

Int. J. Radiation Oncology Biol. Phys., Vol. 55, No. 5, pp. 1216-1225, 2003
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 0360-3015/03/\$ - see front matter



doi:10.1016/S0360-3016(02)04415-2

CLINICAL INVESTIGATION

RADIATION-INDUCED DNA DAMAGE AND REPAIR IN LYMPHOCYTES FROM BREAST CANCER PATIENTS AND THEIR CORRELATION WITH ACUTE SKIN REACTIONS TO RADIOTHERAPY

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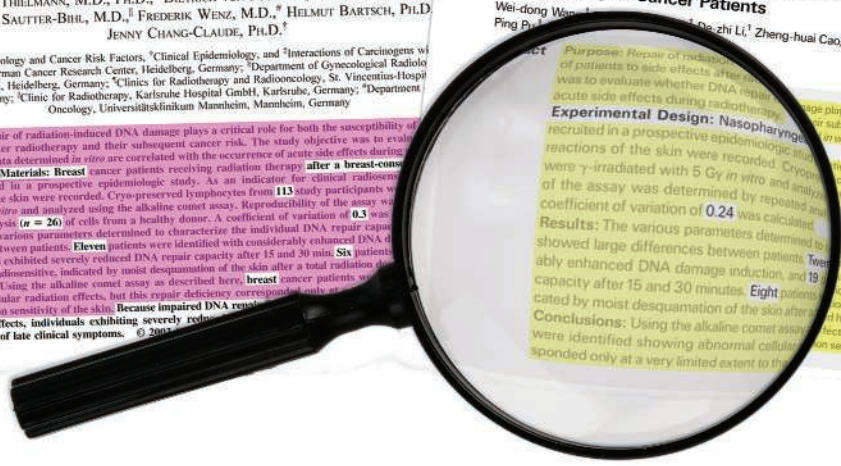
Purpose: Repair of radiation-induced DNA damage plays a critical role for both the susceptibility of side effects after radiotherapy and their subsequent cancer risk. The study objective was to evaluate DNA repair data determined *in vitro* are correlated with the occurrence of acute side effects during radiotherapy. **Methods and Materials:** Breast cancer patients receiving radiation therapy after a breast-conserving operation were recruited in a prospective epidemiologic study. As an indicator for clinical radiosensitivity, reactions of the skin were recorded. Cryo-preserved lymphocytes from 113 study participants were irradiated *in vitro* and analyzed using the alkaline comet assay. Reproducibility of the assay was tested with 5 Gy *in vitro* and analyzed using the alkaline comet assay. A coefficient of variation of 0.3 was repeated analysis ($n = 20$) of cells from a healthy donor. **Results:** The various parameters determined to characterize the individual DNA repair capacity differences between patients. Eleven patients were identified with considerably enhanced DNA damage after 15 and 30 minutes. Six patients and 7 patients exhibited severely reduced DNA repair capacity after 15 and 30 minutes. **Conclusions:** Using the alkaline comet assay as described here, breast cancer patients with abnormal cellular radiation effects, but this repair deficiency corresponded only at a very limited extent to acute radiation sensitivity of the skin. Because impaired DNA repair capacity is a marker for increased radiosensitivity, individuals exhibiting severely reduced DNA repair capacity should be considered as candidates for development of late clinical symptoms. © 2003

Imaging, Diagnosis, Prognosis

Correlation between DNA Repair Capacity in Lymphocytes and Acute Side Effects to Skin during Radiotherapy in Nasopharyngeal Cancer Patients

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Purpose: Repair of radiation-induced DNA damage plays a critical role for both the susceptibility of side effects after radiotherapy and their subsequent cancer risk. The study objective was to evaluate whether DNA repair data determined *in vitro* are correlated with the occurrence of acute side effects during radiotherapy. **Methods and Materials:** Nasopharyngeal cancer patients receiving radiation therapy were recruited in a prospective epidemiologic study. As an indicator for clinical radiosensitivity, reactions of the skin were recorded. Cryo-preserved lymphocytes from 100 study participants were irradiated *in vitro* and analyzed using the alkaline comet assay. Reproducibility of the assay was determined by repeated analysis of cells from a healthy donor. A coefficient of variation of 0.24 was calculated. **Results:** The various parameters determined to characterize the individual DNA repair capacity differences between patients. Twelve patients were identified with considerably enhanced DNA damage induction, and 19 patients exhibited severely reduced DNA repair capacity after 15 and 30 minutes. Eight patients and 7 patients exhibited severely reduced DNA repair capacity after 15 and 30 minutes. **Conclusions:** Using the alkaline comet assay as described here, nasopharyngeal cancer patients with abnormal cellular radiation effects, but this repair deficiency corresponded only at a very limited extent to acute radiation sensitivity of the skin.



Plagiarism Sleuths

A Texas group is trolling through publications worldwide hunting for signs of duplicated material. The thousands of articles they've flagged online raise questions about standards in publishing—and about the group's own tactics

HAROLD "SKIP" GARNER NEVER INTENDED to become an enforcer. The affable computational biologist set out 7 years ago with a modest enough goal: to access the scientific literature more efficiently. With colleagues, he crafted a computer program called eTBLAST that could detect similarities in published abstracts, making it relatively easy to sort through the 19 million papers in a database like MEDLINE and pick out those in a narrow slice of science.

But his group at the University of Texas (UT) Southwestern Medical Center in Dallas quickly realized that eTBLAST had another, tantalizing application. "We could do stuff like find plagiarisms," says Garner. That held definite appeal—but first, Garner wanted to sharpen the program's accuracy. Two years ago, with support from the Office of Research Integrity and the National Institutes of Health, he launched Déjà vu, an online database that bills itself as "a study of scientific publication ethics." It now lists 74,790 pairs of papers drawn from MEDLINE that eTBLAST has found with striking similarities in language

or content. The authors include everyone from Nobel Prize winners to scientists toiling in obscure institutions in every corner of the world. When *Science* conducted random searches of illustrious names, between one-third and one-half showed up in Déjà vu as potential duplicators of their own or others' work. Garner and his crew have built a powerful tool for uncovering repetitive papers—and for raising authors' hackles.

Online sciencemag.org

Podcast interview with author Jennifer Couzin-Frankel.

Over the past year or so, Déjà vu has rapidly gained prominence. It has prompted discussions with journal editors and at least 48 retractions of suspicious papers. In March, a rheumatologist resigned from Harvard Medical School after Déjà vu detected similarities between a review article he had published and an earlier article by a Texas researcher. Some journals now run accepted papers through eTBLAST software, which is freely available, to hunt for duplications prior to publication. Some senior faculty members contacted by *Science* say they would consider using Déjà vu to help guide hiring, promotion, and publication decisions.

But how reliable is Déjà vu, and what do its developers hope to accomplish? *Science* examined many papers listed there and found that Déjà vu casts a wide net, scooping up innocent papers (such as translations) along with suspicious ones. Its large haul raises questions about writing and publication standards for scientific papers; it is also leaving frustrated scientists in its wake. "It's inappropriate to flag these sorts of papers," says Lawrence Solin, a radiation oncologist at the Albert Einstein Healthcare Network in Philadelphia, Pennsylvania, who was angry to learn that he had three pairs of papers in Déjà vu, all written by him. "These people have a serious obligation to do this correctly or not do it at all. And in my view, they are simply not doing this correctly."

The vast majority of listings in Déjà vu, nearly 66,000, are from scientists who, like Solin, appear to be repeating their own previously published work. Repetitious reviews and incremental reports are part of an accepted tradition, and authors say they are less than thrilled to be fingered. Others say Déjà vu makes mistakes—for example, flagging similar studies on different populations.

Downloaded from www.sciencemag.org on August 19, 2009

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◀ **Carbon copy.** Déjà vu detected this pair of suspect papers by different groups of authors; the one highlighted in yellow was published later and recently retracted.

But Déjà vu's masters at UT Southwestern are not just out to nail plagiarists. They are challenging accepted and gray-area practices, particularly the tendency by authors and journals to recast previously published work as novel. "We don't consider ourselves the publication police," says Garner. At the same time, he says, for Déjà vu's team, seeing what makes up the scientific literature has been one "of the most eye-opening experiences in our life."

Worst offenders

Garner and his team of four run an efficient shop. The first step is automated: eTBLAST picks up suspicious papers based on similar titles and abstracts, and Déjà vu slaps them online for anyone to see. But eTBLAST isn't perfect, Garner acknowledges, so these papers are labeled "unverified"—a classification that includes more than 90% of Déjà vu's listings.

Reviewing papers manually is a painstaking task, led primarily by Tara Long, a mathematics major who began working with Garner in 2006 while still in college. If a great deal of text, figures, and references matches that of another paper published earlier, it is classified as a "duplicate." On average, duplicates whose full text has been examined share 85% of their text, says Long. (Each entry consists of two papers, the earlier one and the later one.)

Scrutinizing papers, Long shifts them out of the unverified classification and into one of four main categories: Distinct, Sanctioned, Update, or Duplicate. The first two comprise only appropriate examples of repeated work, whereas in the latter two, suitability varies depending on the circumstance (for example, if a paper was reprinted with permission). Of the 5833 pairs of papers in these four groupings, 2124 are labeled duplicates. Another key question is whether papers have different authors. Déjà vu lists close to 66,000 pairs of papers with shared authors, whereas the rest, just over 9000, have different authors. Of the 2124 listings in the duplicate category, 258 have

different authors on the earlier and later paper, suggesting that they may be examples of plagiarism.

These are the ones Garner's group has focused on most aggressively, systematically contacting authors and journals. They have followed up on 165 cases so far and prompted some acknowledgments of wrongdoing and retractions.

Many apparent instances of plagiarism picked up by Déjà vu reflect a strategy known as "patchwriting"—an underrecognized problem in scientific publishing, according to Garner. Patchwriters lift large portions of the introduction, scientific design, and other sections of a published paper, then plug in details from their own experiment. "They don't take the data, but they take the scientific design," says Beth Notzon, who has taught classes on publication ethics to young physicians at M. D. Anderson Cancer Center in Houston, Texas, and is administrative editor at the *International Journal of Radiation*

much more common in those of Asian ancestry, and reported data from their own patients. The lead author of the original paper, Odilia Popanda of the German Cancer Research Center in Heidelberg, notes that she was rather miffed that the Chinese work, published in 2005, appeared in a higher profile journal, *Clinical Cancer Research*.

The first author of the *Clinical Cancer Research* paper, Wei-dong Wang, an oncologist at Xinqiao Hospital in Chongqing, China, wrote in an e-mail message to *Science* that "our English skill was not good enough to meet the language requirements" of *Clinical Cancer Research*. "To publish our findings as quickly as possible, the first author Dr. Wang organized our results in the similar pattern of Popanda's publication," Wei-dong Wang continued, referring to himself in the message. He stressed, however, that the type of cancer and the results were different.

Wang also wrote that "we have done foolish things" and "we should express our findings in our own words." Wang wrote in a later e-mail message to *Science* that he and his co-authors had decided to withdraw the paper, and it was retracted late last month.

Wang's account of patchwriting jibes with what Notzon has seen in her classes. She was startled to find that many foreign scholars at M. D. Anderson, particularly those from Asia, consider it perfectly appropriate. "We had a young woman visiting from China who taught writing and editing in China, and she said laughingly, 'Oh, we encourage this sort of thing because people don't have good idiomatic English.'" But, Notzon says, patchwriting is "wrong because it's really a kind of plagiarism—they're taking someone else's research idea."

Challenging standards

More discomfiting questions raised by Déjà vu focus on the norms of scientific publishing. Take reviews, which make up about 20% of the listed papers, Long estimates. They often contain duplicated material, particularly from the author's own published articles. "You can't just copy your introduction [on an article]. But to what extent is that wrong? There's definitely a gray area," says Notzon.

When it comes to repetition of their own writing, few scientists see a problem. "When

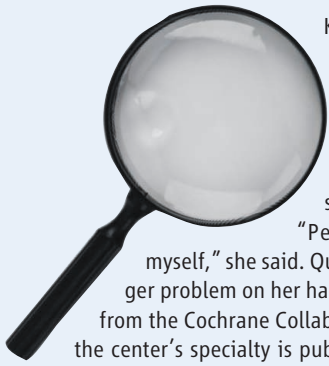


Riding high. Skip Garner, with one of his horses, runs Déjà vu and receives dozens of tips—and complaints.

Oncology, Biology, Physics. "They're able to repeat the whole thing but in a different population of patients."

Notzon's journal was alerted to such a case by Déjà vu. A group in China had, by Déjà vu's estimate, copied more than 95% of a paper on breast cancer first published in 2003 in the *International Journal of Radiation Oncology, Biology, Physics*. The Chinese group changed the focus from breast cancer to nasopharyngeal cancer, which is

Repetition Is Not Duplication



Kay Dickersin, an epidemiologist at Johns Hopkins University in Baltimore, Maryland, grew intrigued by Déjà vu after encountering a case of plagiarism in a class she taught. On a lark, she plugged her own name into the database and was shocked to see a pair of papers she'd authored come up. "People are going to think I'm plagiarizing myself," she said. Quickly, Dickersin realized she had an even bigger problem on her hands: Déjà vu was riddled with papers like hers from the Cochrane Collaboration, whose U.S. center she runs, because the center's specialty is publishing updated reviews of clinical research. They are repetitive by design.

The Cochrane database, containing about 3800 papers in all, has a whopping 2879 papers listed on Déjà vu. We "realized straight away that people would say, 'These guys in Cochrane are just ripping each other off,'" says Nick Royle, CEO of Cochrane, based in Oxford, U.K. He immediately wrote to Harold "Skip" Garner of the University of Texas Southwestern Medical Center in Dallas, who runs Déjà vu.

you labor over a sentence, when you love that sentence, it's really hard to move too many commas around" if you use it again, says Douglas Mann, a cardiologist at Washington University in St. Louis, Missouri, who has five pairs of papers on Déjà vu, all 10 of them reviews authored or co-authored by him. Four sets are "unverified" and one is listed as a duplicate.

"There's going to be redundancy" in review articles, Mann continues, echoing similar comments by others, "but I don't think that's scientific misconduct." Some blame the system. Often when a topic is trendy, journals solicit many reviews from the same author, on the same subject, in a short period of time. Authors respond with repetitive articles. In original research papers, too, wording may overlap substantially. When it comes to writing introductions, "if you have a series of papers on the same topic, I can imagine some of the same narrative getting in there, consciously or unconsciously," says William Gelbart, a geneticist at Harvard University.

More clear-cut is the use of material published by other researchers without proper attribution. Rudolf Weiner, a bariatric surgeon at the hospital Krankenhaus Sachsenhausen in Frankfurt, Germany, was notified of a paper that Déjà vu declared a duplication of obesity research from another bariatric surgeon at Mount Sinai School of Medicine in New York City, Daniel Herron. "Between one-third and half of the article was essentially word for word taken from my article," a review, Herron says.

In an e-mail to *Science*, Weiner, the first

author on the later paper, wrote that one of his co-authors "received the order to create an introduction for this article about morbid obesity" and "he made a copy (obviously) of an introduction from the previous article." Weiner emphasized that the article was an overview, not original research. He declined to answer any additional questions. The co-author in question died suddenly, he says. The article was not retracted, and the journal, *Surgical Technology International*, did



Falsely fingered? Patrick Bossuyt discovered 19 listings under his name and says all are ethical publications.

Garner responded by creating a new category for the Cochrane papers: All 2879 are now listed as "sanctioned," a class of legitimate duplications. "To his credit," says Royle, Garner grasped the problem. Still, Royle is uneasy with the outcome, concerned that the term "sanctioned" will be misconstrued as negative. Dickersin, who admits she might be "paranoid" about showing up in Déjà vu, would rather see the papers removed from the database altogether. But that's something Garner won't do.

Garner has become accustomed to fielding queries from panicked, nervous, or irate scientists. He has written personal notes to more than 100 people in an attempt to assuage concerns. But not once has a listing been pulled, he says, and he won't grant special exemptions, no matter how eminent the researcher.

Does Garner worry about posting inaccurate listings or insinuating that someone has plagiarized when they have not? "Hell, yeah," he says. "This is a touchy subject, and it can affect people's careers." With that in mind, Déjà vu's minders examine papers brought to their attention by the authors, and Garner then writes them to explain that the paper was reviewed and—in most cases—determined to be benign. It's then placed in an innocuous category. Pulling papers, Garner believes, would dilute Déjà vu's potency. "It's valuable to show other categories where things are highly similar," he says, "but also valuable to science." **—J.C.-F.**

not return calls seeking comment.

One duplication spotted by Déjà vu led to a resignation. Rheumatologist Lee Simon of Harvard Medical School in Boston stepped down in March after Déjà vu determined that a review published by him in August 2004 describing new treatments for rheumatoid arthritis was similar to a paper released 13 months earlier, by Roy Fleischmann of UT Southwestern. Simon could not be reached for comment. Harvard spokesperson David Cameron confirmed that Simon had resigned and that Harvard had investigated the case, but gave no details.

Guilt by association

Garner believes that there's no problem with quoting one's own or others' work as long as the later article cites the earlier one and makes clear what's being repeated. Translations are an obvious form of approved duplication. Indeed, a paper that Garner, Long, and their colleagues published earlier this year in *Science* about Déjà vu (*Science*, 6 March, p. 1293) will likely fall into Déjà vu's duplicate category if a translation appears in a Spanish journal, as one has requested. Garner says that because the Spanish version will note the publication in which the article was first published, he has no qualms about appearing in Déjà vu.

But many with whom *Science* spoke disagree: Surfacing in Déjà vu, they say, suggests wrongdoing. They also lament Déjà vu's decision to publicly post tens of thousands of unverified papers. "A list like this that's computer generated can cause much harm and then put the onus on a young scientist to explain away why their entirely appro-

ropriate use of review material got them onto the list,” says Jeffrey Macklis, a neuroscientist at Harvard whose own reviews appear on Déjà vu’s unverified list because of their similarity. Macklis says all of these papers properly cited his previous reviews. If just showing up in Déjà vu suggests wrongdoing, as he worries it does, that’s comparable to McCarthy-era blacklists from the 1950s that, he says, “were feared” in his house. “This is meant to be a shame-and-blame list,” says Karl-Heinz Krause, a physician who studies stem cells at the University of Geneva in Switzerland. He appears in Déjà vu’s duplicate category because, he says, a journal in which he published, *Swiss Medical Weekly*, republished a paper of his in a supplement without notifying him.

Patrick Bossuyt, a clinical epidemiologist at the University of Amsterdam in the Netherlands, anxiously searched Déjà vu after a colleague told him that several of his papers were listed there as “fraudulent.” (In reality, Déjà vu has no such category.) At least 10 of his 19 listings appeared in one of the “safe” categories; the others were mostly unverified, with one labeled a duplicate. The unverified listings, he says, refer to a combination of translations, updates, and distinct papers, whereas the duplicate listing captures two identical introductory articles used to present a series in different issues of *Nature Reviews Microbiology*. Bossuyt calls them all examples of ethical publication but still worries that so many listings could sully his reputation.

Some also question Déjà vu’s accuracy, pointing to papers it had flagged that they deem unique experiments. Nader Rifai, a clinical chemist at Harvard Medical School, appears in three listings in Déjà vu with articles that are “completely different,” he says. One includes two papers that investigated two distinct drugs. Another, for which Rifai is only on the earlier paper and not the later one, examined hormone levels associated with diabetes, with one experiment in men and one in women, he says. Walter Willett, a prominent epidemiologist and nutrition expert at Harvard School of Public Health, had a similar experience: Two of the six unverified listings on which he appears in Déjà vu describe a similar study of high blood pressure performed in different populations, men and women. Willett’s other list-

ings are reviews, which have to “cover the waterfront,” he says. “If you come back and review something in 2 years, it will probably be 80%” like the earlier article.

Shades of gray

Just 2 years after its launch, Déjà vu has become the place to go to for anyone who wants to report suspicions of plagiarism or inappropriate duplication. It receives dozens of tips, Garner says, from “people who reported their previous mentors, their depart-

paper without prior notification—admitted that it had reprinted many papers in a supplement but cited the initial publication. PubMed, however, failed to pick up that the papers were reprinted, and Marty says the journal has notified PubMed to add a comment to this effect. The journals *Annals of Surgery* and *Anaesthesia and Intensive Care* both learned of duplication cases from Déjà vu and now screen accepted articles with eTBLAST, available for free online, before they’re printed. “It gives us more confidence about what we publish,” says Pamela Nevar, the managing editor of *Annals of Surgery*.

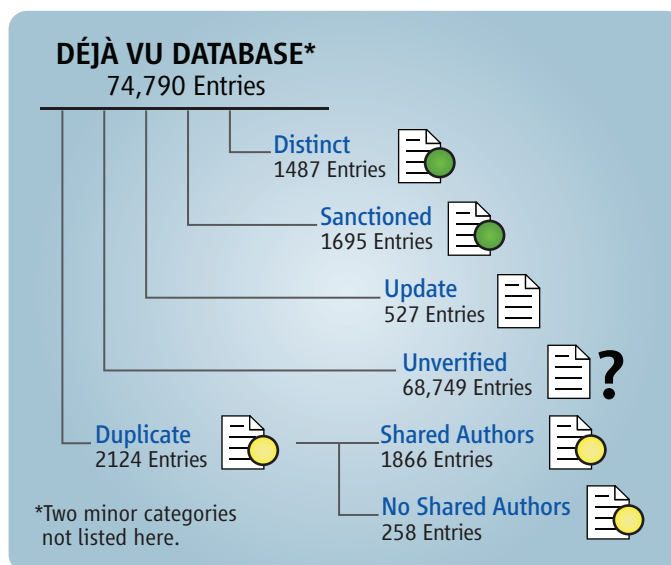
John Loadman, an anesthesiologist in Sydney, Australia, and editor of *Anaesthesia and Intensive Care*, hopes to set up an automated system to check every paper submitted to the journal with eTBLAST. His journal had 21 cases listed in Déjà vu, three of which turned out to be “true cases of duplicate publication,” he says. Loadman doesn’t believe false positives are a problem, as “it’s very easy to work out” which are real.

Some researchers say they would willingly use Déjà vu to check papers when making hiring and promotion decisions. But others—particularly those who say they appear in Déjà vu wrongly—consider that a terrible idea.

Witold Filipowicz, an RNA biologist at the Friedrich Miescher Institute in Basel, Switzerland, says it’s useful for scientists to be “aware that there is a watchdog.” He emigrated from Poland 25 years ago, where at the time, as in other Eastern European countries, promotions, funding, and other career decisions were primarily “based on number of publications,” he says. Although that has changed, Filipowicz estimates that now worldwide, “50% or 70% of what is published is just of no value.” Garner agrees that one issue underscored by Déjà vu is an excess of journals and of review articles in particular.

Still, Filipowicz thinks Déjà vu ought to highlight true plagiarism and lessen its emphasis on articles that are not original research. (One of his own papers, a symposium report based on an earlier publication, has been flagged by Déjà vu as an unverified case.) “If 90% [of listings] are benign,” he says, “they will in a way muddy the real crimes,” distracting attention from where he says it should lie.

—JENNIFER COUZIN-FRANKEL AND JACKIE GROM



Yellow and green. Some of Déjà vu’s categories, such as “duplicate,” may reflect inappropriate publication, whereas others, such as “distinct,” indicate no problem.

ment chairman.” Garner’s group spends hours contacting journals and authors to alert them of Déjà vu’s findings.

Garner says his aim is cleaning up the literature and coaxing scientists and journals to reconsider what’s appropriate. Gelbart, himself a member of the booming club listed in Déjà vu, agrees that including many types of repetitive work is “useful as fodder for the scientific community to decide whether this falls within the norms of acceptable behavior or not.” His pair of listings in Déjà vu were progress reports “written with a lot of boilerplate,” he says, intended to get the word out about FlyBase, a database of fruit fly genes that began in the early 1990s.

Journals have responded to Déjà vu in different ways. Many have ignored inquiries about suspect papers. Journals in India and Egypt contacted by *Science* because the database listed them as having published more than a dozen duplicate papers did not respond.

Some journals have embraced Déjà vu or adjusted their standards because of it. Natalie Marty, managing editor of *Swiss Medical Weekly*—which Krause says republished his