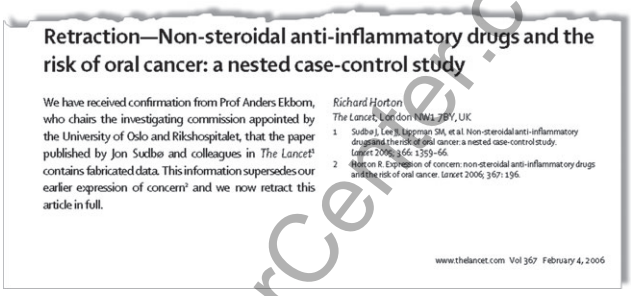
Cancer Fraud Case Stuns Research Community, Prompts Reflection on Peer Review Process

A stunning admission of fraud from a respected Norwegian oral cancer researcher, Jon Sudbø, M.D., Ph.D., D.D.S., has left the cancer research community reeling. According to statements from his hospital and his attorney, Sudbø fabricated data for 900 patients in a study published in October in *The Lancet,* which has now retracted the article. He also "fundamentally mishandled" data for a 2001 article in *The New England Journal of Medicine* and a 2005 article in *Journal of Clinical Oncology*.

The fraud, which blindsided Sudbø's colleagues in the United States, prompted the National Cancer Institute to suspend a 300-patient cancer prevention trial. Just days from launching, the trial was set to study Celebrex (celecoxib) and Tarceva (erlotinib) as chemopreventive agents for oral cancer. Sudbø, chosen to lead trial enrollment exclusively in Scandinavia, was set to receive $312,000 per year through 2009 from the grant. He is now on indefinite leave from the Norwegian Radium Hospital.

Eva Szabo, M.D., who oversees prevention trials for upper aerodigestive cancers at NCI, said in a statement that the institute is reviewing "the entire portfolio" of oral cancer grants to see which others, if any, drew scientific justification from Sudbø's fabrications. "We don't have specifics on numbers" of potentially affected grants, Szabo said. However, given the seminal impact of the now-discredited studies in the field of oral cancer (see News, Vol. 98, No. 2, p. 88, "Years of Research Come to Fruition With Launch of Oral Cancer Prevention Trial"), the damage may range beyond the single suspended grant.

In the United States, the scandal hit home at the University of Texas M. D. Anderson Cancer Center in Houston. Scott Lippman, M.D., director of the Department of Thoracic, Head and Neck Medical Oncology, and three other M. D. Anderson researchers, oncologist Li Mao, M.D., and statisticians J. Jack Lee, Ph.D., and Xian Zhor, M.D., coauthored *The Lancet* article. M. D. Anderson was also the primary recipient of the $9 million NCI grant for the now-suspended prevention trial.



Retraction—Non-steroidal anti-inflammatory drugs and the risk of oral cancer: a nested case-control study

We have received confirmation from Prof Anders Ekbom, who chairs the investigating commission appointed by the University of Oslo and Rikshospitalet, that the paper published by Jon Sudbø and colleagues in *The Lancet*[1] contains fabricated data. This information supersedes our earlier expression of concern[2] and we now retract this article in full.

Richard Horton
The Lancet, London NW1 7BY, UK

1 Sudbø J, Lee JJ, Lippman SM, et al. Non-steroidal anti-inflammatory drugs and the risk of oral cancer: a nested case-control study. *Lancet* 2001; 366: 1359–66.
2 Horton R. Expression of concern: non-steroidal anti-inflammatory drugs and the risk of oral cancer. *Lancet* 2006; 367: 196.

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Norwegian researcher Jon Sudbø has admitted through his attorney that he fabricated data for 900 patients in an article published in *The Lancet* in October. *The Lancet* retracted the article in February.

"We're in a period of reevaluation," said the cancer center's vice president of research administration, Leonard Zwelling, M.D. "We're talking to NCI and we still have a desire to go forward [with the trial]."

Blindsided

Sudbø, through his attorney, took sole blame for the fiction. "His coauthors knew nothing," said Erling Lyngtveit from Oslo. Zwelling confirmed that none of the M. D. Anderson collaborators had an inkling of the fraud being perpetrated in their names. "The first any of us suspected something was wrong was [January 18] when we got a call" from the Norwegian Radium Hospital; Lippman and colleagues simply analyzed the data that Sudbø provided, Zwelling said.

The Norwegian hospital swiftly appointed an investigative committee, headed by Anders Ekbom, M.D., Ph.D., director of clinical epidemiology at the Karolinska Institute in Stockholm, Sweden. The committee includes statisticians, researchers, and administrators from the University of Oslo, the Norwegian Institute of Public Health, Cancer Registry of Norway, and the Cancer Clinic at the Radium Hospital. The committee has promised a full report on Sudbø's entire career, which includes 38 publications dating from 1997, by April 1.

"This is very serious. It's also a deep, personal tragedy for" Sudbø, said Stein Vaaler, strategy director at Rikshospitalet–Radiumhospitalet Health Trust, which funds the Radium Hospital. Sudbø's wife, Wanja Kildal, and twin brother, Asle Sudbø, coauthored the false article in *The Lancet*, but Vaaler said there is no indication that they were involved in the fabrication. They are expected to testify before the committee.

Although Vaaler declined to speculate about Sudbø's motivations, Lyngtveit, his attorney, suggested that the researcher sought accolades and "professional pride."

If Sudbø was seeking respect, then he succeeded. Scientists in the field had hailed the April 26, 2001, NEJM article as an important step toward preventing oral cancer; the other papers in *The Lancet* and *Journal of Clinical Oncology* also drew praise.

The NEJM article received attention because it identified a simple means for identifying people at high risk for mouth cancer. The article reported that patients with an abnormal number of chromosomes in cells taken from precancerous mouth lesions (leukoplakia) were at high risk for developing cancer; those with a

normal number of chromosomes, conversely, were at low risk. Sudbø and coauthors concluded the article by recommending that leukoplakia displaying aneuploidy be treated "as true carcinomas." NEJM published a note in late January saying that one of the figures in the article had been labeled as a picture of a second leukoplakia sample when, in fact, it was simply a magnification of an earlier figure. As for the rest of the article, NEJM said it will wait for the conclusions of the university's formal inquiry before making further assessments. The NEJM statement also said the journal "had similar concerns" about an April 1, 2004, article from Sudbo.

The March 20, 2005, JCO article extended the 2001 NEJM findings, reporting the genetic risk marker in 23 (8%) of 275 heavy smokers. The specific fabrications in that article are unknown.

But it was the most recent paper, from the Oct. 7, 2005, issue of *The Lancet*, that tipped researchers off to the fabrications. The study supposedly drew data from patients listed in the Cohort of Norway (CONOR), an epidemiological database. When Camilla Stoltenberg, M.D., who works with CONOR, read the article, the fabrications leapt from the page. "The Cohort of Norway didn't even exist for the time period when data collection supposedly took place," said Stoltenberg, director of the Division of Epidemiology at the Norwegian Institute of Public Health. She contacted the Radium Hospital with the information, which then set the fraud investigation in motion.

In an e-mail statement, M. D. Anderson's Lippman wrote that *The Lancet* paper did not play a role in the design of the now-suspended clinical trial. Instead, the rationale for testing celecoxib and erlotinib as inhibitors of oral cancer has, "if anything, grown stronger with new data in the past year." Lippman cited published clinical- and laboratory-based articles that support the clinical trial and shed light on the purported mechanism of celecoxib and erlotinib in the chemoprevention of oral cancer. "The whole rationale [for the trial] is not shot, not by a long shot," said Zwelling.

Peer-Review Questions

The Sudbø case comes on the heels of the South Korean cloning scandal, in which researcher Woo Suk Hwang admitted to falsifying data regarding stem cell lines supposedly derived from cloned human embryos. Both cases have prompted journal editors to take a hard look at the peer-review and internal quality-control processes. "It's like a bank robbery. It's rare, but when it does happen we have to look for vulnerabilities in the system," said Barnett S. Kramer, M.D., editor in chief of the *Journal of the National Cancer Institute.*

Donald Kennedy, editor in chief of *Science*, which published the Hwang article, said in a statement that *Science* is "considering options for providing additional procedural safeguards." For example, the journal is considering "requiring all authors to detail their specific contributions to the research submitted and to sign statements of concurrence with the conclusions of the work." Over the past several years, several medical journals, including the *Journal of the American Medical Association,* have begun requiring authors to provide details of their specific contributions prior to publication. JAMA also requires one author to claim "sole responsibility" for the integrity of each submission.

The *Journal of the National Cancer Insitute* has made no specific changes to its submission and peer-review policies in light of the Sudbø case, but Kramer said that the episode has triggered internal discussion about methods to examine submitted manuscripts and illustrations for evidence of fraud or data manipulation. He pointed out, however, that no practical system could reliably detect well-concealed fraud by a scientist intent on covering his or her tracks.

Peer review's strength, said Kramer, is determining whether reported data

Citations for Research Articles Under Investigation

Cancer researcher Jon Sudbø admitted through his attorney to fabricating or mishandling data in several research articles, and an investigative committee is reviewing all of Sudbø's research and publications. None of Sudbø's coauthors are under investigation. The citations of articles known to be in question are as follows:

Sudbø J, Lee JJ, Lippman SM, Mork J, Sagen S, Flatner N, et al. Non-steroidal anti-inflammatory drugs and the risk of oral cancer: a nested case-control study. Lancet 2005; 366:1359–66.

The population-based database claimed to be the source of data for 908 patients in this study was not available to researchers at the time the study was carried out. The Lancet *formally retracted this article in February*.

Sudbø J, Kildal W, Risberg B, Koppang HS, Danielsen HE, Reith A. DNA Content as a prognostic marker in patients with oral leukoplakia. N Engl J Med 2001;344:1270–8.

Micrographs stated to be from two different patients were found to be the same image at different magnifications. NEJM has issued an "expression of concern" and is awaiting the conclusions of the investigative committee before taking further action.

Sudbø J, Lippman SM, Lee JJ, Mao L, Kildal W, Sudbø A, et al. The influence of resection and aneuploidy on mortality in oral leukoplakia. N Engl J Med 2004;350:1405–13.

This article used the same subjects as the article above, so NEJM also included the recent article in its expression of concern.

Sudbø J, Samuelsson R, Risberg B, Heistein S, Nyhus C, Samuelsson M, et al. Risk markers of oral cancer in clinically normal mucosa as an aid in smoking cessation counseling. J Clin Oncol 2005;23: 1927–33.

The specific concerns in this article are unknown.

support an author's assertions. "The system is geared toward evaluating the study design, to gauge whether it supports the interpretation being made. What it can't get at is determining whether the primary and raw data are true. There are so many steps in processing the raw data, and there are many ways an investigator or data manager could change the data."

While the Sudbø and Hwang cases have drawn attention to research fraud, Kramer said that the frequency of such scams cannot be known. "We know only about the cases where someone blows the whistle. We have no idea what the true numerator is.

"That said, whenever something like this happens, the editorial board addresses it and sees if there are any implications for journal policy. Telltale signs of fabrication are always a moving target, and we discuss that. But when it comes to outright fabrication, editors remain, to a large extent, at the mercy of the investigators who submit the final products of their research."

—Brian Vastag

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