Supreme Court case involved the drug Zicam, which caused permanent hearing loss in some users. Another drug, rofecoxib (Vioxx), was taken off the market because of adverse cardiovascular effects. The drug companies involved did not report those adverse effects because of lack of statistical significance in the original drug tests (Rev. Soc. Econ. 2016;74:83–97; doi:10.1080/00346764.2016.1150730).

ASA panelists encouraged using alternative methods “that emphasize estimation over testing, such as confidence, credibility, or prediction intervals; Bayesian methods; alternative measures of evidence, such as likelihood ratios or Bayes Factors; and other approaches such as decision-theoretic modeling and false discovery rates.” However, any method can be used invalidly. “If success is defined based on passing some magic threshold, biases may continue to exert their influence regardless of whether the threshold is defined by a P value, Bayes factor, false-discovery rate, or anything else,” wrote panelist John Ioannidis, Ph.D., professor of medicine and of health research and policy at Stanford University School of Medicine in Stanford, Calif.

Some panelists argued that the P value per se is not the problem and that it has its proper uses. A P value can sometimes be “more informative than an interval”—such as when “the predictor of interest is a multicategorical variable,” said Clarice Weinberg, Ph.D., who was not on the panel. “While it is true that P values are imperfect measures of the extent of evidence against the null hypothesis, confidence intervals have a host of problems of their own,” said Weinberg, deputy chief of the Biostatistics and Computational Biology Branch and principal investigator of the National Institute of Environmental Health Sciences in Research Triangle Park, N.C.

“If success is defined based on passing some magic threshold, biases may continue to exert their influence regardless of whether the threshold is defined by a P value, Bayes factor, false-discovery rate, or anything else.”

Beyond simple misinterpretation of the P value and the associated loss of information, authors consciously or unconsciously but routinely engage in data dredging (aka fishing, P-hacking) and selective reporting. “Any statistical technique can be misused and it can be manipulated especially after you see the data generated from the study,” Kramer said. “You can fish through a sea of data and find one positive finding and then convince yourself that even before you started your study that would have been the key hypothesis and it has a lot of plausibility to the investigator.”

In response to those practices and concerns about replicability in science, some journals have banned the P value and inferential statistics. Others, such as JNCI, require confidence intervals and effect sizes, which “convey what a P value does not: the magnitude and relative importance of an effect,” wrote panel member Regina Nuzzo, Ph.D., professor of mathematics and computer sciences at Gallaudet University in Washington, D.C. (Nature 2014;506:150–2).

How can practice improve? Panel members emphasized the need for full reporting and transparency by authors as well as changes in statistics education. In his commentary, Don Berry, Ph.D., professor of biostatistics at the University of Texas M.D. Anderson Cancer Center in Houston, urged researchers to report every aspect of the study. “The specifics of data collection and curation and even your intentions and motivation are critical for inference. What have you not told the statistician? Have you deleted some data points or experimental units, possibly because they seemed to be outliers?” he wrote.

Kramer advised researchers to “consult a statistician when writing a grant application rather than after the study is finished; limit the number of hypotheses to be tested to a realistic number that doesn’t increase the false discovery rate; be conservative in interpreting the data; don’t consider P = 0.05 as a magic number; and whenever possible, provide confidence intervals.” He also suggested, “Webinars and symposia on this issue will be useful to clinical scientists and bench researchers because they’re often not trained in these principles.” As the ASA statement concludes, “No single index should substitute for scientific reasoning.”

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Physical Activity Associated With Fewer Cancers

By Susan Jenks

Even moderate leisure-time physical activity may protect against 13 cancers, according to a massive observational study that appeared May 16 in JAMA Internal Medicine (doi:10.1001/jamainternmed.2016.1548).

But which type of exercise brings the most benefit is not yet clear, researchers say, nor is exercise alone likely to account for its association with a lower cancer risk in colon, breast, and endometrial cancers, among others. “Physical activity is not a stand-alone, magic bullet,” said William McCarthy, Ph.D., adjunct professor in the department of health services in the Fielding School of Public Health at the University of California, Los Angeles. “The biggest bang [in risk reduction] comes when exercise is coupled with a Mediterranean-style diet and not smoking.”

Still, McCarthy said, the recent joint study by researchers at the National
Cancer Institute and the American Cancer Society highlights exercise’s importance to cancer risk and overall health, despite what he described as years of skepticism in the scientific community. “It’s a shot in the arm for those of us doing exercise studies for years,” he said.

Researchers at both organizations analyzed pooled data for the self-reported leisure-time physical activities of 1.44 million people in 12 U.S. and European studies conducted between 1982 and 2004. Analyzing data from those combined studies gave investigators greater statistical power than a single study.

“Most of the data in our study had never before been published, or in many cases, results had been published early on, but with no follow-up,” said Steven C. Moore, Ph.D., M.P.H., lead author and an investigator at NCI. “By pooling the data ourselves, we were able to pick and choose what to study, allowing us to produce stronger findings and minimizing heterogeneity.”

Median follow-up time was 11 years. During that period, roughly 186,000 new cases of cancer occurred—the highest numbers seen in those cancers with the highest incidence in the general population as well: prostate, breast cancer, lung cancer, and colon cancer.

Each of the 12 studies had a common theme, with the general understanding that exercises were done only for fitness, not as part of daily activities, Moore said. Also, in each study, investigators compared the metabolic activity expended, grouping people by percentile from most active to least active. Most people in the studies, Moore said, engaged in moderate activity, primarily walking, expending roughly three times the number of calories used while sitting.

The median among participants was 150 minutes per week of moderate-intensity activity. That level dovetails with the minimum level of exercise that the U.S. government recommends—that, or 75 minutes each week of vigorous, heart-pumping activities, such as running or swimming.

Moore described the nation’s physical activity guidelines as “spot-on.” But for other outcomes, such as weight loss, or potentially stronger cancer prevention, the levels of physical activity should be higher, he said.

Future studies will look at the type, intensity, and volume of exercise that bring the best results, Moore said, adding “all three still need better characterization.”

**Rising Benefit**

The authors looked at how exercise affected 26 cancers. In general, people who exercised more saw an association with a 7% lower risk of developing any type of cancer, compared with more sedentary individuals, despite the known limitations of self-reporting. But the most compelling finding was that the most active exercisers—those in the top 10% of the statistical analysis—were at least 20% less likely than the least active to develop certain cancers, including esophageal, stomach, kidney, and liver cancers. And the data confirmed a lowered risk for colon, breast, and endometrial cancers, as hundreds of studies have suggested.

Overall, the investigators observed the strongest association between exercise and lower cancer risk in esophageal adenomas (a 42% lower risk) and the weakest in two malignancies, melanoma and prostate cancer.

> “Exercise is very consistently associated with reduced inflammation, not only for all cancers, but all conditions, including heart disease, diabetes, and even Alzheimer’s disease.”

Prostate cancer showed evidence of a modestly higher association with cancer risk among men who exercised more, said Alpa Patel, Ph.D., a coauthor and investigator at the American Cancer Society in Atlanta. “But we don’t believe that to be a biologically true finding,” she said. “Physically active men are far more likely to be screened and, if you’re screened, you see more cancers.”

Similarly, researchers attributed the small spike in melanoma to certain habits of more-active individuals: not only an increased likelihood of screening but also, during exercise, more exposure to the sun’s UV rays.

One surprising finding concerned body mass index, which made little difference in results. But the finding did not mean that no independent protective effect was present even in obese or overweight individuals who exercised actively, only slightly less than anticipated, Patel said.

For example, the top exercisers had a 16% lower risk than the least active of developing colon cancer, without adjusting for body mass index, she said. But after researchers accounted for this variable, the risk still remained 13% lower in the physically active group.

“One of the most exciting things about our study is it boosts the benefits of exercise much more broadly” to the general population, Patel said.

**Metabolic Pathways**

Exactly how exercise exerts its beneficial effects in cancer risk remains an area of active research.

Moore said he and his colleagues generally believe that changes in sex hormones, insulin resistance, and inflammation are the mechanisms through which exercise protects against cancer.

A more precise understanding of these mechanisms “would not only strengthen the biological plausibility of the physical activity–cancer association, but could aid in identifying molecular targets for intervention,” wrote Marilie Gammon, Ph.D., an epidemiologist from the Gillings School of Global Public Health in Chapel Hill, N.C., in an editorial accompanying the study. But although Gammon praised the researchers for their work, she noted that physical activity is “just one of a cluster of healthy behaviors” that may contribute to their findings.

McCarthy agreed, citing a good diet as one healthy behavior, needing further emphasis because of its close interaction with the inflammatory response. “Exercise is very consistently associated with reduced inflammation, not only for all cancers, but all conditions, including heart disease, diabetes, and even Alzheimer’s disease,” McCarthy said. And although exercise lowers inflammation in the gut, its presence can undercut a good diet, he said, illustrating how closely the two work together to ensure good health.

“In this study, the organs most affected are the digestive organs, and they disproportionately interact with nu-
Mammaprint Reveals Who Can Skip Chemotherapy for Breast Cancer

By Charles Schmidt

Commercial biomarkers that guide clinical decisions in breast cancer appeared on the market just over a decade ago. In April, researchers unveiled long-awaited, prospective phase III results for the European market leader: a 70-gene assay called Mammaprint. The new data show that many patients whom the assay identified as having low risk of recurrence can safely avoid chemotherapy. Researchers presented the results at the American Association for Cancer Research’s annual meeting in New Orleans.

The U.S. Food and Drug Administration approved Mammaprint in 2007, citing evidence that it could predict whether a woman’s breast cancer is likely to return within 5–10 years. Published a year earlier in *JNCI*, the evidence came from a study of 302 women diagnosed with node-negative, stage T1–T2 breast cancer between 1980 and 1998 who hadn’t received adjuvant systemic therapy. The authors concluded that Mammaprint adds independent prognostic information and identifies women with a low risk of metastases and death more reliably than clinical factors such as age, tumor size, and tumor grade. But that retrospective early study relied on frozen tumor samples for genetic analysis. Despite FDA approval, many U.S. experts were therefore unconvinced that Mammaprint should play a role in chemotherapy treatment decisions. Indeed, in updated clinical practice guidelines published last February, the American Society of Clinical Oncology (ASCO) recommended against using Mammaprint for that purpose. ASCO panelists claimed they couldn’t determine whether the assay identifies women for whom chemotherapy is likely to be ineffective. But they also wrote that they were awaiting results from MINDACT, the prospective phase III trial sponsored by the Brussels-based European Organisation for Research and Treatment of Cancer (EORTC).

According to Lyndsay N. Harris, M.D., chair of the ASCO Breast Cancer Guidelines Advisory Group and director of the Breast Cancer Program at Case Western Reserve University School of Medicine in Cleveland, the data appear to offer “level 1 evidence that the 70-gene assay is associated with improved patient outcomes.” However, ASCO panelists still need to review the published MINDACT data before possibly revising their decision against it, she said. Those data are expected later this year.

The ASCO guidelines approved five molecular assays in various stages of development. The guidelines limited recommended uses to women with hormone receptor (HR)–positive, HER2-negative, node-negative breast cancer. Many such women have low risks of incurable recurrence after treatment with surgery, radiation, or hormonal therapy. Chemotherapy can reduce that risk by an additional 30%, but it also produces potentially life-threatening toxic effects in 2%–3% of otherwise healthy women. Whether chemotherapy’s added benefits justify the potential harm to low-risk patients often isn’t clear. Therefore, clinicians are turning to molecular assays for new insights.

[Some 94% of patients in which Mammaprint predicted a low recurrence risk had metastasis-free survival at 5 years regardless of whether they underwent chemotherapy.] “That’s the fundamental message. This is the group for which Mammaprint could be most helpful.”

The test with the longest history, the 21-gene Oncotype DX assay (among those ASCO recommended), classifies risk of recurrence as low, medium, high. A massive National Cancer Institute–sponsored study, the TAILORx trial, is evaluating Oncotype DX. That study recently published data showing that 98% of women in the low-risk group remained free of distant metastases 5 years after hormonal therapy. Researchers generally agree that high-risk women need chemotherapy. But whether chemotherapy benefits the roughly 60% of patients in the medium-risk category remains an open question. Therefore, TAILORx randomized medium-risk patients to treatment with either hormonal therapy alone or hormonal therapy plus chemotherapy. Those results are not yet available. But according to Nancy Davidson, M.D., professor of oncology at the University of Pittsburgh Cancer Institute, the results should eventually offer information to help predict how treatment decisions informed by molecular screening influence survival.

Oncotype DX and Mammaprint both address similar needs, but their gene signatures are dissimilar. The former measures genes associated with the estrogen receptor and HER2 pathways, whereas the latter measures genes involved in tumor proliferation, metastasis, angiogenesis, and other disease processes. Moreover, whereas Oncotype DX groups risk into three categories, Mammaprint describes risks as only high or low. The MINDACT trial evaluated nearly 7,000 patients in two ways. Researchers both used Mammaprint to genetically screen patients’ tumors and assessed patients with Adjuvant! Online, a tool that uses clinical criteria such as age and tumor size to predict breast cancer recurrence. Often, patients deemed high risk by Mammaprint were likewise deemed high risk by Adjuvant Online! and vice versa. However, in about 1,500 patients, Mammaprint predicted low recurrence risk, whereas Adjuvant! Online predicted the opposite. According to Martine Piccart, M.D., Ph.D., professor of oncology at