the altitude and radiation terms shown in Table I. For male and female arteriosclerotic heart disease, male and female lung cancer, male and female intestinal cancer, female breast cancer, and male leukemia, the estimated percentages of residual extrabinomial variability "explained" by radiation and altitude were 29, 27, 42, 8, 24, 40, 41, and 35%, respectively. This suggests other environmental factors may be related to city-to-city variation in mortality from these causes. In fact the larger standardized residuals from some of the covariate-adjusted models including altitude and radiation appeared to be nonrandom geographically. In particular, cities with markedly higher than fitted mortality from arteriosclerotic heart disease tended to be in the northeast, while those

with lower than expected mortality were south central. Cities with higher than expected lung cancer mortality tended to be south central while those with lower than expected mortality were north central. There were no discernible geographical patterns in the residuals from the fits to intestinal cancer mortality or leukemia mortality. The largest excesses in breast cancer mortality were in Montana, Illinois, Ohio, and Pennsylvania, while lower than predicted breast cancer mortality was noted in Oklahoma and Tennessee.

DISCUSSION

Unfortunately, aside from the usual caution that association does not imply causality, three fundamental problems complicate the interpretation of our findings: possible confounding with unmeasured factors, measurement errors in establishing background radiation levels, and cofunctionality of predictors. These will be discussed in turn.

1. Confounding factors. Many factors may produce variation in mortality rates among U.S. cities. Such factors include smoking patterns, demographic characteristics (ethnicity, migration patterns, availability of tertiary care medical facilities), and environmental factors, such as variations among cities in snow cover, building materials, insulation, radon levels, and water quality. Such data, which to be relevant to 1960 mortality would have to reflect exposures experienced in the 1950s, are simply not available. We have included as covariates population and percentage foreign-born to adjust at least partially for urban crowding and demographic factors. But the possibility that altitude and background radiation are behaving in part as surrogates for unmeasured but associated factors means that our conclusions are necessarily tentative.

2. Dose determination. While population-weighted altitude is known, the measurement of background radiation levels was crude. The contribution of fallout from atmospheric testing in the 1950s has been removed (*13*). Similarly, the contribution of radiologic diagnostic procedures has been neglected. Finally, many of the metropolitan areas in our sample had no direct measurements available of terrestrial background levels since they did not lie in regions included in the Aerial Radiological Measurement Surveys, and such cities were assigned one of two levels (*13*), depending on whether or not they were located in the eastern coastal plain.

3. Cofunctionality of predictors. Characterizing the relationship between mortality and neutron radiation and altitude is complicated by the fact that neutron levels are a log-linear function of altitude. This means that the models in Table I including both altitude and neutron "effects" could alternatively be considered to be nonlinear functions of altitude alone or even of neutron radiation alone.

With these caveats in mind, the patterns we have noted are consistent with a protective effect associated with reduced oxygen pressure of inspired air and a deleterious effect associated with exposure to low levels of neutron radiation. No effect of non-neutron radiation was evident, except possibly on mortality from breast cancer.

The apparent neutron radiation effect we see is puzzling, especially since the coefficients shown in Table I, if taken literally as deaths per 100,000 per mrem, are too large by at least an order of magnitude, based on BEIR (*17*) projections of risk. How-

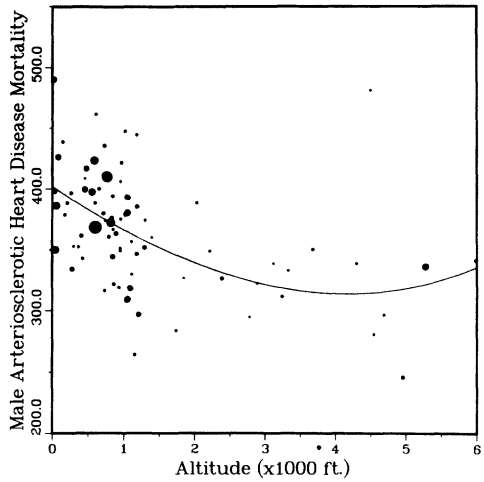

FIG. 2. The fitted linear model involving altitude and neutron radiation (as in Table I) can alternatively be expressed as a nonlinear function of altitude alone. This shows the fit for male arteriosclerotic heart disease mortality. Data points have here been adjusted to the median percentage foreign-born.

ever, the A-bomb dosimetry has now been revised and effects of the neutron component of the exposure are being reassessed. Moreover, extrapolation from the acute, relatively high exposures experienced in Hiroshima and Nagasaki to chronic, low-level exposure is problematic. Based on rodent studies, the effect per rad of a given total dose may decrease with fractionation of dose for γ radiation but may increase with fractionation for neutron radiation (*18, 19*), suggesting that linear extrapolation from the Japan data may tend to overestimate low-dose effects of γ but underestimate low-dose effects of neutron radiation. Even so, the coefficients shown seem large. Another consideration is that, while the energy spectrum for cosmic neutron radiation is known to be quite constant across altitudes in the lower atmosphere (*20*), there is some uncertainty associated with the choice of the neutron quality factor (*21*). This suggests that the numeric estimates provided in Table I should not be taken overly literally. However, resetting the quality factor would have no effect on the nonneutron coefficients, or on the reported significance levels, the only effect being to multiply each neutron coefficient and standard error by an appropriate factor.

One plausible interpretation of the neutron radiation "effects" shown is that they appear in these models only because there is curvature in the relation between mortality and altitude for some of these specific causes. This interpretation is particularly tempting in the case of arteriosclerotic heart disease, since we know of no data linking radiation to arteriosclerosis. Since the neutron dose can be expressed as a function of altitude, the models given in Table I can each be written in terms of the covariates and altitude alone (with no radiation term). The resulting fitted curves corresponding to covariate-adjusted male and female arteriosclerotic heart disease mortality and male lung cancer mortality are shown in Figs. 2, 3, and 4, respectively.

Our negative findings with regard to nonneutron background are consistent with most other studies comparing regions with similar altitudes but different levels of

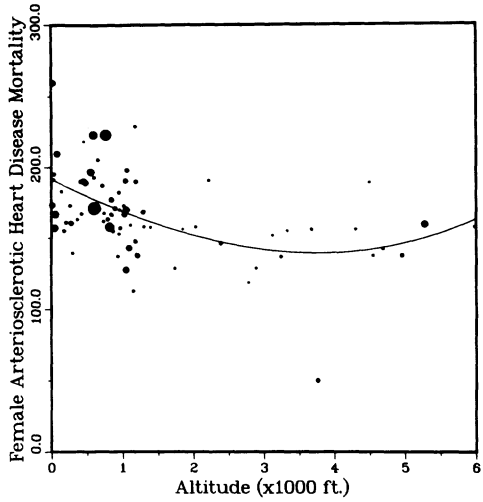

FIG. 3. This shows the fit for female arteriosclerotic heart disease mortality. Data points have here been adjusted to the median percentage foreign-born.

background radiation (*22–26*). Again this could be related to sublinearity of dose response at chronic low doses for γ radiation.

The possibility that factors associated with high altitude protect against cancer is consistent with findings from other ecological studies. Burton (*27*) compared age-specific world-wide cancer incidence and mortality rates with altitude. Comparing the six locations at highest altitude with the six locations at lowest altitude, he found

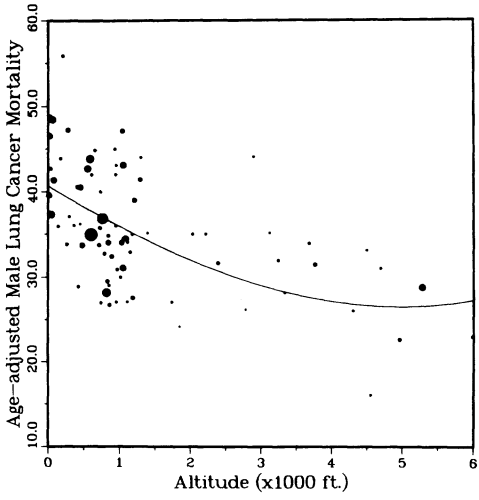

FIG. 4. This shows the fit for male lung cancer mortality. Data points have here been adjusted to the median population size.

that both incidence and mortality for cancer were similar up to about age 60 but diverged markedly thereafter in the older age groups where most cancer mortality is seen. Overall, cancer mortality was reduced at the higher altitudes. In the United States, comparison of mortality rates for 34 specific cancer sites for selected low- and high-altitude counties (*28*), with adjustment for confounding by industrialization, urbanization, and ethnicity, showed lower rates at higher altitudes, with the contrast being strongest for cancers of the tongue and mouth, esophagus, larynx, and lung and for melanoma.

The decline in mortality from cardiovascular disease with altitude has also been noted before (*29–31*). Adaptation to high-altitude hypoxia is associated with increased production of myoglobin and increased vascularization of heart muscle and (based on studies conducted by WHO (*32*) in Lima, Peru, and La Paz, Bolovia) the coronary blood flow and oxygen consumption of the heart are reduced in the native highlander, suggesting increased cardiac efficiency of oxygen utilization. In rats adapted to simulated high-altitude hypoxia, both the mortality following coronary artery ligation and the extent of the resulting necrosis were markedly reduced (*33*).

There are many physiological changes associated with adaptation to breathing thinner air (*11*). To the extent that such adaptations are incomplete, tissues will have less access to oxygen, especially tissues which are directly exposed to oxygen, such as the lung and oropharyngeal cavity. Byers (*34*), noting a predilection of lung cancer for the upper lobes, suggested that this may be related to better oxygenation of the upper lobes, and that reduced tissue availability of oxygen may also explain the epidemiologic observation that high altitude is associated with reduced mortality from lung cancer.

Evidence that oxygen may produce toxic and mutagenic effects, even at physiologic levels (*35–38*), may be relevant. Reactive forms of oxygen may play an important role in a variety of disease processes, including carcinogenesis and the development of arteriosclerosis, as was recently reviewed by Pryor (*39*). Finally, oxygen has long been recognized as a potent radiosensitizer, which suggests that part of the altitude effect may reflect synergy between oxygen and background radiation or between oxygen and other carcinogenic exposures.

In conclusion, in ecologic studies relating mortality from malignancies and heart disease to levels of background radiation, it is improper to assume that altitude is physiologically unimportant. When we adjust linearly for altitude, the negative correlations between mortality and background radiation all disappear or become positive. By contrast, in every such case the negative correlations with altitude hold up under simultaneous adjustment for background radiation. Our results are consistent with a protective effect of reduced oxygen pressure of inspired air, a deleterious effect of neutron radiation, and no effect of nonneutron radiation. We see no support here for the claim that ionizing radiation is beneficial at low doses.

RECEIVED: April 29, 1987; REVISED: June 16, 1987

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