**Why “An estimate of the science-wise false discovery rate and application to the top medical literature” is false**

**SUPPLEMENTARY MATERIAL**

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**Appendix References 1:**

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See also the series of papers in the entire November 2012 issue of Perspectives on Psychological Sciences. For an overview of the empirical evidence on biases and low credibility in the economics literature, see upcoming review:

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**Appendix References 2:**

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**Appendix text 1:**

I was highly intrigued by the distributions of *P*-values in Figure 3 of the paper that had been accepted by *Biostatistics* and that was forwarded to me so as to write a Discussion paper. Visibly, the distributions had no *P*-values at 0.05, although values of *P*<0.05 and *P*=0.05 are commonplace for claiming significance in most biomedical fields that I am aware of. Then, I probed the raw data file pvalueData that Jager and Leek has posted online and realized that I could reproduce none of the figure panels that I probed. I wrote to the editor about this in an e-mail:

“Dear Butch,

Since this is an intriguing paper, I have done a bit further reproducibility checking. I am sorry to burden you with this, but I want to make sure that I have the correct raw dataset. For example, the raw pvalue data in the R file that you told me to download doesn't seem to correspond even remotely to what is shown in the figure 3 of the manuscript which is supposed to show these same raw data. For example, take AJE 2010: there are only 103 p-values<0.05 in the R file, of which 41 (40%) are 0.001 or less. However, the respective figure 3 panel (bottom right corner) gives over 600 p-values of 0.001 or less and these seem to represent something like 80% of the data. I have compared several years/journals against what is shown in figure 3 panels and I get very different distributions. There is tons of things that are wrong with this paper, but at a minimum I would hope that the very basic numbers are correct. So, I suspect that maybe I am looking at some wrong data file? Could you please clarify this for me? I attach the data in the pvalue file converted in a plain spreadsheet so you can see quickly what I mean.

Sorry for my confusion, please let me know if I have the right data. A million thanks in advance!

Best wishes,

John”

The editor very kindly got back to me immediately:

“Dear John,

I will write the authors to double check on your request and get back to you.

Sincerely,

Butch”

and 5 days later he wrote again to clarify the situation that had been solved:

“Hi John,

Your diligence has indeed uncovered some difficulties in the presentation of figures 3 and 4 which the authors have corrected. I enclose the following message from the authors:

"I have now rerun/checked the code. I fixed the label permutation in Figure 3 of our paper and the same label permutation in Figure 4. The numbers in the text do not change. I also made Figure 3 on the frequency rather than the density scale. This does not affect any of the numeric results. Please thank the discussant for his/her help in identifying this potentially confusing issue with Figure 3 and convey our apologies for the different figure labels. Please also let them know I have pushed the new code to Github (the p-value data collected by the discussant has not changed, so his/her excel table should still work)."

Let me know if this is to your satisfaction. Again I appreciate you catching these errors.

Sincerely,

Butch”

Apparently what happened is that the 5 journals had been messed up in Figures 3 and 4. Even though the coding error was clearly minor and easy to commit even by extremely experienced and excellent analysts, it resulted in all the figure panels becoming wrong. As all seasoned methodologists know, minor coding errors causing total havoc is quite common (I have seen it happen in my own work). I think that it is ironic that a paper that claims to prove the reliability of the literature had completely messed up the two main figures that represent the core of all its data and its main results. The vast majority of papers don’t have several discussants probing at them, so I suspect such simple but major errors that can invalidate entire figures are not that uncommon in the published biomedical literature.

At any rate, assuming that the replaced figures and data are now congruent and correct, as one can see there are still no *P*-values in the 0.05 position, even though there are 470 such P-values (251/470 truncated and the vast majority of the 470 considered “significant” by their authors) in the R file. Non-consideration of these *P*-values in the FDR calculations affects the overall results substantially and yields a falsely low overall FDR of 14%. For some journal-year pairs the impact is very large.

Let us take for example AJE for the years 2002 and 2003. Jager and Leek estimate an FDR of ~40% for AJE in the papers it published in 2002 and ~0% in the papers it published in 2003. Such a major change in the credibility of the same journal within a single year is implausible based on common sense, especially given that the sample of examined *P*-values is not very small in either year.

However, one easy explanation is the neglect of counting the 0.05 values in the FDR calculations. Here are the proportions of *P*-values of 0.001 or less and of 0.04-0.05 in 2002 and 2003 depending on whether truncated only, all, or none of the 0.05 values are considered or not.

Proportion of *P*-values

0.001 or less 0.04-0.05

Year 2002 Year 2003 Year 2002 Year 2003

Truncated 0.05 and =0.05 counted 34% (29/85) 42% (33/78) 20% (17/85) 18% (14/78)

Truncated 0.05 counted 36% (29/81) 43% (33/77) 16% (13/81) 17% (13/77)

Neither counted (Jager and Leek) 38% (29/77) 52% (33/64) 12% (9/77) 0% (0/64)

The inclusion of the entire 0.05 *P*-value cluster as 0.05 in the FDR calculations would diminish the difference between years 2002 and 2003 and bring both FDR estimates in the vicinity of ~50%. Even these are under-estimates given that many authors claim discoveries and research findings by applying “spin” even for many *P*-values above 0.05 (see Boutron et al., JAMA 2010).

I checked by hand all the AJE papers from 2002 and 2003 where *P*-values of 0.05 had been extracted by the Jager and Leek automated script. Of the truncated ones, only one was >0.05 (thus non-statistically significant), all others were <0.05; as of those reported as equal to 0.05 (=0.05), in all of them the authors claimed they had found associations (one author used the term “weak”, the others did not bother to qualify further). Whenever it was possible to tell from additional information presented in the respective full papers, most of the “*P*<0.05” values were modest (relatively close to 0.05 rather than, say, =<0.001).

What is worse for the Jager and Leek analysis, I found that it was quite common for many authors to use the clause “*P*<0.05” to summarize a large number of independent nominally significant associations, while this summary function was much more rare for other levels of truncated *P*-value thresholds. Let us consider for example abstract PMID=14652300 published in AJE in 2003. The abstract says:

“In univariate analysis, older age, lower educational levels, sedentary work, body mass index of > or 25 kg/m2, and anti-HCV positivity were significantly associated with type 2 diabetes (p<0.05)”

From this text, the automated script of Jager and Leek extracts one 0.05 value, but in fact the single “p<0.05” refers to 5 different claimed associations that are mostly independent (or weakly correlated, in contrast to the highly correlated/overlapping associations that are often reported with separate *P*-values in many other abstracts, see point 2.13). Then the Jager and Leek analysis does not include even that one 0.05 value that was extracted by their script. The full text of this AJE paper does not even show these univariate results, but it shows a table with age-stratified multivariable results and 7 odds ratios in these tabulated results are nominally statistically significant, 6 of which have very modest *P*-values close to 0.05, if one were to convert the presented odds ratios and confidence intervals into the respective *P*-values (see point 2.13). Eventually, should one count 0, 1, 5, or 7 P-values out of that single sentence in an abstract? And if so, what *P*-values? The eventual results of the FDR calculations will be totally different, ranging from ~0% to >80%, depending on what strategy is adopted. The situation of inferring the FDR of the medical literature from the abstracts of published articles seems hopeless. It is even more hopeless when it comes to unstructured abstracts of observational epidemiological studies where anything goes.

**Appendix References 3:**

For the 10 references randomly sampled by Jager and Leek, see their Supplementary Material. The additional 10 references that I sampled randomly are:

1. Lancet. 2007 Dec 8;370(9603):1907-14.

Effect of the cholesteryl ester transfer protein inhibitor, anacetrapib, on

lipoproteins in patients with dyslipidaemia and on 24-h ambulatory blood pressure

in healthy individuals: two double-blind, randomised placebo-controlled phase I

studies.

Krishna R, Anderson MS, Bergman AJ, Jin B, Fallon M, Cote J, Rosko K, Chavez-Eng

C, Lutz R, Bloomfield DM, Gutierrez M, Doherty J, Bieberdorf F, Chodakewitz J,

Gottesdiener KM, Wagner JA.

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Comment in

Lancet. 2007 Dec 8;370(9603):1882-3.

Nat Clin Pract Cardiovasc Med. 2008 Jun;5(6):302-3.

BACKGROUND: The inhibition of cholesteryl ester transfer protein (CETP) is

considered a potential new mechanism for treatment of dyslipidaemia. Anacetrapib

(MK-0859) is a CETP inhibitor currently under development. We aimed to assess

anacetrapib's effects as monotherapy on low-density lipoprotein cholesterol

(LDL-C) and high-density lipoprotein cholesterol (HDL-C) and on 24-h ambulatory

blood pressure.

METHODS: We did two double-blind, randomised, placebo-controlled phase I studies.

In the first study, 50 patients with dyslipidaemia (LDL-C 100-190 mg/dL; 40

active, 10 placebo) aged 18-75 years received anacetrapib doses of 0, 10, 40,

150, or 300 mg orally once a day with a meal for 28 days. Standard lipid and

lipoprotein monitoring, safety monitoring, and anacetrapib concentrations for

pharmacokinetics were done. In the second study, 22 healthy participants aged

45-75 years received either 150 mg of anacetrapib once a day or matching placebo

with a meal for 10 days in each crossover period, in a randomised sequence, with

at least a 14-day washout between the treatment periods. Continuous 24-h

ambulatory blood pressure monitoring was done on day -1 and day 10 of each

treatment period in this study. The primary or secondary endpoints of safety and

tolerability were assessed in both studies by monitoring clinical adverse

experiences, physical examinations, vital signs, 12-lead electrocardiogram, and

laboratory safety. Analysis was per protocol. These trials are registered with

ClinicalTrials.gov, number NCT00565292 and NCT00565006.

FINDINGS: In the dyslipidaemia study, one patient withdrew consent and one was

excluded from the data analysis for HDL-C and LDL-C because complete pre-dose

measurements were not available. Anacetrapib produced dose-dependent

lipid-altering effects with peak lipid-altering effects of 129% (mean 51.1 [SD

3.8]-114.9 [7.9] mg/dL) increase in HDL-C and a 38% (138.2 [11.4]-77.6 [7.9]

mg/dL) decrease in LDL-C in patients with dyslipidaemia. In the 24-h ambulatory

blood pressure study in healthy individuals, least squares difference between

anacetrapib and placebo groups on day 10 were 0.60 (90% CI -1.54 to 2.74;

p=0.634) mm Hg for systolic blood pressure and 0.47 (90% CI -0.90 to 1.84;

p=0.561) mm Hg for diastolic blood pressure.

INTERPRETATION: Anacetrapib seems to exhibit HDL-C increases greater than those

seen with other investigational drugs in this class and LDL-C lowering effects

similar to statins. Despite greater lipid-altering effects relative to other

members of this class, anacetrapib seems not to increase blood pressure,

suggesting that potent CETP inhibition by itself might not lead to increased

blood pressure.

PMID: 18068514 [PubMed - indexed for MEDLINE]

2. N Engl J Med. 2006 Mar 9;354(10):1021-30.

Thalidomide and hematopoietic-cell transplantation for multiple myeloma.

Barlogie B, Tricot G, Anaissie E, Shaughnessy J, Rasmussen E, van Rhee F, Fassas

A, Zangari M, Hollmig K, Pineda-Roman M, Lee C, Talamo G, Thertulien R, Kiwan E,

Krishna S, Fox M, Crowley J.

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Sciences, Little Rock, AR 72205, USA. barlogiebart@uams.edu

Comment in

N Engl J Med. 2006 Mar 9;354(10):1076-8.

N Engl J Med. 2008 Jul 10;359(2):210-2.

N Engl J Med. 2006 Jun 1;354(22):2389-90; author reply 2389-90.

BACKGROUND: High-dose therapy with melphalan can prolong survival among patients

with multiple myeloma. We assessed whether the addition of thalidomide, which has

activity against advanced and refractory myeloma, would further improve survival.

METHODS: Between October 1998 and February 2004, 668 patients with newly

diagnosed multiple myeloma received two cycles of intensive melphalan-based

chemotherapy, each supported by autologous hematopoietic stem-cell

transplantation. A total of 323 were randomly assigned to receive thalidomide

from the outset until disease progression or undue adverse effects, and 345 did

not receive thalidomide. The primary end point was the five-year event-free

survival rate. Secondary end points were complete response and overall survival.

RESULTS: After a median follow-up of 42 months among survivors, the thalidomide

and control groups had rates of complete response of 62 percent and 43 percent,

respectively (P<0.001), and five-year event-free survival rates of 56 percent and

44 percent (P=0.01). The five-year rate of overall survival was approximately 65

percent in both groups (P=0.90). Median survival after relapse was 1.1 years in

the thalidomide group and 2.7 years in the control group (P=0.001). Severe

peripheral neuropathy and deep-vein thrombosis occurred more frequently in the

thalidomide group than in the control group.

CONCLUSIONS: When incorporated into high-dose therapy for myeloma, thalidomide

increased the frequency of complete responses and extended event-free survival at

the expense of added adverse effects without improving overall survival.

(ClinicalTrials.gov number, NCT00083551.).

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PMID: 16525139 [PubMed - indexed for MEDLINE]

3. Lancet. 2008 Nov 29;372(9653):1906-13. doi: 10.1016/S0140-6736(08)61525-1. Epub

2008 Oct 22.

Effect of tesofensine on bodyweight loss, body composition, and quality of life

in obese patients: a randomised, double-blind, placebo-controlled trial.

Astrup A, Madsbad S, Breum L, Jensen TJ, Kroustrup JP, Larsen TM.

Department of Human Nutrition, Faculty of Life Sciences, University of

Copenhagen, Denmark.

Comment in

Lancet. 2008 Nov 29;372(9653):1859-60.

Lancet. 2009 Feb 28;373(9665):719; author reply 720.

Lancet. 2009 Feb 28;373(9665):719; author reply 720.

BACKGROUND: Weight-loss drugs produce an additional mean weight loss of only 3-5

kg above that of diet and placebo over 6 months, and more effective

pharmacotherapy of obesity is needed. We assessed the efficacy and safety of

tesofensine-an inhibitor of the presynaptic uptake of noradrenaline, dopamine,

and serotonin-in patients with obesity.

METHODS: We undertook a phase II, randomised, double-blind, placebo-controlled

trial in five Danish obesity management centres. After a 2 week run-in phase, 203

obese patients (body-mass index 30-</=40 kg/m(2)) were prescribed an energy

restricted diet and randomly assigned with a list of randomisation numbers to

treatment with tesofensine 0.25 mg (n=52), 0.5 mg (n=50), or 1.0 mg (n=49), or

placebo (n=52) once daily for 24 weeks. The primary outcome was percentage change

in bodyweight. Analysis was by modified intention to treat (all randomised

patients with measurement after at least one dose of study drug or placebo). The

study is registered with ClinicalTrials.gov, number NCT00394667.

FINDINGS: 161 (79%) participants completed the study. After 24 weeks, the mean

weight loss produced by diet and placebo was 2.0% (SE 0.60). Tesofensine 0.25 mg,

0.5 mg, and 1.0 mg and diet induced a mean weight loss of 4.5% (0.87), 9.2%

(0.91), and 10.6% (0.84), respectively, greater than diet and placebo (p<0.0001).

The most common adverse events caused by tesofensine were dry mouth, nausea,

constipation, hard stools, diarrhoea, and insomnia. After 24 weeks, tesofensine

0.25 mg and 0.5 mg showed no significant increases in systolic or diastolic blood

pressure compared with placebo, whereas heart rate was increased by 7.4 beats per

min in the tesofensine 0.5 mg group (p=0.0001).

INTERPRETATION: Our results suggest that tesofensine 0.5 mg might have the

potential to produce a weight loss twice that of currently approved drugs.

However, these findings of efficacy and safety need confirmation in phase III

trials.

PMID: 18950853 [PubMed - indexed for MEDLINE]

4. JAMA. 2004 Jun 2;291(21):2563-70.

Impact of the Mexican program for education, health, and nutrition (Progresa) on

rates of growth and anemia in infants and young children: a randomized

effectiveness study.

Rivera JA, Sotres-Alvarez D, Habicht JP, Shamah T, Villalpando S.

Instituto Nacional de Salud Pública, Centro de Investigación en Nutrición y

Salud, Cuernavaca, Mexico. jrivera@correo.insp.mx

Comment in

JAMA. 2004 Jun 2;291(21):2639-41.

CONTEXT: Malnutrition causes death and impaired health in millions of children.

Existing interventions are effective under controlled conditions; however, little

information is available on their effectiveness in large-scale programs.

OBJECTIVE: To document the short-term nutritional impact of a large-scale,

incentive-based development program in Mexico (Progresa), which included a

nutritional component.

DESIGN, SETTING, AND PARTICIPANTS: A randomized effectiveness study of 347

communities randomly assigned to immediate incorporation to the program in 1998

(intervention group; n = 205) or to incorporation in 1999 (crossover intervention

group; n = 142). A random sample of children in those communities was surveyed at

baseline and at 1 and 2 years afterward. Participants were from low-income

households in poor rural communities in 6 central Mexican states. Children (N =

650) 12 months of age or younger (n = 373 intervention group; n = 277 crossover

intervention group) were included in the analyses.

INTERVENTION: Children and pregnant and lactating women in participating

households received fortified nutrition supplements, and the families received

nutrition education, health care, and cash transfers.

MAIN OUTCOME MEASURES: Two-year height increments and anemia rates as measured by

blood hemoglobin levels in participating children.

RESULTS: Progresa was associated with better growth in height among the poorest

and younger infants. Age- and length-adjusted height was greater by 1.1 cm (26.4

cm in the intervention group vs 25.3 cm in the crossover intervention group)

among infants younger than 6 months at baseline and who lived in the poorest

households. After 1 year, mean hemoglobin values were higher in the intervention

group (11.12 g/dL; 95% confidence interval [CI], 10.9-11.3 g/dL) than in the

crossover intervention group (10.75 g/dL; 95% CI, 10.5-11.0 g/dL) who had not yet

received the benefits of the intervention (P =.01). There were no differences in

hemoglobin levels between the 2 groups at year 2 after both groups were receiving

the intervention. The age-adjusted rate of anemia (hemoglobin level <11 g/dL) in

1999 was higher in the crossover intervention group than in the intervention

group (54.9% vs 44.3%; P =.03), whereas in 2000 the difference was not

significant (23.0% vs 25.8%, respectively; P =.40).

CONCLUSION: Progresa, a large-scale, incentive-based development program with a

nutritional intervention, is associated with better growth and lower rates of

anemia in low-income, rural infants and children in Mexico.

PMID: 15173147 [PubMed - indexed for MEDLINE]

5. JAMA. 2005 Jun 1;293(21):2634-40.

Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of

symptomatic atrial fibrillation: a randomized trial.

Wazni OM, Marrouche NF, Martin DO, Verma A, Bhargava M, Saliba W, Bash D,

Schweikert R, Brachmann J, Gunther J, Gutleben K, Pisano E, Potenza D, Fanelli R,

Raviele A, Themistoclakis S, Rossillo A, Bonso A, Natale A.

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Clinic Foundation, Cleveland, Ohio 44195, USA.

Comment in

Evid Based Med. 2006 Feb;11(1):16.

CONTEXT: Treatment with antiarrhythmic drugs and anticoagulation is considered

first-line therapy in patients with symptomatic atrial fibrillation (AF).

Pulmonary vein isolation (PVI) with radiofrequency ablation may cure AF,

obviating the need for antiarrhythmic drugs and anticoagulation.

OBJECTIVE: To determine whether PVI is feasible as first-line therapy for

treating patients with symptomatic AF.

DESIGN, SETTING, AND PARTICIPANTS: A multicenter prospective randomized study

conducted from December 31, 2001, to July 1, 2002, of 70 patients aged 18 to 75

years who experienced monthly symptomatic AF episodes for at least 3 months and

had not been treated with antiarrhythmic drugs.

INTERVENTION: Patients were randomized to receive either PVI using radiofrequency

ablation (n=33) or antiarrhythmic drug treatment (n=37), with a 1-year follow-up.

MAIN OUTCOME MEASURES: Recurrence of AF, hospitalization, and quality of life

assessment.

RESULTS: Two patients in the antiarrhythmic drug treatment group and 1 patient in

the PVI group were lost to follow-up. At the end of 1-year follow-up, 22 (63%) of

35 patients who received antiarrhythmic drugs had at least 1 recurrence of

symptomatic AF compared with 4 (13%) of 32 patients who received PVI (P<.001).

Hospitalization during 1-year follow-up occurred in 19 (54%) of 35 patients in

the antiarrhythmic drug group compared with 3 (9%) of 32 in the PVI group

(P<.001). In the antiarrhythmic drug group, the mean (SD) number of AF episodes

decreased from 12 (7) to 6 (4), after initiating therapy (P = .01). At 6-month

follow-up, the improvement in quality of life of patients in the PVI group was

significantly better than the improvement in the antiarrhythmic drug group in 5

subclasses of the Short-Form 36 health survey. There were no thromboembolic

events in either group. Asymptomatic mild or moderate pulmonary vein stenosis was

documented in 2 (6%) of 32 patients in the PVI group.

CONCLUSION: Pulmonary vein isolation appears to be a feasible first-line approach

for treating patients with symptomatic AF. Larger studies are needed to confirm

its safety and efficacy.

PMID: 15928285 [PubMed - indexed for MEDLINE]

6. N Engl J Med. 2005 Nov 3;353(18):1912-25.

Natalizumab induction and maintenance therapy for Crohn's disease.

Sandborn WJ, Colombel JF, Enns R, Feagan BG, Hanauer SB, Lawrance IC, Panaccione

R, Sanders M, Schreiber S, Targan S, van Deventer S, Goldblum R, Despain D, Hogge

GS, Rutgeerts P; International Efficacy of Natalizumab as Active Crohn's Therapy

(ENACT-1) Trial Group; Evaluation of Natalizumab as Continuous Therapy (ENACT-2)

Trial Group.

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Comment in

N Engl J Med. 2005 Nov 3;353(18):1965-8.

BACKGROUND: Natalizumab, a humanized monoclonal antibody against alpha4 integrin,

inhibits leukocyte adhesion and migration into inflamed tissue.

METHODS: We conducted two controlled trials to evaluate natalizumab as induction

and maintenance therapy in patients with active Crohn's disease. In the first

trial, 905 patients were randomly assigned to receive 300 mg of natalizumab or

placebo at weeks 0, 4, and 8. The primary outcome was response, defined by a

decrease in the Crohn's Disease Activity Index (CDAI) score of at least 70

points, at week 10. In the second trial, 339 patients who had a response to

natalizumab in the first trial were randomly reassigned to receive 300 mg of

natalizumab or placebo every four weeks through week 56. The primary outcome was

a sustained response through week 36. A secondary outcome in both trials was

disease remission (a CDAI score of less than 150).

RESULTS: In the first trial, the natalizumab and placebo groups had similar rates

of response (56 percent and 49 percent, respectively; P=0.05) and remission (37

percent and 30 percent, respectively; P=0.12) at 10 weeks. Continuing natalizumab

in the second trial resulted in higher rates of sustained response (61 percent

vs. 28 percent, P<0.001) and remission (44 percent vs. 26 percent, P=0.003)

through week 36 than did switching to placebo. Serious adverse events occurred in

7 percent of each group in the first trial and in 10 percent of the placebo group

and 8 percent of the natalizumab group in the second trial. In an open-label

extension study, a patient treated with natalizumab died from progressive

multifocal leukoencephalopathy, associated with the JC virus, a human

polyomavirus.

CONCLUSIONS: Induction therapy with natalizumab for Crohn's disease resulted in

small, nonsignificant improvements in response and remission rates. Patients who

had a response had significantly increased rates of sustained response and

remission if natalizumab was continued every four weeks. The benefit of

natalizumab will need to be weighed against the risk of serious adverse events,

including progressive multifocal leukoencephalopathy. (ClinicalTrials.gov

numbers, NCT00032786 and NCT00032799.)

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PMID: 16267322 [PubMed - indexed for MEDLINE]

7. [NOTE: THIS ARTICLE INCLUDED P-VALUES IN ABSTRACT BUT WAS MISSED BY THE SCRIPT OF JAGER AND LEEK] Am J Epidemiol. 2004 Aug 1;160(3):248-58.

A prospective study of folate intake and the risk of pancreatic cancer in men and

women.

Skinner HG, Michaud DS, Giovannucci EL, Rimm EB, Stampfer MJ, Willett WC, Colditz

GA, Fuchs CS.

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Laboratory and human studies suggest that folate intake may influence the risk of

some cancers. However, prospective information about the relation between folate

intake and the risk of exocrine pancreatic cancer is limited. The authors

examined the relation of dietary folate intake to the risk of pancreatic cancer

in two large prospective US cohorts. Folate intake was assessed by food frequency

questionnaire in 1984 in women and in 1986 in men. Multivariate relative risks

were adjusted for age, energy intake, cigarette smoking, body mass index,

diabetes, and height. During 14 years' follow-up in each cohort, 326 incident

cases of pancreatic cancer were identified. Compared with participants in the

lowest category of folate intake, participants in increasing 100- micro g

categories of total energy-adjusted folate intake had pooled multivariate

relative risks for pancreatic cancer of 1.08, 1.10, and 1.03 (95% confidence

interval: 0.74, 1.43; p(trend) = 0.99). For energy-adjusted folate from food, the

pooled relative risks for increasing 100- micro g categories of intake were 0.81,

0.89, and 0.66 (95% confidence interval: 0.42, 1.03; p(trend) = 0.12). There was

no statistical interaction between folate intake and methionine, alcohol, fat, or

caffeine. The results from these two large prospective cohorts do not support a

strong association between energy-adjusted folate intake and the risk of

pancreatic cancer.

PMID: 15257998 [PubMed - indexed for MEDLINE]

8. Lancet. 2003 Jul 12;362(9378):95-102.

Radiotherapy and tamoxifen in women with completely excised ductal carcinoma in

situ of the breast in the UK, Australia, and New Zealand: randomised controlled

trial.

Houghton J, George WD, Cuzick J, Duggan C, Fentiman IS, Spittle M; UK

Coordinating Committee on Cancer Research; Ductal Carcinoma in situ Working

Party; DCIS trialists in the UK, Australia, and New Zealand.

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Comment in

Lancet. 2003 Oct 4;362(9390):1154; author reply 1155-6.

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Lancet. 2003 Oct 4;362(9390):1155; author reply 1155-6.

BACKGROUND: As a consequence of mammographic breast screening programmes, ductal

carcinoma in situ is diagnosed with increasing frequency. Mastectomy for

localised ductal carcinoma in situ is thought to be an over-treatment by many

physicians, but there is much controversy as to whether complete local excision

alone is sufficient. We aimed to assess the effectiveness of adjuvant

radiotherapy and tamoxifen.

METHODS: We used a 2x2 factorial design in a randomised controlled trial. Between

May, 1990, and August, 1998, 1701 patients recruited from screening programmes

were randomised to both treatments in combination or singly, or to none, or to

either one (eg, radiotherapy) with an elective decision to give or to withhold

the other (ie, in this case tamoxifen). Patients had complete surgical excision

of the lesion confirmed by specimen radiography and histology. Patients have been

followed up at least once a year. Median follow-up was 52.6 (range 2.4-118.3)

months. Our primary endpoint was the incidence of ipsilateral invasive disease.

FINDINGS: Ipsilateral invasive disease was not reduced by tamoxifen but

recurrence of overall ductal carcinoma in situ was decreased (hazard ratio 0.68

[0.49-0.96]; p=0.03). Radiotherapy reduced the incidence of ipsilateral invasive

disease (0.45 [0.24-0.85]; p=0.01) and ipsilateral ductal carcinoma in situ (0.36

[0.19-0.66]; p=0.0004), but there was no effect on the occurrence of

contralateral disease. There was no evidence of interaction between radiotherapy

and tamoxifen.

INTERPRETATION: Radiotherapy can be recommended for patients with ductal

carcinoma in situ treated by complete local excision; however, there is little

evidence for the use of tamoxifen in these women.

PMID: 12867108 [PubMed - indexed for MEDLINE]

9. N Engl J Med. 2009 Jun 11;360(24):2503-15. doi: 10.1056/NEJMoa0805796. Epub 2009

Jun 7.

A randomized trial of therapies for type 2 diabetes and coronary artery disease.

BARI 2D Study Group, Frye RL, August P, Brooks MM, Hardison RM, Kelsey SF,

MacGregor JM, Orchard TJ, Chaitman BR, Genuth SM, Goldberg SH, Hlatky MA, Jones

TL, Molitch ME, Nesto RW, Sako EY, Sobel BE.

Collaborators: Detre KM, Kelsey SF, Brooks MM, Orchard TJ, Thomas SB, Tyrrell KS,

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Comment in

Kardiol Pol. 2009 Aug;67(8):932-4; discussion 935.

N Engl J Med. 2009 Oct 1;361(14):1408; author reply 1409-10.

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N Engl J Med. 2009 Oct 1;361(14):1407-8; author reply 1409-10.

N Engl J Med. 2009 Oct 1;361(14):1408-9; author reply 1409-10.

N Engl J Med. 2009 Jun 11;360(24):2570-2.

Internist (Berl). 2010 May;51(5):674-6.

Ann Intern Med. 2009 Oct 20;151(8):JC4-5.

BACKGROUND: Optimal treatment for patients with both type 2 diabetes mellitus and

stable ischemic heart disease has not been established.

METHODS: We randomly assigned 2368 patients with both type 2 diabetes and heart

disease to undergo either prompt revascularization with intensive medical therapy

or intensive medical therapy alone and to undergo either insulin-sensitization or

insulin-provision therapy. Primary end points were the rate of death and a

composite of death, myocardial infarction, or stroke (major cardiovascular

events). Randomization was stratified according to the choice of percutaneous

coronary intervention (PCI) or coronary-artery bypass grafting (CABG) as the more

appropriate intervention.

RESULTS: At 5 years, rates of survival did not differ significantly between the

revascularization group (88.3%) and the medical-therapy group (87.8%, P=0.97) or

between the insulin-sensitization group (88.2%) and the insulin-provision group

(87.9%, P=0.89). The rates of freedom from major cardiovascular events also did

not differ significantly among the groups: 77.2% in the revascularization group

and 75.9% in the medical-treatment group (P=0.70) and 77.7% in the

insulin-sensitization group and 75.4% in the insulin-provision group (P=0.13). In

the PCI stratum, there was no significant difference in primary end points

between the revascularization group and the medical-therapy group. In the CABG

stratum, the rate of major cardiovascular events was significantly lower in the

revascularization group (22.4%) than in the medical-therapy group (30.5%, P=0.01;

P=0.002 for interaction between stratum and study group). Adverse events and

serious adverse events were generally similar among the groups, although severe

hypoglycemia was more frequent in the insulin-provision group (9.2%) than in the

insulin-sensitization group (5.9%, P=0.003).

CONCLUSIONS: Overall, there was no significant difference in the rates of death

and major cardiovascular events between patients undergoing prompt

revascularization and those undergoing medical therapy or between strategies of

insulin sensitization and insulin provision. (ClinicalTrials.gov number,

NCT00006305.)

2009 Massachusetts Medical Society

PMCID: PMC2863990

PMID: 19502645 [PubMed - indexed for MEDLINE]

10. Lancet. 2002 Jan 19;359(9302):219-25.

Counting alleles to predict recurrence of early-stage colorectal cancers.

Zhou W, Goodman SN, Galizia G, Lieto E, Ferraraccio F, Pignatelli C, Purdie CA,

Piris J, Morris R, Harrison DJ, Paty PB, Culliford A, Romans KE, Montgomery EA,

Choti MA, Kinzler KW, Vogelstein B.

Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of

Medicine, Baltimore, MD 21231, USA.

Comment in

Lancet. 2002 Jan 19;359(9302):183-4.

BACKGROUND: Chromosome imbalances occur in many cancers and represent important

biological properties of tumours. However, measurements of such imbalances are

difficult. We used a new, quantitative approach to investigate the prognostic

value of chromosome imbalances in early-stage colorectal cancers.

METHODS: We studied 180 patients with no evidence of lymph-node or distant

metastases at the time of surgery. DNA from paraffin-embedded tumours was tested

for imbalances of chromosome 8p and 18q by digital SNP (single-nucleotide

polymorphism)-a technique in which each allele in a sample is directly counted.

Surviving patients had median follow-up of 68 months, and disease recurrence was

used as the clinical endpoint.

FINDINGS: Tumours were divided into three groups: "L" tumours (n=93) had allelic

imbalances of chromosomes 8p and 18q, "L/R" tumours (n=60) had allelic imbalances

of either chromosome 8p or 18q but not both, and "R" tumours (n=27) retained

allelic balance for both chromosomes. 5-year disease-free survival was 100% (95%

CI 80-100) for patients with R tumours, 74% (61-87) for patients with L/R

tumours, and 58% (47-69) for those with L tumours. These differences were

significant (p<0.0001) and were independent of other variables--eg, Duke's stage

A tumours of class L were much more likely to recur than Duke's stage B tumours

of class R (p=0.002).

INTERPRETATION: In patients without metastasis, allelic imbalance is a better

predictor of prognosis than histopathological stage.

PMID: 11812558 [PubMed - indexed for MEDLINE]