Oak Ridge Cancer Findings Hotly Disputed

A surprising epidemiology study published in March fuels debate over assessing the risks of occupational exposures to radiation. Political views provoke a co-author to pull her name from the study.

THE FIRST STUDY TO LINK cancer mortality with occupational exposures to radiation at Oak Ridge National Laboratory (ORNL) has drawn strident criticism from a host of nuclear physicians and radiobiologists who dispute the conclusions drawn from analysis of death rates among workers at the federal nuclear research and testing site. The report is perhaps the first to raise the possibility that exposure to levels of radiation considered safe may increase the risk of developing a variety of cancers.

Published in the March 20, 1991 Journal of the American Medical Association (JAMA), the paper reports that deaths due to leukemia occurred 63% more frequently among white male workers hired between 1943 and 1972 at ORNL than among the general population of the United States. When comparing workers to workers, the epidemiologists from the University of North Carolina and Oak Ridge Associated Universities (ORAU) found that all-cause mortality increased 2.68% per 10 mSv (1 rem), and all-cancer mortality increased 4.94% per 10 mSv (1 rem). The authors, Steve Wing, PhD; Carl M. Shy, MD; Joy L. Wood, MS; Susanne Wolf, MPH; Donna L. Cragle, PhD; and E.L. Frome, PhD, emphasize that this excess mortality failed to appear in earlier studies and only became evident 20 years after exposure. Reports of excess leukemia mortality at Oak Ridge appeared in an earlier study.

ORNL Photo

This Oak Ridge National Laboratory technician is shielded from radioactive isotopes by thick concrete and over four feet of layered glass.

Renegade Science

"This is a renegade paper," says William R. Hendee, PhD, "The data and conclusion do not fit with the model that we have been using for a long time to estimate the dangers of radiation exposure." Dr. Hendee wrote an editorial accompanying the paper in JAMA when he was vice president of the group on science and technology at the American Medical Association. He has since left the AMA to become senior associate dean for research and technology at the Medical College of Wisconsin.

Scathing criticism of the study has issued from such authorities as Rosalyn Yalow, PhD, the Nobel laureate and outspoken authority on the risks of radiation. "I'm surprised that this paper was published," Dr. Yalow told *Newsline*. "I am not impressed that there's an increased incidence of cancer." Henry N. Wagner, Jr., MD, of Johns Hopkins Medical Institutions called the paper an "aberration," and added, "I'm surprised it passed peer review. The study has too many weak points to accept the conclusions." Further stirring the swirl of controversy, ORAU epidemiologist Shirley Fry, kept her name off the study over objections to political views it expressed.

The study's primary author, epidemiologist Steve Wing, PhD, of the University of North Carolina, says he wasn't prepared for the kind of response the paper received. Some people "have reacted with great hostility," he says. His team continues to analyze the data to see if any other factors might explain away the excess mortality that appeared 20 years after workers were exposed to radiation. The researchers followed the workers through 1984.

CAUSE (Lag in y)	Dose Category, mSv 0	0-19	20-39	40-59	60-79	80-99	100-119	≥120
ALL CAUSES (20)								
Observed	737	619	75	33	20	2	8	32
Expected	755.8	613.8	74.4	28.8	14.0	5.8	4.0	19.3
ALL CANCER (20)								
Observed	154	169	20	14	5	0	5	13
Expected	170.9	164.1	21.1	8.6	3.9	1.9	1.3	6.3
LUNG CANCER (0)								
Total Workers								
Observed	15	59	10	7	1	1	2	9
Expected	22.4	58.4	9.6	4.5	2.2	1.4	0.8	3.8
LUNG CANCER (0)								
Nonmonthly								
Observed	13	42	8	7	1	1	2	8
Expected	13.7	45.3	8.2	4.9	2.3	1.7	1.0	4.9
LEUKEMIA (10)								
Observed	7	15	6	0	0	0	0	2
Expected	8.9	15.8	2.5	1.0	0.5	0.3	0.2	0.9

***Table 1: Cause Specific Numbers of Observed and Expected Deaths in Categories of External Penetrating Radiation Doses Among White Male Workers Hired at ORNL Between 1943 and 1972 as Reported by Wing,* et al.**
From the *Journal of the American Medical Association,* March 20, 1991

No Dosage Response

Detractors of the study focus on the shortcomings of the leukemia findings. Leukemia caused 28 of the 1524 deaths that the study considered, a number too low to draw conclusions about the effects of chronic, low-level radiation exposure, says Dr. Wagner of Johns Hopkins. Seven of the leukemia deaths occurred in people who had no recorded exposure to radiation, he adds, and seven died from chronic lymphocytic leukemia, which is not linked to radiation exposure.

The recorded radiation exposures showed no dosage response relationship to leukemia mortality, says Bertrand Brill, MD, PhD, an authority on the biological effects of radiation and director of nuclear medicine research at the University of Massachusetts in Worcester. "There was no increasing frequency of leukemia with increasing doses of radiation," he says, which suggests that other factors are responsible for the elevated leukemia death rate compared to the general population.

"A lot of people have jumped on the leukemia findings," responds Dr. Wing. "These are not new — they were reported in the Oak Ridge study published in 1985." He agrees that the leukemia findings "are very limited." But he holds firm to the new findings that radiation doses may have contributed to the appearance of excess all-cancer mortality within the Oak Ridge cohort. What he finds unusual is the appearance of excess mortality with additional time, not with additional doses of radiation.

Confounding Data

"I didn't expect to see an association between radiation and cancer," the epidemiologist says. He was surprised because such an association failed to appear in the previous studies and because extrapolation of analyses of the data on survivors of the atomic bombs dropped on Japan implies that radiation levels at Oak Ridge should have no measurable

impact. The latest Oak Ridge data raise the troubling question: Do low levels of ionizing radiation over long periods of time spur increases of cancer? The study doesn't answer that question, says Dr. Wing, "but it does suggest an effect."

Dr. Yalow and others flatly deny the claim that excess all-cancer mortality is attributable to radiation because the worker cohort showed no increase in leukemia as radiation dose equivalents increased (see table on page 12N). "If you look at the data on those workers that had doses of radiation it's apparent that there's no increase in leukemia," says Dr. Yalow. Leukemia is the cancer most sensitive to radiation exposure, notes Dr. Wagner. The lack of a leukemia response to exposure weakens the case for low-dose radiation carcinogenesis, he says. "I think the conclusions are incorrect."

Positive Finding, Negative Reaction

"All of the sudden because there is a positive finding everybody's jumping up and screaming," says co-author Donna L. Cragle, PhD, director of the Center for Epidemiologic Research at Oak Ridge Associated Universities (ORAU). She maintains that the paper's conclusions are well supported. She sums up those conclusions as follows: "There is a significant excess of leukemia when you compare mortality to the U.S. population as a whole, but when you look for a dosage response, it's not there. There is a significant relation between radiation exposure and all-cancer mortality comparing workers to workers." She emphasizes that the rate of increase of all-cancer mortality is derived from only seven follow-up years from the last study. "When we follow the population into the future, the rate may change," she says.

The question remains how radiation figures in the increased risk the epidemiologists observed. Pressed for an answer, Dr. Cragle says, "The risk is related to something that is related to radiation exposure. I feel that there is some sort of an [radiation] effect." Dr. Brill and other detractors hasten to point out that workers were exposed to a variety of carcinogens and the leukemia-causing solvent benzene in research labs at Oak Ridge. Data on exposure to chemicals and factors like cigarette smoking and medical x-rays were not compiled in the study. Dr. Wing and colleagues, however, did discuss such confounding factors in their paper.

"Exposures to other chemicals are important things to factor in to come up with the true numbers," says Dr. Cragle.

> "It's not the basis for a conclusion that there's a causal relation between occupational exposure to radiation and an increased incidence in cancer."

The authors rule out smoking as a significant confounder. Their analyses show that radiation doses did not correlate well with non-cancer (and largely smoking-related heart and lung disease) mortality, which reduces the likelihood that smoking could account for the link between radiation and mortality. "It makes you feel that smoking could not possibly produce that large of an effect," says Dr. Cragle.

What is needed now, she says, is a study that looks at cancer incidence among the workers along with information on smoking and occupational exposures to chemicals. "Until that kind of analysis is done we'll still be wondering," she says. "We know the story is not finished until we follow the cohort to extinction," says Dr. Wing. "But we should try and remember that the previously reported studies are not the end of the story either."

Science or Soapboxing?

Objections to the paper, however, don't end with the disputed conclusions. Many scientists have voiced disfavor over political statements — "soapboxing" said one scientist — tacked on the final page of the paper. Epidemiologist Shirley Fry, MB, MPH, formerly the director of the Center for Epidemiologic Research at ORAU, withheld her name from the study because of her objections to comments about the nuclear industry. "I had some reservations about the paper, the last two paragraphs [of the comment section] in particular," she says. In those paragraphs Dr. Wing writes that:

> ...the public health impact of these radiation exposures and the industry that produces them extend far beyond the low-dose occupational exposures themselves...The exposures of workers in this setting, and any attending health effects, depends on the historical development of an industry linked to a concentration of resources in military spending, which itself has gross health effects...

Dr. Fry says, "I didn't think that had a place in the paper — it doesn't present a balanced view of the benefits of radiation. I think the data are good quality data and they have been carefully analyzed, but I don't think the data support or warrant the comments." Dr. Fry, now assistant division chairman for health studies in the medical sciences division at ORAU, is studying mortality in several populations of workers at DOE sites.

Dr. Wing likes to put politics out front, even in science. He says it's important to consider not only particular agents, but also the context of exposure to those agents. The essence of his reasoning is as follows: Radiation exposures occur in the context of the nuclear power industry and nuclear weapons production. The nuclear power industry, he believes, encourages energy consumption and nuclear weapons production redirects resources that could be used in public health. Both, he says, create waste with potential to effect public health. These issues have greater significance than the effects of occupational exposure to low-level radiation, he says. "I worry that the study is going to fan the flames about low dose radiation, but those concerns only distract us from bigger public health

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Cancer Findings

(continued from page 13N)

problems caused by energy policy, the nuclear industry, and the military."

Dr. Fry says the editorializing casually dismisses the benefits offered by the nuclear industry, particularly the benefits of nuclear medicine technology developed at Oak Ridge. She decries Dr. Wing's linkage of Oak Ridge to weapons production.

Co-author Dr. Cragle says that "to a certain extent" she disfavored the comments. "I told Steve that as first author he had the choice and he preferred to let the journal's editors decide if they were appropriate." (The editors of JAMA declined to discuss the peer review and approval of any individual article.) Judging the responses she's heard, Dr. Cragle says, "Most people's distaste lies with the expositional paragraphs in the discussion."

Dr. Wing likes to put politics out front, even in science.

Just a Piece in the Puzzle

Although critical of aspects of the paper, Dr. Fry defends the work as a whole. She's concerned that the findings of the paper are being widely misinterpreted. "It's not the basis for a conclusion that there's a causal relation between occupational exposure to radiation and an increased incidence in cancer," she says. More than 80% of the study population remains alive, meaning the current study draws its conclusions from less than 20% of the population, rendering it far from definitive. "By its nature," says Dr. Fry, "epidemiology makes progress very slowly and relies on many studies."

"I think people fear the paper is causing people to worry when there is no reason to," says fellow epidemiologist Dr. Cragle. Downplaying the significance of the paper, she says it has far too little impact to start revising standards for radiation exposure. "That's not the way epidemiology works," she says, "this paper is just another piece in the puzzle." Even if the low-level effects of radiation proved absolutely true, Dr. Cragle notes, Oak Ridge workers today —whose radiation exposures are much lower than in the 1930s and 40s—would not be affected. "They were getting two to three rems a year back then," she says. "It's unusual for [workers at DOE facilities] to get a rem anymore."

Dr. Hendee says, though the findings may prove insignificant, they pose a challenge. "We've been seduced into the belief that we can have the benefits without any risk," he says. "Now we face evidence that that's not true." The challenge is to understand the strange increased risk of cancer mortality that has appeared after a 20 year lag. Dr. Fry says, if projected over the entire population, this finding would imply that most cancers are caused by low levels of lifetime exposure to radiation. "That doesn't seem biologically possible," she says. "It's a finding that's unexplainable."

J. Rojas-Burke

News Briefs

Letter from the Editors re: International PET

It is most gratifying to editors to know that the assembled published material has been read and found useful. It is therefore a bittersweet moment when we receive a letter identifying errors. We are pleased that *Newsline* is read so carefully but disappointed that the oversights were not found by us and corrected prior to publication.

In the recent PET issue (*Newsline*, April 1991), specifically the article "The International State of PET," two readers (to date) have pointed out errors of omission and commission. Professor Dr. W.D. Heiss from the Max-Planck Institute for Neurologische Forschung and the Klinik Fur Neurologie at the Universitat zu Koln (Cologne) informs us that the first PET installations in Germany were at the Kernforschungsanlange in Julich in 1979 and in Hannover in 1979–80. The PET facility in Cologne was established in 1981 and is possibly the most active center in Germany with a total of over 4000 cases studied to date. The Koln center has organized and hosted several international PET meetings as well as smaller workshops. Prof. Dr. Heiss also reports that the PET scanner at Heidelberg was installed in 1986 and that PET installations have been recently established in Dusseldorf, Aachen and Essen.

The status of PET in France was also neglected by our review.

Dr. B. Weissman informs us that the reported PET facility at the Royal Prince Alfred Hospital Camperdown, Sydney, is in its earliest stages of construction and certainly has not been completed.

We apologize to our readership for these errors and commit ourselves to better confirmation of sources as well as a more thorough report in the near future on the status of PET in the international community.

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