Introduction: Not everything you read is true

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Conflicts of Interest

Research support: Elekta Instrument, AB

One year ago…

AAPM 2016 JUL 31–AUG 4

Statistical Failings That Keep Us All in the Dark

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Presentations

8:30 AM : ***Introduction: Not Everything You Read Is True*** - D Schlesinger, Presenting Author
9:00 AM : ***Statistical Failings That Can Keep Us All in the Dark*** - J Sloan, Presenting Author

In the meantime….

The truth is hard to come by

still

Session Educational objectives

1. Learn about the presence of statistical problems in published studies
2. Identify common signs and symptoms of potential problems in various types of statistical tests
3. Learn methods for correctly implementing statistical analyses of the type commonly found in clinical publications

Cellphone use causes cancer

PUBLIC HEALTH

Major Cell Phone Radiation Study Reignites Cancer Questions

Exposure to radio-frequency radiation linked to tumor formation in rats

By Dina Fine Maron on May 27, 2016 Vitale en español

SCIENTIFIC AMERICAN.

Led by the National Toxicology Program (NTP) under the NIH

Rodents exposed to calibrated RF (GSM and CDMA) radiation for 9 hours/day over 2 years

Division into groups by SAR exposure

Association between exposure and cardiac schwannoma in male rodents (no association in female rodents)

http://www.cancer.gov/about-cancer/causes-prevention/risk/radiation/cell-phones-fact-sheet

Cellphone use causes cancer – maybe?

ars TECHNICA BIZ & IT TECH SCIENCE POLICY CARS GAMING & CULTURE FORUMS

SCIENTIFIC METHOD —

Study that found cell phones cause cancer in rats is riddled with red flags

Researchers strangely release partial results without formal review, cause alarm.

BETH MOLE - 5/31/2016, 11:25 AM

Study was released before complete peer-review on a pre-publication website

Control rats showed less than expected natural rate of tumor incidence and died early

Incidence of tumor development correlates with age, so the early control death may have magnified the statistical findings

http://arstechnica.com/science/2016/05/study-that-found-cell-phones-cause-cancer-in-rats-is-riddled-with-red-flags/

Human studies are mostly one-sided

Publication Year	Study	Type	# participants	Outcome
2010	Interphone Study Group	Case-control study	~5000 cases; ~5000 matched controls; 13 countries	No overall risk*
2001 (updated 2007, 2011)	Danish cohort study	Cohort study	358,000	No association
2013 (updated 2014)	Million Women Study	Prospetive cohort study	791,710	Yes (acoustic neuroma), then no association
2014	CERENAT	Multicenter case control	447 cases, 892 matched controls	No association with regular use; yes association with heaviest use
2011	Swedish pooled analysis	Pooled analysis of 2 case control studies	1251 cases, 2438 controls	Increased risk of glioma

The result of studies of thousands of animals and hundreds of thousands of people, supported by millions of dollars in funding, is that we have no definitive answer to the question of cellphone use and cancer.

So….

How confident can we be about studies like this:

SRS for lung cancer: Does morning or afternoon make a difference?

Abstract

BACKGROUND: Circadian cell-cycle progression causes fluctuating radiosensitivity in many tissues, which could affect clinical outcomes. The purpose of this study was to determine whether outcomes of single-session gamma knife radiosurgery (GKRS) for metastatic nonsmall cell lung cancer (NSCLC) differ based on treatment time.

METHODS: Fifty-eight patients received GKRS between 10:00 am and 12:30 pm and 39 patients received GKRS between 12:30 pm and 3:00 pm. The mean peripheral dose was 18.6 Gy. The mean tumor size was 7.3 cm^3. Magnetic resonance imaging was used to score local control at 3 months. Cause of death (COD) was categorized as central nervous system (CNS)-related or systemic.

RESULTS: Demographic and disease characteristics of the 2 groups were similar. Local control at 3 months was achieved in 97% (35/36) of patients who underwent GKRS early in the day versus 67% (8/12) of patients who underwent GKRS later in the day (chi-square, P = .014). Early GKRS was associated with better survival (median 9.5 months) than late GKRS (median 5 months) (Kaplan-Meier log-rank test, P = .025). Factors contributing to better survival in a Cox regression model included early treatment time (P = .004) and recursive partition analysis class (P < .001). Cause of death in the early treatment group was CNS-related in 6% (3/47) of patients versus 24% (8/34) of patients in the late treatment group (chi-square test, P = .026).

CONCLUSIONS: GKRS for metastatic NSCLC had better local control, better survival, and a lower rate of CNS-related cause of death when given earlier in the day versus later in the day. These retrospective data should encourage future study in brain radiosurgery and non-CNS stereotactic body radiotherapy series.

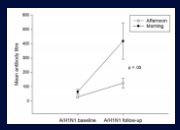
D. Rahn, et al., Cancer 177(2), 2011.

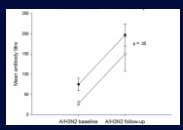
But…maybe we were onto something in this case…..

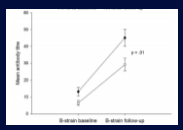
Vaccine. 2016 May 23;34(24):2679-85. doi: 10.1016/j.vaccine.2016.04.032. Epub 2016 Apr 26.

Morning vaccination enhances antibody response over afternoon vaccination: A cluster-randomised trial.

Long JE[1], Drayson MT[2], Taylor AE[3], Toellner KM[2], Lord JM[4], Phillips AC[5].



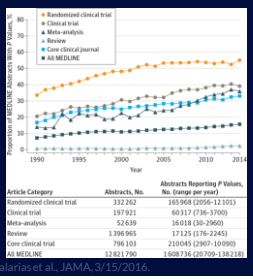




Radiation Oncology is full of similar studies

Reporting statistical tests has become a requirement

Medicine increasingly relies on p-values



Article Category	Abstracts, No.	Abstracts Reporting *P* Values, No. (range per year)
Randomized clinical trial	332 262	165 968 (2056-12 101)
Clinical trial	197 921	60 317 (736-3700)
Meta-analysis	52 639	16 018 (30-2960)
Review	1 396 965	17 125 (176-2245)
Core clinical trial	796 103	210 045 (2907-10 090)
All MEDLINE	12 821 790	1 608 736 (20 709-138 218)

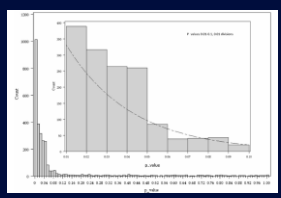
Original Investigation

Evolution of Reporting *P* Values in the Biomedical Literature, 1990-2015

JAMA The Journal of the American Medical Association

Chavalarias et al., JAMA, 3/15/2016.

p-values just below p=0.05 are over-represented



The distribution of probability values in medical abstracts: an observational study

Conclusions:

p-values immediately below 0.05 appear to be over-represented in the literature relative to their expected frequency

Shows evidence of systematic error including publication bias, selective reporting, methodological errors, or fraud.

. Ginsel, et al., BMC Res Notes 8, 2015.

Try it yourself: there are many ways to achieve a desired story

FiveThirtyEight

http://fivethirtyeight.com/features/science-isnt-broken/#part2

The ASA's statement on p-values: context, process, and purpose

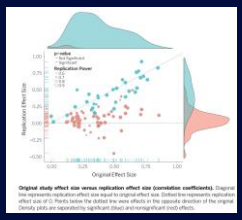
Ronald L. Wasserstein & Nicole A. Lazar

1. *P-values can indicate how incompatible the data are with a specified statistical model.*
2. *P-values do not measure the probability that the studied hypothesis is true, or the probability that the data were produced by random chance alone.*
3. *Scientific conclusions and business or policy decisions should not be based only on whether a p-value passes a specific threshold*
4. *Proper inference requires full reporting and transparency*
5. *A p-value, or statistical significance, does not measure the size of an effect or the importance of a result.*
6. *By itself, a p-value does not provide a good measure of evidence regarding a model or hypothesis.*

. Wasserstein et al., The American Statistician, 2016.

What we think is the truth often can't be replicated

One study's result is not necessarily the truth



Original Effect Size

Original study effect size versus replication effect size (correlation coefficients). Diagonal line represents replication effect size equal to original effect size. Dotted line represents replication effect size of 0. Points below the dotted line were effects in the opposite direction of the original. Density plots are separated by significant (blue) and nonsignificant (red) effects.

Open Science Collaboration, Science, 49, 2015.

RESEARCH ARTICLE

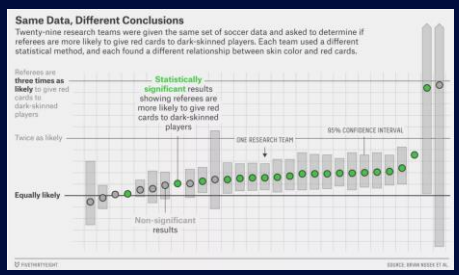
PSYCHOLOGY

Estimating the reproducibility of psychological science

Open Science Collaboration*†

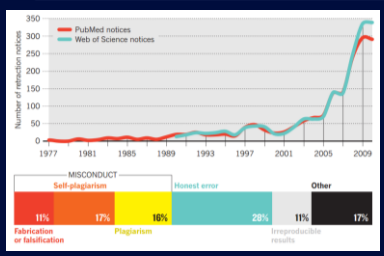
http://news.harvard.edu/gazette/story/2016/03/study-that-undercut-psych-research-got-it-wrong/)

http://projects.iq.harvard.edu/psychology-replications/



http://fivethirtyeight.com/features/science-isnt-broken/#part2

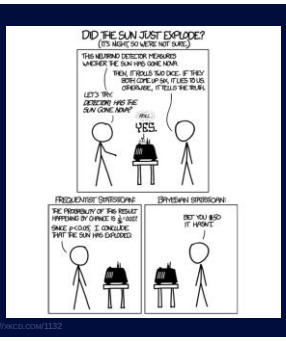
The number of retractions is sharply rising



nature.com

R. Van Noorden, Nature, 478, 2011.

A lack of statistical fluency may be part of the problem



HTTP://XKCD.COM/1132

Many medical physicists receive little training in practical statistics as applied to clinical outcomes studies

However…these studies are at the heart of our profession.

How to recognize when the statistics don't quite add up?

But…we can learn to be better