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New Breast Cancer Data Flaws

Discrepancies Found In Patient Files Cloud Lumpectomy Study Reliability

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BEVERLY HILLS, Calif. — The nation's oldest and largest breast cancer research group, still reeling from revelations that it used fraudulent data from a Canadian surgeon, apparently relied on inaccurate data from American researchers in reaching its widely reported conclusions about the safety of lumpectomy.

One Southern California research center, which recruited more than 300 patients for the group's breast cancer studies, enrolled several who later proved ineligible and included others without their written consent. Some patients even were reported as alive after they died.

The cancer study group, known as the National Surgical Adjuvant Breast and Bowel Project (NSABP), has been under attack since March, when the Tribune reported that the Canadian, Dr. Roger Poisson, had been found guilty of scientific misconduct for falsifying or fabricating data on 99 breast cancer patients from Montreal.

The NSABP responded to the disclosure by insisting that the fraud had not affected any of its studies, including a landmark 1985 report concluding that women who received lumpectomies were likely to live as long, and to experience no greater recurrence of cancer, than women who underwent more disfiguring total mastectomies.

But records maintained by the Memorial Cancer Research Foundation of Southern California, one of the NSABP's oldest contributors and its principal source of patients in the Los Angeles area, contain what appear to be inaccuracies and discrepancies that raise questions about the integrity of the NSABP's data on the 2,163 women who participated in the lumpectomy study.

Investigators from the National Cancer Institute (NCI), which funds and oversees the NSABP, arrived here on Friday after the foundation's chairman, David Plotkin, a prominent Beverly Hills oncologist, advised NCI officials that he had made some of his NSABP files available to the Chicago Tribune and asked that they be officially reviewed by the NCI.

The NCI already is auditing other institutions, including Tulane University and Louisiana State University. According to preliminary reports, NCI investigators have been unable to confirm the eligibility of more than 100 patients enrolled by the two universities in several NSABP studies.

Although it was similar discrepancies involving patient consent and eligibility that led to the federal investigation that resulted in Poisson's misconduct finding, there is no evidence that any deliberate fraud occurred at the Memorial Cancer Research Foundation or at the two Louisiana sites.

The only scientist besides Poisson to have come under investigation for scientific misconduct is Dr. Bernard Fisher, the NSABP's founder and longtime chairman, who was deposed by the NCI following disclosure of the Poisson case, and who now has been accused by NCI of having published data he knew was falsified by Poisson.

Fisher and the NSABP have portrayed the Poisson case as an unfortunate but isolated instance of tainted data that slipped through the organization's system of auditing patient files from member institutions.

But if the Louisiana records and the California files examined by the Tribune are representative of those at nearly 400 other NSABP institutions, the NSABP's data on lumpectomy and other aspects of breast cancer research may

be far less conclusive than currently is believed.

Among the most disturbing revelations in the Plotkin example is that NSABP auditors have been aware for years that the Memorial Cancer Research Foundation was recruiting and enrolling breast cancer patients who did not meet eligibility requirements.

In the spring of 1990, the NSABP discovered that Poisson had altered the recorded date of a breast cancer operation to make a patient eligible for an important study of the clinical effects of chemotherapy. A few weeks earlier, an NSABP auditor uncovered a similar discrepancy in the files of the California foundation.

Two years earlier, the foundation had reported to NSABP headquarters at the University of Pittsburgh that the lymph nodes of a patient enrolled in an NSABP colon cancer study were free of cancer.

According to the pathology report in the patient's file, however, no nodes could have been examined for evidence of cancer because none had been found by the woman's surgeon. When the auditor saw the report she declared the patient ineligible and removed her from the study.

Then, when the auditor examined a second file selected at random, that of a breast cancer patient enrolled in an NSABP chemotherapy study, she found the woman had been reported to Pittsburgh as one whose tumor was not dependent for its growth on the hormones estrogen and progesterone.

The negative report suggested that the woman probably would not have benefited from the drug tamoxifen, which blocks estrogen production. In her file, however, were three other laboratory reports showing that the woman's tumor in fact had been highly dependent on both hormones.
Based on the NSABP's own research, those reports would have made the woman a candidate for tamoxifen, either in addition to, or instead of, the much harsher chemotherapy she received as part of the study.

"A serious problem has been identified with this institution with respect to the accuracy of the data reported to the NSABP," the auditor concluded. "One patient has been declared ineligible, and the other patient has wrong hormonal receptor assay values."

In contrast to what was about to happen to Poisson, the discovery of irregularities at the Memorial Cancer Research Foundation appears to have triggered no alarm and prompted no investigation. Although a report of the audit apparently was forwarded to the National Cancer Institute, NCI officials either did not notice the report or ignored it.

Unlike Poisson, who by all accounts was viewed as an eccentric and an outsider by the American medical community, Plotkin long has been a member of the breast cancer establishment.

In addition to having been honored by the American Cancer Society, Plotkin is co-author with Fisher of a half-dozen of the NSABP's most notable research articles. He has been a member of the NSABP's executive committee and has helped to design some of the group's studies, as well as serving three consecutive terms on the NCI's Breast Cancer Task Force.

In a recent interview, Plotkin estimated that the NCI, through the NSABP, has paid his foundation some $450,000 in federal funds during the past 20 years in return for recruiting more than 300 patients for a dozen NSABP cancer studies. Though it is less than half the sum paid to Poisson, it places the Memorial Cancer Research Foundation in the top ranks of NSABP affiliates.

Rather than sending audit teams to examine more of Plotkin's files, as happened with Poisson in Montreal, the NSABP appears to have let the California matter drop. Although the breast cancer patient later was placed on tamoxifen by her physician, the NSABP unaccountably decided to leave the colon cancer patient in the study for which she had been declared ineligible.

Plotkin said he had never seen the NSABP audit report and could not offer any explanation for the misreporting of data on the two patients. In response to a reporter's request, he agreed to permit the examination of a sample of his other NSABP records for similar discrepancies.

The files of 18 patients, all of them enrolled in the NSABP's lumpectomy study, were selected from among 311 women recruited by Plotkin on behalf of the NSABP. Although the Memorial Cancer Research Foundation enrolled 29 patients in the lumpectomy study, Plotkin said the remaining 11 files had been placed in storage and rendered inaccessible by the recent Los Angeles earthquake.

In several of the 18 cases, however, women appear to have been enrolled despite indications in their records that they might have been ineligible.

Some patients apparently were recruited and enrolled after their operations rather than before, as NSABP regulations required, and others without having signed consent documents advising them of the risks of participation and the alternative treatments available.

At least one patient appeared to have been enrolled and treated despite her decision not to participate in the lumpectomy study. Some patients who had suffered recurrences of cancer following their operations were reported to Pittsburgh as cancer-free, while others who had died were reported as alive and well.

Plotkin, who was present during the Tribune's examination of the 18 files, agreed that patient data had been misrecorded and misreported to the NSABP. But he denied that he ever deliberately altered any data or withheld any information to make a patient eligible for an NSABP study.

"Am I Roger Poisson?" Plotkin asked. "Certainly not. Would I in any way falsify any records? Absolutely not. But the human stuff-are there mistakes in my records? You bet."

Although the consent violations raise serious questions about whether the patients involved understood what they had agreed to, the inclusion of ineligible patients threatens the statistical integrity of any clinical trial by masking possible differences in outcome between groups.

Earlier studies from Europe, for example, had suggested that, for women with early-stage breast cancer, lumpectomy might be as safe as mastectomy. But some of the European studies were not well designed statistically, and others were limited in the number of patients enrolled and the way they were selected, treated and followed.

The NSABP study, in comparison, was planned to ensure the maximum possible validity of its results, even to the point of eliminating any possible bias associated with the choice of operation the subjects received.

Under a system known as "pre-randomization," once a patient agreed to participate in the lumpectomy study, the treatment she received was determined by NSABP headquarters in Pittsburgh: lumpectomy alone; lumpectomy followed by radiation of the breast from which the tumor had been removed; or total mastectomy, which involves removing the entire breast.

As explained in the consent form that all study participants were required to sign before enrollment, randomization "means that the treatment will not be selected by my surgeon or by me, but will be by chance."

In several of the cases examined by the Tribune, however, patients apparently were enrolled in the lumpectomy study by the Memorial Cancer Research Foundation after having had their operations or after deciding which operation to have, eliminating the statistical benefits of randomization.

One woman was enrolled five days after her lumpectomy, a second woman eight days afterward. Documents in a third woman's file provide conflicting accounts, but include one suggesting she was enrolled more than a month after her lumpectomy. The records of several other patients indicated they had chosen their treatments before enrollment.

Asked about the apparent protocol violations, Plotkin said he believed enrolling women in the study following their operations had been a common practice among other institutions participating in the study. "It has to have happened a lot," he said.

For a woman who already had a lumpectomy, Plotkin noted, "the chances were two out of three" that the treatment randomly chosen by Pittsburgh would match the operation that had already taken place.

"If they had a lumpectomy and it came up lumpectomy, everything was fine," Plotkin said. "If it was lumpectomy with radiation, all you had to do was start them on radiation. If it was mastectomy, you just told them, `We think maybe you should have the gold standard treatment, and that's a mastectomy.' "

Plotkin said he did not know of any cases in which women who had had a lumpectomy actually were given a mastectomy simply to match them with the NSABP protocol.

In two of the cases examined, however, patients apparently were assigned to the total mastectomy group after they chose to have lumpectomies. Both were enrolled in the study anyway, with the notation that they had declined to accept their assigned treatments.

The NSABP lumpectomy study was designed so there would be no significant differences between the women who received lumpectomies and those who received mastectomies, a balance required to ensure that any differences in their survival were due to the operations they received.

In several cases, however, patients appeared to have been enrolled despite indications that they had clinical characteristics that would have rendered them ineligible.

One woman's surgical report, for example, noted evidence of skin edema, or swelling, which according to NSABP regulations automatically would have prevented her enrollment.

Two other files contained documents recording the size of a patient's tumor as greater than the 4-centimeter limit set by NSABP, but suggesting that the tumors had been reported to NSABP as smaller than 4 centimeters.

A third patient's file described her tumor as having been "0.0" centimeters, with the notation that "no measurement" had been taken. The woman was enrolled in the study anyway.

Tumors from three other patients appeared to have been biopsied more than two weeks before surgery, in violation of another condition for eligibility. In one instance the biopsy date appeared to have been written over with another date that made the patient eligible.

Several files contained documents that provided conflicting accounts of important clinical information. One recorded the size of a patient's tumor both as 8 centimeters and as 4 centimeters, and others had different dates for biopsies and operations on the same patients.

Some files lacked surgical reports of operations the patients supposedly received. One patient reported to the NSABP as having had a mastectomy was described on her death certificate as never having had an operation for breast cancer.

A second woman was recorded variously as having had a lumpectomy followed six days later by a mastectomy, and as having had only the lumpectomy. Another patient's file mentioned two lumpectomies four days apart. Two files contained documents that raised questions about whether any breast surgery had even been performed.

Plotkin said he suspected some of the latter discrepancies could be explained by the tendency of some surgeons to upgrade operations, describing biopsies as lumpectomies and lumpectomies as mastectomies, in order to garner higher fees.

As in the case of the colon cancer patient, some of the apparent ineligibilities eventually were detected by NSABP auditors. Indeed, NSABP records show that the Memorial Cancer Research Foundation ranked first in the percentage of patients enrolled in the lumpectomy study who were later deemed ineligible.

In one such case, a patient was excluded after she was found to have been enrolled even though her physician knew she had two widely separated tumors in the same breast-which would have precluded a lumpectomy-rather than the single tumor required for participation in a study in which lumpectomy was a random option.

The number of ineligibilities among Plotkin's patients might have been seen by Pittsburgh as a red flag, but apparently it was not. In each instance, the ineligible patients simply were removed from the study while the foundation was left free to go on enrolling new recruits.

In a number of the 18 cases examined, moreover, it appeared that women had been enrolled in the study, and even operated on, before their written consent had been obtained, raising questions about whether they understood the full ramifications of the surgery and treatment they received.

The consent document used by the NSABP explains the complications that might follow a lumpectomy, such as scarring "and a decrease in the size of the operated breast." It also warns that "there could be other cancers in the breast which are undetectable now but which could become apparent later, and would require total removal of the breast at that time."

The consent form notes that "radiation therapy could cause permanent hardening of the breast," and that chemotherapy, which was to be administered to all patients whose cancers had spread to the lymph nodes, had potentially severe effects on the immune system.

"It is also possible," the consent document states, "that there may be delayed effects from the drugs which could appear months or years after completion of the treatment."

The document points out that other methods could be used to treat the patient's cancer, including the more drastic radical mastectomy, radical mastectomy plus radiation therapy, and radiation therapy alone.

In four of the cases examined, consent documents were not dated, or not signed by the patient's physician, or both. In four other cases, the consent forms were dated weeks or months after the patients' operations had taken place.

The date on one consent form, originally dated four days after the woman's operation, appeared to have been obliterated with correction fluid and written over with the date of the patient's operation.

One woman apparently never gave any consent at the time of her enrollment. When the lapse was discovered more than two years after she had been entered in the study, the NSABP asked her physician to obtain a retroactive consent.

One woman signed her consent form beneath the notation, "I do not wish to participate in this investigative study." Records show, however, that the woman nevertheless was enrolled, treated with a lumpectomy and chemotherapy, and followed until the time of her death.

In addition to enrolling and treating patients, the Memorial Cancer Research Foundation, like all NSABP contributors, was responsible for monitoring those patients closely and reporting any recurrence of cancer, subsequent breast operations, or deaths-the vital statistics that form the basis for the NSABP's continuing reports on the safety of lumpectomy compared with mastectomy.

According to NSABP records, however, the foundation appears to have lost track of at least three of the 29 patients in the lumpectomy study. No follow-up reports on one woman have been filed since 1987, and none on another since 1985. Some recurrences and even deaths appeared to have been reported to NSABP long after the fact or not at all.

One woman's mastectomy went unmentioned in reports to NSABP for nearly two years. Another, whose recurrence of cancer and subsequent mastectomy were not reported for 15 months, consequently was listed as a cancer-free lumpectomy patient in the NSABP's 1985 article.

A woman who developed advanced metastatic cancer was reported to the NSABP the following month as "alive and well." Another woman, who died in December 1992, was reported in March 1993 as "alive and well."

That woman still is on file at the NSABP as a cancer-free survivor. So is a second woman who developed metastatic breast cancer and died a year ago. Although the second woman's file contains a note reading: "Pt.

Expired 5/93," the last report submitted to the NSABP describes her, too, as "alive and well."

Following the disclosure of the misconduct finding against Poisson, the NSABP submitted an article to the New England Journal of Medicine, where the original lumpectomy articles appeared, offering assurances that the study's conclusions had not been changed by the falsifications in Montreal.

Because the latest Journal manuscript contains data received by NSABP through last September, it would include presumably both of the dead California women as among those who are alive and cancer-free.

The Journal's editor, Dr. Jerome Kassirer, said last week he already had put on hold plans to publish the manuscript, until it became clear whether data from physicians other than Poisson also will have to be expunged.

"If we turn up more fabrications, I'm not about to publish a re-analysis of a re-analysis," Kassirer said. "That's why I've suspended it. I want to wait and see what the story is."

Plotkin, who appeared surprised and shaken by the apparent discrepancies in his files, attributed some of them to errors by the succession of medical students he has employed as part-time "data managers" over the years.

He suggested that other errors probably stemmed from the fact that he never had seen many of the patients he enrolled in NSABP studies.

The great majority of the women he enrolled in NSABP studies, Plotkin said, actually had been recruited by other doctors across Southern California-some of whom he did not even know-in hopes of winning one of the expense-paid trips Plotkin's foundation offered to physicians who enrolled six patients in a year.

The trips, Plotkin said, usually were to attend a convention of the NSABP, often held "in places like Florida and New Orleans. And then, you know, the guy tacks on a vacation at the end."

In addition to the trips and some reimbursement for office expenses, Plotkin said a principal motive for a physician to recruit patients for the NSABP was the positive impression an association with a prestigious research group makes on other patients.

"You go to one of their meetings and come back and tell your patients you've just been to a conference where they've been talking about the latest stuff," he said. "Patients really like that."