research update

FROM THE JOURNALS Edited highlights of Richard Lehman's blog on http://bmj.co/Lehman

Aspirin with your cabbage?

Most people who undergo coronary artery surgery take aspirin. Nobody knew whether they should carry on or stop when they had their CABG. Now we have the results of a big multinational trial: "Among patients undergoing coronary artery surgery, the administration of preoperative aspirin resulted in neither a lower risk of death or thrombotic complications nor a higher risk of bleeding than that with placebo." But I'm puzzled to note that the patients were only "eligible for the trial if they had not been taking aspirin regularly before the trial or had stopped taking aspirin at least 4 days before CABG surgery." So why is the article title "Stopping vs. continuing aspirin before coronary artery surgery"? I checked with the authors and was told that the trial was designed this way to allay fears that aspirin continued right up to surgery might pose a bleeding risk. Most of the patients were indeed taking long term aspirin, which was stopped just for the four days before surgery. I think I understand this, but it still makes the title a poor match for what actually happened in the trial.

N Engl J Med 2016, doi:10.1056/NEJMoa1507688

Less chemo for ovarian cancer

When my mother was recovering from debulking surgery for ovarian cancer, I stepped aside to discuss the next steps with the registrar in charge. "The boss probably wants her in a trial, but I'll suggest we just put her on some very gentle chemo", he said to my great relief. Her next (and last) 10 months were far from pleasant, but at least she did not have to go through neutropenia, neuropathy, and the other common miseries of chemotherapy with paclitaxel and carboplatin. Nowadays most people with ovarian cancer get bevacizumab, which does genuinely lengthen survival, and paclitaxel and carboplatin still form part of the regimen. What happens if you give the paclitaxel more intensively, every week instead of every three weeks? "Overall, weekly paclitaxel, as compared with paclitaxel administered every 3 weeks, did not prolong progression-free survival among patients with ovarian cancer."

N Engl J Med 2016, doi:10.1056/NEJMoa1505067

No, leave my appendix in please

Of great interest to most of us is a paper pulled out of *JAMA* Surgery from December 2015 and commented on under the heading "Shared decision making in uncomplicated appendicitis: it is time to include nonoperative management." The original paper was a cohort study of 65 patients/families who chose appendicectomy (median age 12 years) and 37 patients/families who chose non-operative management (median age 11 years). A quarter of the non-operative group went on to need operative treatment within a year, but that means that the rest did not, so reducing costs and treatment burden overall. The investigators concluded that "When chosen by the family, nonoperative management is an effective treatment strategy for children with uncomplicated acute appendicitis, incurring less morbidity and lower costs than surgery." The commentator went on to state: "Because clinicians will soon be obligated by law to provide information about all potential forms of treatment about appendicitis, surgeons would be well served to take a leadership role in proactively developing decision aids to inform patients about the benefits and risks for both nonoperative antibiotic treatment and surgical treatment of appendicitis. Decision aids would include information on the known and accepted risks and benefits of operative intervention vs antibiotic therapy alone." Absolutely.

JAMA 2016, doi:10.1001/jama.2016.0168

Carotid choices

"In the Carotid Revascularization Endarterectomy versus Stenting Trial, we found no significant difference between the stenting group and the endarterectomy group with respect to the primary composite end point of stroke, myocardial infarction, or death during the periprocedural period or any subsequent ipsilateral stroke during 4 years of follow-up. We now extend the results to 10 years." And they find exactly the same thing. There seems absolutely nothing to choose between these options. So does that present an ideal opportunity for shared decision making? I don't think so. If there is absolutely nothing to choose between two things, how do you make a choice? Toss a coin? Leave it to NICE? Trust your doctor?

N Engl J Med 2016, doi:10.1056/NEJMoa1505215

Mind your backs

And speaking of non-pharmacological interventions, how about mindfulness? The mindfulness based stress reduction programme has apparently featured in over 100 randomised controlled trials, this latest one being in people aged 65 or more with chronic back pain. In a highly selected population of mean age 74.5, the overall effect of mindfulness training was small and poorly sustained, although a few participants showed noticeable benefit. Worth a try then? Possibly. Something to be mindful of.

JAMA Intern Med 2016, doi:10.1001/jamainternmed.2015.8033

The BMJ is an Open Access journal. We set no word limits on *BMJ* research articles, but they are abridged for print. The full text of each *BMJ* research article is freely available on thebmj.com.

The online version is published along with peer and patient reviews for the paper, and a statement about how the authors will share data from their study.

The linked commentaries in this section appear on thebmj.com as editorials. Use the citation given at the end of commentaries to cite an article or find it online.

ORIGINAL RESEARCH Population based observational study

Primary prevention and risk factor reduction in coronary heart disease mortality among working aged men and women in eastern Finland over 40 years

Jousilahti P, Laatikainen T, Peltonen M, et al

Cite this as: *BMJ* 2016;352:i721
Find this at: http://dx.doi.org/10.1136/bmj.i721

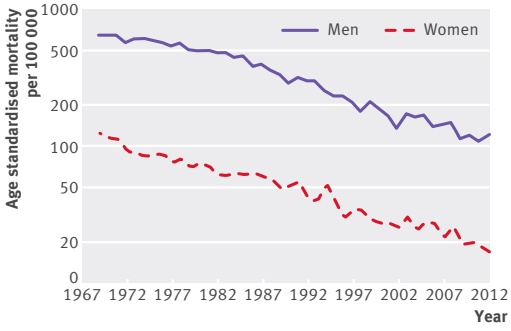
Study question How much do changes in the three main risk factors for cardiovascular disease (smoking prevalence, serum cholesterol, and systolic blood pressure) contribute to reductions in coronary heart disease mortality observed among working aged men and women in eastern Finland?

Methods Predicted changes in coronary heart disease mortality were estimated by a logistic regression model using risk factor data collected in nine consecutive, population based, risk factor surveys conducted every five years since 1972. Data on observed mortality were obtained from the National Causes of Death Register. The study population consisted of 34 525 men and women aged 30-59 years who participated in the national FINRISK studies between 1972 and 2012 in eastern Finland.

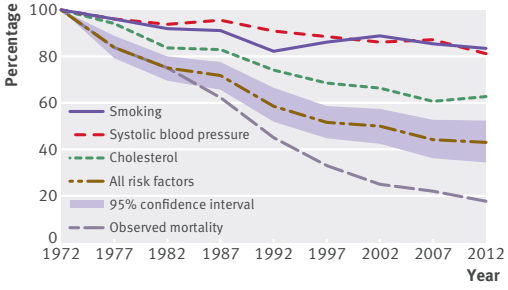
Study answer and limitations From the early 1970s to 2012, coronary heart disease mortality decreased by 82% among men and 84% among women. During the first 10 years of the study, changes in the three main risk factors contributed to nearly all of the observed reduction in mortality. In the last 10 years of the study, about two thirds (69% in men and 66% in women) of the reduction could be explained by changes in risk factors, and the remaining one third by other factors. The study's main limitation was the declining participation rate in the last population surveys, and potential measurement error.

What this study adds Reductions in disease burden and mortality due to coronary heart disease can be achieved through the use of population based primary prevention programmes. Key for prevention is population wide reduction of cardiovascular risk factors through lifestyle changes.

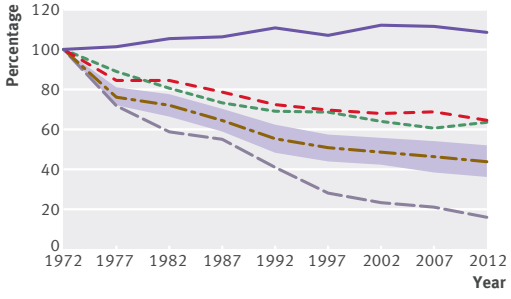
Funding, competing interests, data sharing The study received no external funding, but was supported by the Finnish Foundation for Cardiovascular Research. The authors declare no competing interests. Additional information is available from the corresponding author.



Age standardised mortality from coronary heart disease in 1969-2012 (logarithmic scale), for working aged men and women (age 35-64 years) in eastern Finland



Predicted and observed reduction (%) in coronary heart disease mortality in men aged 35-64 years, 1972-2012



Predicted and observed reduction (%) in coronary heart disease mortality in women aged 35-64 years, 1972-2012

East Finland city of Kuopio

Prostatic radiotherapy and second malignancies

ORIGINAL RESEARCH Systematic review and meta-analysis

Second malignancies after radiotherapy for prostate cancer

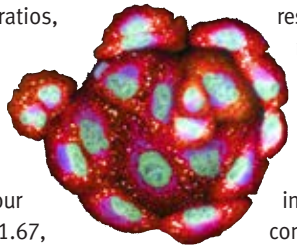
Wallis CJD, Mahar AL, Choo R, et al

Cite this as: *BMJ* 2016;352:i851
Find this at: http://dx.doi.org/10.1136/bmj.i851

Study question Is radiotherapy for the treatment of prostate cancer associated with the subsequent development of second malignancies (new primary cancers)?

Methods We performed a systematic review and meta-analysis of the Medline and Embase databases to identify observational studies that assessed the risk of second malignancy for patients with a diagnosis of prostate cancer by exposure to radiotherapy. Outcomes included second cancers of the bladder, colorectal tract, rectum, lung, and haematologic system. Two reviewers selected studies and extracted information. Risk of bias was assessed with the Newcastle-Ottawa scale. Outcomes were synthesised with random effects models and Mantel-Haenszel weighting. Unadjusted odds ratios and multivariable adjusted hazard ratios, where available, were pooled.

Study answer and limitations We identified 21 studies with moderate risk of bias. There was increased risk of bladder (four studies; adjusted hazard ratios 1.67, 95% confidence interval 1.55 to 1.80), colorectal (three studies: 1.79, 1.34 to 2.38), and rectal cancers (three studies; 1.79, 1.34 to 2.38), but not haematological (one study; 1.64, 0.90 to 2.99) or lung cancers (two studies; 1.45, 0.70 to 3.01) after radiotherapy compared with those unexposed to radiotherapy. These findings were consistent across adjustment for baseline patient and tumour factors as well as lag time restrictions. The odds of second cancer varied depending on radiotherapy modality: treatment with external beam radiotherapy was consistently associated with increased odds while brachytherapy was not. Among the patients who underwent radiotherapy, from individual studies, the highest absolute rates reported for bladder, colorectal, and rectal cancers were 3.8%, 4.2%, and 1.2%, respectively, while the lowest reported rates were 0.1%, 0.3%, and 0.3%. Limitations include the reliance on observational studies that could have residual confounding, a lack of important information about confounders and comorbidities, and the small number of studies in many of our subgroups thus limiting the power in our conclusions.



What this study adds This comprehensive review of the literature suggests that radiotherapy treatment for prostate cancer is associated with an increased risk of cancers within the radiotherapy field (bladder, colorectal, and rectal cancers) but not outside the field (lung and haematologic cancers).

Funding, competing interests, data sharing The study was funded by the Ajmera Family chair in urologic oncology awarded to RKN. The funder had no input in the design or conduct of the study, the interpretation of the results, the preparation of the manuscript or the decision to submit for publication. The authors declare no competing interest. All data are publicly available in the source manuscripts.

COMMENTARY Unlikely to change therapeutic decisions for those with high grade prostate cancer

Despite a well recognised association between exposure to radiation and carcinogenesis, defining and quantifying such a link in men given radiotherapy for prostate cancer has been difficult.[7-9]

In their paper, Wallis and colleagues[10] refresh the existing data with an updated comprehensive systematic review and meta-analysis of 21 studies. Their analysis suggests an increased risk of bladder (odds ratio 1.39), rectal (1.62), and colorectal (1.68) cancers.

But what are the real world implications for individual patients? Despite an impressive relative risk, the absolute risk remains small, and the cancers discovered, although certainly requiring treatment, might not be lethal. This is particularly true of smaller bladder cancers discovered incidentally during cystoscopy for radiation related haematuria. Ultimately, clinicians and patients must decide together whether, for example, the roughly 1.4-1.7-fold increase in relative risk of a second malignancy after a 10 year lag period justifies alternative treatments. Young patients with few comorbidities might factor this risk into their decision making, whereas older patients or those with competing health risks might not and indeed should not.

> Despite an impressive relative risk, the absolute risk remains small

Brachytherapy (high radiation dose to a small volume of tissue) was not associated with a detectable increase in risk. Therefore, the current move towards smaller tighter treatment volumes might well shift the contemporary risk back towards unity. Many studies included in this analysis were performed at a time when older poorly targeted radiation techniques were used, and large volumes of normal pelvic tissue were irradiated during treatment.

While the absolute risk of second malignancy seems small, there might be subgroups with higher absolute risks and others for whom risks are negligible. Prospective analyses with large multi-institutional databases and registries could help identify them.

For now, we note the risk of second malignancy confirmed by Wallis and colleagues and believe that management discussions and consent forms should feature this information. Perhaps most importantly, this study confirms our belief that second malignancy should be added to the already long list of avoidable hazards associated with treatment for those men with low risk prostate cancer who simply need no treatment at all. Concern about second malignancies should not, however, stand in the way of an effective and well studied treatment being given to men with higher grade, lethal prostate cancer for whom the potential benefit simply dwarfs the risk.

Anthony L Zietman
azietman@partners.org
See thebmj.com for author details

Cite this as: *BMJ* 2016;352:i1073
Find this at: http://dx.doi.org/10.1136/bmj.i1073

Gender gap in first authorship of research papers

ORIGINAL RESEARCH Observational study (1994-2014)

Trends and comparison of female first authorship in high impact medical journals

Filardo G, da Graca B, Sass DM, Pollock BD, Smith EB, Martinez MA

Cite this as: *BMJ* 2016;352:i847
Find this at: http://dx.doi.org/10.1136/bmj.i847

Study question How has the representation of women among first authors of original research published in high impact general medical journals changed from 1994 to 2014, and does it differ between journals?

Methods This was an observational study including all original research articles published in *Annals of Internal Medicine*, *Archives of Internal Medicine*, *The BMJ*, *JAMA*, *Lancet*, and the *New England Journal of Medicine* (*NEJM*) for one issue every alternate month from February 1994 to June 2014. Prevalence of female first authorship and its adjusted association with time of publication and journal were assessed using a multivariable logistic regression model that accounted for number of authors, study type and specialty/topic, continent where the study was conducted, and the interactions between journal and time of publication, study type, and continent.

Study answer and limitations After adjustment, female first authorship increased significantly from 27% in 1994 to 37% in 2014 (P<0.001). Compared with the mean across all six journals, first authors were significantly less likely to be female in the *NEJM* (adjusted odds ratio 0.68, 95% confidence interval 0.53 to 0.89) and significantly more likely to be female in *The BMJ* (1.30, 1.01 to 1.66) over the study period. It was not possible to determine whether female first authors are more likely to submit to particular journals or whether the differences in journals' review processes affect publication of female first authors.

What this study adds This study provides an updated, rigorous examination of women's representation among first authors of original research papers, showing that underrepresentation of women among the leaders of high impact original research is a continuing concern.

Funding, competing interests, data sharing
This work was funded in part by the Bradley Family Endowment to the Baylor Health Care System Foundation. The study dataset is available from the corresponding author on request.

COMMENTARY Parity of authorship should be a priority for journals, universities, and funding agencies

Women have been attending medical school in numbers equal to or greater than those of men since 1996 in the United Kingdom,[1] and in nearly equal numbers in the United States since 2003.[2] But substantial gender differences in rank and leadership remain in academic medicine.

In their paper,[3] Filardo and colleagues examined the prevalence of female first authorship among original research articles published over the past two decades in six high impact general medical journals. The authors report some good news—an overall increase in the prevalence of female first authorship. However, they also report that female first authorship plateaued in later years, with no further gains between 2009 and 2014. Of additional concern was the recent decline in female first authorship in two of the six journals (see full version on thebmj.com).[3]

Women comprise only 30% of research principal investigators funded by the National Institutes of Health,[4] and lower funding rates among women are also evident at the European Research Commission.[5] Correcting the serious loss of human capital and experience resulting from unequal participation by women in research should be an urgent priority. Gender inequity must be tackled at the level of journals, universities, and funding agencies.

Correcting the serious loss of human capital resulting from unequal participation by women in research should be an urgent priority.

Policy and commitment

Journals should report their acceptance rates for research by gender of author, editor, and reviewer to test whether unconscious bias may be affecting publication of research authored by women.[6] Masking reviewers to the identity of authors may minimise the effect of unconscious gender (and other) biases and could be evaluated. The genders of the editor-in-chief, other editors, and editorial board members may also influence the kind of topics given priority at particular journals. These factors can also affect the diversity of reviewers and the likelihood of submissions from women.

Institutional commitment and gender equity policies at universities and funding agencies could make a substantial difference to women's career success. Taking a lead from the social sciences, Boyle and colleagues advocate five steps for universities: publish the gender breakdown in key areas, including promotions, appointments, and rewards; embed gender equity issues into working practices; support women's career progression through the development of promotion criteria that focus on quality rather than quantity; engage men in championing gender equality, including shared parental leave; and celebrate women's achievements equally, in a public way.[10]

Funding agencies can equalise representation on review panels, ensure that reviewers have been trained in minimising unconscious bias, and publish data by gender on funding applications, success rates, and monetary allocation.[10] The European Research Commission's Scientific Council has already launched initiatives to improve gender equity that aim for balance in research teams and decision making

The equal representation of women in research matters for science, for patients, and ultimately for public health. Filardo and colleagues' study ought to encourage universities, funding agencies, and journals to examine their policies, renew their commitments to gender equity, and reduce the enduring and damaging symptom of lagging female authorship.

Kathryn M Rexrode
krexrode@partners.org
See thebmj.com for author details

Cite this as: *BMJ* 2016;352:i1130
Find this at: http://dx.doi.org/10.1136/bmj.i1130