Some Pitfalls in Studies of Low-Dose Ionizing Radiation: The Healthy Dose Effect, Significance Questing, and Exposure Reductionism

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Epidemiological studies of human health effects of low-dose ionizing radiation exposures may suffer from a number of methodological pitfalls. Three of these pitfalls—the healthy dose effect, significance questing, and exposure reductionism—are discussed and illustrated with examples from the Portsmouth Naval Shipyard workers study. [PSRQ 1992;2:33–39]

The relationship between human health effects and exposures to low doses of ionizing radiation is a topic that continues to be vigorously debated. Epidemiological studies of exposed populations often produce conflicting results, even when the same population is studied [1,2], that add to, rather than decrease, the level of controversy. For example, in 1978, Najarian and Colton [3] published the results of a proportional mortality analysis of Portsmouth Naval Shipyard workers in which a fivefold excess of leukemia and a twofold excess of all cancers combined were reported for workers who had received low doses of ionizing radiation. This was followed by a report by Rinsky and colleagues [4] that concluded that no excesses were present for all causes of death, all cancers, lymphatic and hematopoietic cancers combined, or leukemia. The discrepancy between these two investigations was later attributed to the presence of selection bias, measurement bias, and misclassification in the proportional mortality study [5]. More recently, a case control study of these same shipyard workers reported risk ratios of 1.4 for all leukemias combined (95% confidence limits [CL] = 0.4, 4.7) and 2.2 for myeloid leukemia (95% CL = 0.5, 10.2) among workers whose cumulative doses were at least 10 millisieverts (mSv) (1 rem) [6]. These findings were largely dismissed on the basis that they were not statistically significant, even though a twofold increase in the relative risk for myeloid leukemia was observed. The use of different study designs would account for some of the differences in results that

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colleagues [4]. The standardized mortality ratios for nonradiation workers are 98 for all causes of death, 100 for all cancers, and 106 for leukemia, when all of these estimates should be considerably less than 100 if the healthy worker effect were operative. On the other hand, the standardized mortality ratios for workers with cumulative doses of at least 0.01 mSv are 78 for all causes of death, 92 for all cancers, and 84 for leukemia. These ratios suggest that the healthy worker effect was operative for the subcohort of badged workers but not for the subcohort of nonradiation workers [4].

It is well known among epidemiologists that selection of an appropriate control group (reference population) is crucial to obtaining valid risk estimates. At times, major debates regarding epidemiological findings have focused on the comparison group that was used (e.g., exogenous estrogens and endometrial cancer). Despite the large literature that exists describing the pitfalls of the healthy worker effect as the result of the use of a general population reference, such comparison groups continue to be routinely used in epidemiological studies of employed populations. At times, such comparisons may be required; however, whenever possible, the use of properly defined internal controls may be substituted. Care must be taken, however, that an internal healthy worker effect, or healthy dose effect in the case of radiation workers, does not characterize the study population and continue to bias study results toward the null value.

EXPOSURE REDUCTIONISM

Misclassifying exposed study subjects as unexposed or unexposed subjects as exposed will result in the risk being underestimated in a cohort study if the misclassification is nondifferential [12]. The Portsmouth Naval Shipyard workers report [4,7] used seven dose categories, four of which were composed of doses below 10 mSv. The use of so many dose categories was unwarranted in light of the small number of workers with leukemia that were observed at these dose levels. (Only three cases occurred among those workers with cumulative doses of less than 10 mSv.) Also, such a fine categorization of lifetime cumulative doses assumes a level of accuracy in dose estimation that is open to question. The current lower limit of detection for thin-layer dosimetry (TLD) badges which have been in use since the 1970s is about 0.1 mSv (10 mrem). However, film badges that predate the TLD badges were far less accurate and possessed a higher threshold limit of detection [12]. Depending on the type of dosimeter, the shielding factor, and the type of radiation being measured, dosimetry results have been found to vary by as little as 11% and by as much as 90% for neutrons and by as little as 31% and as much as 62% for gamma rays [13].

The use of such fine exposure categories below 10 mSv is an example of exposure or dose reductionism. Such a practice results in the misclassification of dose, which in turn biases estimates of the effect toward the null value. A more informative approach would have been to use a large dose category such as 10 mSv or less as the reference category for badged workers. Most other studies of nuclear workers have used at least 1 rem (10 mSv) as the reference dose category when comparing categories of exposure [8,9,14–17]. As previously mentioned, if nondifferential exposure misclassification is present when such a dose reference category is used, the result is to underestimate the risk [12]. It appears that more exposure misclassification may be present for Portsmouth workers when dose reductionism is practiced and seven as opposed to four dose categories are used.

Another argument exists against using such small dose categories in studies of nuclear workers. Exposures that were accumulated over many years would usually be based on small amounts of exposure unless an accidental excursion was experienced. At least two concerns exist with regard to the accumulation of small doses over many years. As mentioned above, during the formative years of the nuclear industry, monitoring for exposure entailed dosimetry that was less accurate than has been the case in more recent years. The manner in which exposure to background radiation was factored into occupational dose estimates is sometimes problematic. For example, it appears that at one point the dosimetry that was done at Rocky Flats did not control for background. Consequently, individual dose estimates would be artificially inflated for that period of time.

A second concern entails the influence of background exposures vis-à-vis occupational exposures that are accumulated over many years. It is conceivable that background doses over a long working history would exceed occupational doses. If the background dose is high enough, if the occupational dose is low enough, and if the dosimetry is inaccurate, misclassification of occupational dose estimates may result.

The use of sufficiently large exposure categories on the basis of occupational doses will help somewhat to alleviate problems posed by very small dose measures. In addition, the fact that everyone is exposed to background and the control exercised by most investigators of calendar year will help to decrease the influence of cumulative background dose on risk estimates by occupational dose category. Finally, all of those problems covering the use of very small exposures and concerns about background, to the extent that they cause exposure misclassification, will cause the risk to be underestimated.

SIGNIFICANCE QUESTING

The pitfalls of undue reliance on tests of statistical significance in epidemiological research have received considerable attention. Rothman [18] succinctly describes the pitfalls of relying on significance tests for scientific inference and defines such reliance as "significance questing." The inherent shortcoming of a significance test is that it mixes information both on the strength of the association between exposure and disease and on how precisely this association is measured. Consequently, a significance test does not provide unambiguous information on either the strength of the association or the precision of the effect estimate.

Reliance on significance tests was used in several instances in the Portsmouth Shipyard workers study. The first was in the evaluation of standard mortality rates (SMRs) for several subcohorts of workers. The second was in evaluating observed and expected values for various dose categories. As is the case with several studies of nuclear workers [8,14,16], the dose-response analysis relied primarily on a test for overall trend. Evaluation of dose-category-specific estimates of effect was ignored. Estimates of risk by each dose category were not individually considered, perhaps because of the small numbers of observations in each dose category (which is to be expected if small dose categories are used) and also perhaps because of the emphasis on significance questing.

The reliance on significance tests of trend in the previous reports diverted attention from several interesting effect estimates by dose category that exist in the data presented in the two original reports. For example, the observed/expected values for leukemia by dose category that appear in Table VI of the study by Rinsky and colleagues [4] are 0.8, 0.0, 0.5, 1.1, 1.9, 0.0, and 5.0.

The risk estimates for the mortality ratios (relative to the lowest exposure category) are 0.0, 0.6, 1.4, 2.5, 0.0, and 2.8. The overall pattern is consistent with an increase in the relative risk as dose category increases, even though a selection bias is present in the above data, and even though small dose categories with sparse data were used, which would make it more difficult to detect a statistically significant trend. Also, the trend test that was used tests for the presence of a linear trend. A nonlinear trend would remain largely undetected.

Since studies of nuclear workers, such as the shipyard workers, who received low doses of ionizing radiation at low dose rates have only been completed within the past decade or so, we are just beginning to accumulate the results of these studies regarding any health effects that may occur at such low dose levels. Therefore, investigators should not limit themselves to searching only for linear trends; they should also allow for the possibility of nonlinear trends. Further, measures that gauge the strength of an association, not just its statistical significance, should be used when evaluating data for the presence of an association between exposure and disease.

The findings reported below illustrate the results of reanalyses that use cumulative dose categories of less than 10 mSv, 10 to 49.9 mSv, 50 to 149.9 mSv, and at least 150 mSv based on previously published cumulative doses (Table 3) [4,7]. Workers who had

Table 3. Standardized Mortality Ratios for Leukemia by Dose Category

	Cumulative Dose (mSv)			
	<10	10–49	50–149	150+
Person-years	89,558	21,769	8,350	2,778
Observed	4	3	0	1
Expected	5.7	1.6	0.7	0.2
SMR (O/E)	0.7	1.9	0.0	5.0
Rel. risk	1.0	2.7	0.0	7.1

Source: Rinsky RA, Zumwalde RD, Waxweiler RJ, et al. [4]
mSv = millisieverts; SMR (O/E) = standardized mortality ratio (observed/expected); Rel. = relative.

never been monitored for radiation exposure were not included, so as to eliminate possible bias caused by the healthy dose effect.

Rates for all causes of death, all cancers, all lymphopoietic and hematopoietic cancers combined, and all leukemias were calculated by dividing the number of observed cases for each respective cause of death by the number of person-years for each dose category. Relative risk estimates were then calculated by dividing the rate for each dose category by the rate for the lowest dose category (10 mSv). To account for the possibility of confounding by age and calendar period, observed and expected numbers of deaths were collapsed into the four dose categories mentioned above. An estimate of relative risk by dose category was then obtained by taking the ratio of the observed over expected number of deaths for high dose categories relative to the lowest dose category.

Mortality rates and relative risk estimates for all causes of death do not increase as dose category increases. When all cancers are considered, only the risk estimate for the highest dose category is elevated when compared with the lowest dose category. Although no cases are observed for lymphatic and hematopoietic cancers combined or for all leukemias in the dose category 50 to 149.9 mSv, the rate ratios for both of these causes of death are elevated for the 10 to 49.9 mSv and 150+ mSv dose categories. In the case of leukemia, a threefold excess is present among workers with cumulative doses of 10 to 49.9 mSv, and an eightfold excess, which is based on one observed case, is observed among employees with cumulative doses of at least 150 mSv. These findings show that the relative risk of leukemia and of lymphatic and hematopoietic cancers combined increases as the cumulative dose increases, regardless of any test for linear trend. Further, the use of internally standardized risk estimates that adjust for age and calendar year slightly decreases these estimates, but not appreciably so.

CONCLUSION

These findings, although imprecise, suggest that the relative risk for leukemia is elevated among Portsmouth Naval Shipyard workers and that the risk for leukemia increases as the lifetime cumulative external radiation doses that were experienced by these workers increases. Further, the relative risk increases in a similar fashion for lymphatic and hematopoietic cancers combined but does not increase in such a fashion for all causes of death or for all cancers combined.

These results are more in keeping with the findings that were originally reported by Najarian and Colton [3] and the recently published case-control study of Portsmouth Naval Shipyard workers [4]. They are also consistent with the results of several other studies of nuclear workers that have been published in recent years. Smith and Douglas [14] observed a dose-response trend for leukemia among British Nuclear Fuels workers, and Wilkinson and colleagues [9] observed an elevated relative risk for leukemia among Rocky Flats workers. (A dose-response trend was not observed for Rocky Flats workers.) Both of these cohorts included workers who could have been exposed to plutonium as well as to external radiation. Studies of nuclear workers at the Oak Ridge National Laboratory [15,19] and the Mound Laboratory [17] also report evidence of increased leukemia, and dose-response trends are also suggested in the most recent of these studies. Interestingly, no increase in leukemia has been found among Hanford workers [8], and no leukemias have yet been found among exposed workers at Britain's Atomic Weapons Establishment [20]. A number of other studies of nuclear workers that show an excess for leukemia [21,22] did not have information on external radiation doses. Another investigation did not have enough exposed workers to consider the effects of exposure [23].

The differences in these results compared with those previously published may be due to several pitfalls that have received varying attention in the literature on low-dose radiation effects. These errors include bias caused by the healthy dose effect, dose reductionism, which results in exposure misclassification, and significance questing rather than estimation of dose-category-specific effects.

The selection bias that has been suggested as existing among Portsmouth Naval Shipyard radiation workers may be defined as the healthy dose effect. This type of bias has been referred to as the healthy worker effect when comparisons of occupational cohorts are made with the general population. Such bias has not been widely recognized as a problem when internal comparisons are made within an employee cohort.

The healthy dose effect may constitute a serious bias when exposed workers are compared with unmonitored workers, who are assumed to be unexposed but who may also differ from workers who are monitored for exposure. This type of bias should be carefully assessed in studies of employed populations when internal comparisons are made between exposed and unexposed employees and especially when dose-response analyses are conducted. Analyses designed to ascertain the comparability of unmonitored and monitored subjects should be conducted before associations between exposure and disease are considered.

In summary, the results of this reanalysis suggest that the relative risks for leukemia and for all lymphatic and hematopoietic cancers combined are elevated among Portsmouth Naval Shipyard workers who received cumulative doses to external ionizing radiation of at least 10 mSv, and the risk increases as dose category increases. There are several reasons why these excesses were not identified in the previous follow-up study: 1) reliance was placed on the use of statistical significance tests without concomitant consideration of estimates of the strength of the association between exposure and disease; 2) the use of dose categories that were too small resulted in exposure misclassification and also made more difficult the detection of statistically significant findings; 3) interest was focused on linear rather than both linear and nonlinear trends; and 4) perhaps most interestingly, the presence of a little-recognized form of selection bias, the healthy dose effect, may have caused an underestimate of the effect of exposure. ❧

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