research update

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

Cholera: still not defeated

Endemic cholera is one of those diseases that remind us how unequal the world still is. Cholera from the Indian subcontinent swept Europe in the 1820s and '30s but had virtually disappeared a few decades later, because of improvements in our water supply. Yet it still kills tens of thousands of people in the lands of its origin. It's taken more than a century of effort to produce a modestly immunogenic vaccine like the one trialled here. This is the killed whole-cell-only oral cholera vaccine called Shanchol, which was introduced in 2009 and costs $1.85 per dose.

The present trial was conducted in the slums of Mirpur, Dhaka, where endemic cholera typically peaks during March and April and the highest rates are seen in young children. Its purpose was to study the effect of using a single dose only. The protective efficacy over six months or more was 40% against all cholera episodes and 63% against severely dehydrating cholera episodes in older children and adults, but much lower in children under 5. So, in the second decade of the 21st century we still don't have a good method of protecting the most vulnerable group from cholera. Oh, hang on, we do. Give them a clean water supply.

N Engl J Med doi:10.1056/NEJMoa1510330

EAT and suckle

"The Enquiring about Tolerance (EAT) trial was conceived to determine whether the early introduction of common dietary allergens (peanut, cooked hen's egg, cow's milk, sesame, whitefish, and wheat) from 3 months of age in exclusively breast-fed infants in the general population would prevent food allergies, as compared with infants who were exclusively breast-fed for approximately 6 months." Buoyed by the peanutty success of its previous LEAP trials, a team from our own St Thomas' Hospital ventured further back in life to prevent a wider range of food allergies. But it was difficult, and the result was that the trial did not show the efficacy of early introduction of allergenic foods in an intention to treat analysis because not many 3 month old babies showed a great desire to eat sesame and peanuts. There were hints of success in the little babies who could be persuaded to eat these substances instead of sticking solely to mummy's goodness.

N Engl J Med doi:10.1056/NEJMoa1514210

Pancreatic cancer choices

We all know it might be us one day. Vague upper abdominal discomfort and weight loss lead to an ultrasound examination, then to computed tomography, then to an awkward conversation about treatment options and how long there might be left, given the stage of the cancer. Cancer of the pancreas is overtaking breast cancer as a cause of death in the United States, and at least 80% of it is incurable, with no progress in the past few decades. In this French led trial, patients with locally advanced disease who responded to four months of gemcitabine based induction chemotherapy were randomised to carry on with gemcitabine alone, to have added erlotinib, or to have chemoradiotherapy (54 Gy plus capecitabine). They survived for a median of a year plus a month or four. There was no statistically significant difference between groups, except that erlotinib produced the most adverse effects.

JAMA doi:10.1001/jama.2016.4324

Antibiotic blame game

A study of antibiotic prescribing for ambulatory patients in the United States five years ago shows that about a third of prescriptions were unnecessary according to a "group of experts." That sounds about right to me. The comparator should be an audit of the experts' own actual practice.

JAMA doi:10.1001/jama.2016.4151

Loopy on clarithromycin

Regimens containing clarithromycin are widely used to eradicate *Helicobacter pylori*, and a few cases of immediate neuropsychiatric disturbances have been reported. Pharmacovigilance these days can be done on a grand scale, using population databases, and this association was tested here using the Clinical Data Analysis and Reporting System database in Hong Kong. People taking clarithromycin containing eradication courses were indeed at a fourfold higher risk of reporting neuropsychiatric symptoms, but only while they were actually taking the drugs.

JAMA Intern Med doi:10.1001/jamainternmed.2016.1586

Necrotising microbiome

Tiny premature babies scare the microbiome out of me. As if respiratory distress syndrome isn't bad enough, they are also prey to necrotising enterocolitis. It makes intuitive sense to blame bad germs for this condition, and this study confirms that. The researchers studied 2492 stool samples from 122 infants in a primary cohort of Kentucky babies born weighing less than 1500 g, of whom 28 developed necrotising enterocolitis; 94 infants were used as controls. The microbial community structure in case stools differed significantly from those in control stools. A relative abundance of gammaproteobacteria (ie, Gram negative facultative bacilli) and relative paucity of strict anaerobic bacteria (especially negativicutes) precede necrotising enterocolitis. These differences emerged only after the first month of age. So maybe the answer lies in accentuating the negativicutes.

Lancet doi:10.1016/S0140-6736(16)00081-7

Alcohol, diet, and risk of breast cancer

ORIGINAL RESEARCH Prospective cohort study

Five year change in alcohol intake and risk of breast cancer and coronary heart disease among postmenopausal women

Dam MK, Hvidtfeldt UA, Tjønneland A, Overvad K, Grønbæk M, Tolstrup JS

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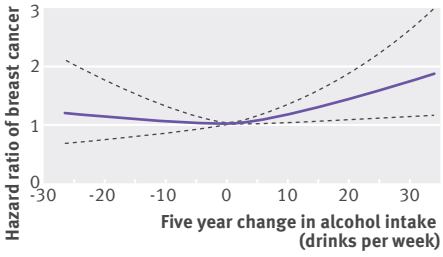
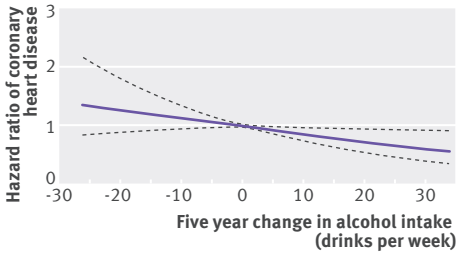
Find this at: http://dx.doi.org/10.1136/bmj.i2314

Study question Do postmenopausal women who increase their alcohol intake over a five year period have a higher risk of breast cancer and lower risk of coronary heart disease than those who maintain their stable alcohol intake?

Methods 21 523 postmenopausal women who participated in the Diet, Cancer, and Health Study in Denmark were eligible for the study. Change in alcohol intake was recorded (between two examinations undertaken in 1993-98 and 1999-2003) as exposure for breast cancer, coronary heart disease, and all cause mortality, occurring during 11 years of follow-up using Cox proportional hazards models. Analyses were adjusted for known risk factors for breast cancer, coronary heart disease, and mortality.

Study answer and limitations During the study, 1054, 1750, and 2080 cases of breast cancer, coronary heart disease, and mortality occurred, respectively. Participants who increased alcohol intake over the five year period had a higher risk of breast cancer and a lower risk of coronary heart disease than those with stable alcohol intake. For instance, women who increased alcohol intake by seven or 14 drinks per week (corresponding to one or two drinks more per day) had a hazard ratio of breast cancer of 1.13 (95% confidence interval 1.03 to 1.23) and 1.29 (1.07 to 1.55), respectively, compared to women with stable intake. Corresponding hazard ratios for coronary heart disease were 0.89 (0.81 to 0.97) and 0.78 (0.64 to 0.95), respectively. Residual confounding in the results was possible. Alcohol intake was self-reported and possibly underestimated. Drinking patterns were not taken into account.





Hazard ratios of breast cancer and coronary heart disease among postmenopausal women by five year change in alcohol intake. Dashed lines=95% confidence intervals

What this study adds Results support the hypotheses that alcohol is associated with breast cancer and coronary heart disease in opposite directions.

Funding, competing interests, data sharing No funding was given. The authors have no competing interests or additional data to share.

ORIGINAL RESEARCH Population based cohort study

Fruit and vegetable consumption in adolescence and early adulthood and risk of breast cancer

Farvid MS, Chen WY, Michels KB, Cho E, Willett WC, Eliassen AH

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Study question Is consumption of fruit and vegetables in adolescence and early adulthood associated with subsequent risk of breast cancer in premenopausal and postmenopausal women?

Methods Incident cases of breast cancer were documented over 22 years of follow-up in 90 476 premenopausal women aged 27-44 from the Nurses' Health Study II who completed a questionnaire on diet in 1991, 44 223 of whom completed a questionnaire about their diet during adolescence in 1998.

Study answer and limitations There were 3235 cases of invasive breast cancer during follow-up to 2013. Of these, 1347 cases were among women who completed a questionnaire about their diet during adolescence. Total fruit consumption during adolescence was associated with lower risk of breast cancer (hazard ratio 0.75 (95% confidence interval 0.62 to 0.90) for highest (median 2.9 servings/day) *v* lowest (0.5 servings/day) fifth of consumption. The association was independent of adult fruit intake. There was no association between total intake of vegetables or fruit juice in either adolescence or early adulthood and risk, but higher intake of fruits and vegetables rich in α carotene in early adulthood was associated with lower risk. The association with adolescent fruit intake was stronger for oestrogen and progesterone receptor negative cancers. Limitations include the potential for measurement error, residual confounding, and type I errors. In addition, diet in adolescence was recalled after up to 30 years; however, diagnoses were made after diet was recalled, precluding the possibility of differential recall. Although most participants were white, it is unlikely that underlying biological associations differ by race.

What this study adds This study suggests that higher intake of fruit during adolescence could reduce the risk of breast cancer.

Funding, competing interests, data sharing This study was supported by the National Institutes of Health and The Breast Cancer Research Foundation. MSF was supported by the Japan Pharmaceutical Manufacturers Association. There were no potential competing interests. More information about the study is available at http://www.nurseshealthstudy.org.

COMMENTARY Public health messages should focus on alcohol and obesity while we wait for clearer evidence on dietary components

Two linked papers in *The BMJ* shed new light on the relation of alcohol and diet with the two commonest diseases in women in western countries: breast cancer and ischaemic heart disease.[1 2] After following the health of nearly 22 000 postmenopausal women in Denmark, Dam and colleagues[1] report that, compared with women with a stable intake of alcohol, women who increased their alcohol intake by two drinks per day during five years of follow-up had an increase in risk of breast cancer of about 30% but a decrease in risk of ischaemic heart disease of about 20%.

The results for breast cancer are in line with previous research, and the authors argue that the association with changes in alcohol intake provides stronger evidence that the relation is causal. For ischaemic heart disease, the apparent benefit in women who reported an increase in alcohol consumption is still potentially biased if women with poor health are under-represented in this group.

Public health implications

In relation to public health, the adverse effect of increased alcohol consumption on breast cancer risk is important—alcohol is responsible for about 11% of female breast cancers in the United Kingdom.[3] However, we still do not know whether a decrease in alcohol intake in middle age leads to a subsequent reduction in breast cancer risk. Dam and colleagues found no evidence for such a decrease, but had little statistical power to answer this question.

The true effect of alcohol on risk of ischaemic heart disease remains uncertain. There may be some benefit with low to moderate intakes of alcohol, but this could be outweighed by an increased risk of breast cancer and other morbidities. Furthermore, risk of ischaemic heart disease can be reduced substantially by other lifestyle changes, as well as by drugs such as statins shown to be effective in primary prevention.

In a second paper, Farvid and colleagues[2] examine whether fruit and vegetable consumption during adolescence and early adulthood might affect subsequent risk for breast cancer. The authors studied 90 000 nurses in the United States who reported their diet in early adulthood, of whom half also recalled their usual diet during adolescence. Fruit intake in early adulthood and vegetable intake in adolescence or adulthood were not associated with subsequent breast cancer risk, but high fruit consumption (2.9 *v* 0.5 servings per day) during adolescence was associated with a roughly 25% lower risk of breast cancer diagnosed in middle age.

SIMON DACK/ALAMY

The adverse effect of increased alcohol consumption on breast cancer risk is important—alcohol is responsible for about 11% of female breast cancers in the United Kingdom

The relation between diet and breast cancer risk has been studied for over 40 years. The only unequivocal findings are that risk is increased by alcohol (risk increases by about 10% for each additional daily drink) and by obesity (risk in obese postmenopausal women is about 50% higher than in thin postmenopausal women). For fruit and vegetable intake in adult life, a recent pooled analysis of 20 cohort studies showed no association with total breast cancer risk.[4] The effects of diet in early life have not been much studied, but there are examples of other factors measured at early ages that affect lifetime risk. For example, early menarche increases breast cancer risk, and there is evidence that relative fatness during childhood and adolescence is associated with a reduction in lifetime risk of breast cancer.[5]

Variation by cancer subtype

Further analyses by Farvid and colleagues[2] suggest that the magnitude of the association between adolescent fruit intake and breast cancer risk varied by hormone receptor status, and was most marked for breast tumours negative for oestrogen and progesterone receptors. Although this finding was based on a small number of study participants, it is of interest because a few recent studies have raised the possibility that diet could influence the risk for specific subtypes of breast cancer. For example, Jung and colleagues reported that high intakes of vegetables (but not fruit) were associated with a reduced risk of oestrogen receptor-negative breast cancer, but were not associated with risk of oestrogen receptor-positive breast cancer, with statistically significant heterogeneity between the subtypes.[4]

Much more evidence is needed before we can draw conclusions on the reported protective association between adolescent fruit intake and breast cancer risk, but these foods have well known beneficial effects on health, and efforts should continue to increase intake of both fruit and vegetables at all ages. In the UK, for example, mean consumption of fruit and vegetables at ages 11-18 years is only three portions per day, with only about 10% reaching the recommended target of five portions a day.[6]

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Association between the Value-Based Purchasing pay for performance programme and patient mortality in US hospitals

Figueroa JF, Tsugawa Y, Zheng J, Orav EJ, Jha AK

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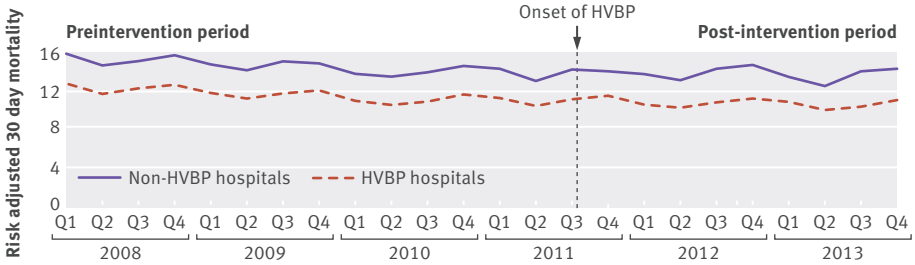

Risk adjusted 30 day mortality rates for target conditions between hospitals participating or not participating in the Hospital Value-Based Purchasing (HVBP) programme, 2008 to 2013

Study question Was the introduction of the Hospital Value-Based Purchasing (HVBP) pay for performance programme associated with any improvements in 30 day mortality for the three incentivised medical conditions in US hospitals?

Methods The authors analysed national data from 2008 to 2013 on Medicare beneficiaries admitted to hospital with the three incentivised conditions: heart failure, acute myocardial infarction, and pneumonia. Patient level linear spline regression models were fitted to examine the association between the introduction of the HVBP programme and 30 day mortality using medical conditions not incentivised by HVBP as a comparison series and a group of hospitals not participating in the programme as controls.

Study answer and limitations Introduction of the HVBP programme was not associated with improvements in 30 day mortality beyond secular trends. Improvements in patient outcomes may require complex system changes that could take longer for an effect to be observed than the three year period of our study compared with rethinking pay for performance.

What this study adds This study shows the ineffectiveness of the HVBP programme on patient outcomes, and suggests that nations considering similar pay for performance programmes may want to consider alternative models to improve patient outcomes.

Funding, competing interests, data sharing This study received no support from any organisation. The authors had no financial relationships with any organisation that might have an interest in this work in the previous three years, and have no other relationships or activities that could have influenced this work. The authors have no further data to share.

Trends in mortality between hospitals participating and not participating in US Hospital Value-Based Purchasing (HVBP) programme

Variables	Quarterly change in mortality (%)		Difference (95% CI) in difference in trend (% point difference)	P value for difference in difference
	HVBP hospitals	Non-HVBP hospitals*		
Target conditions:				
Preintervention	−0.13	−0.14	−0.03 (−0.08 to 0.13)	0.35
Post-intervention	−0.03	−0.01		
Difference (95% CI)	0.10 (0.09 to 0.12)	0.13 (0.08 to 0.18)		
Acute myocardial infarction:				
Preintervention	−0.18	−0.18	0 (−0.19 to 0.19)	0.98
Post-intervention	−0.04	−0.05		
Difference (95% CI)	0.14 (0.10 to 0.18)	0.14 (−0.05 to 0.33)		
Congestive heart failure:				
Preintervention	−0.07	−0.11	−0.05 (−0.13 to 0.04)	0.27
Post-intervention	0.02	0.03		
Difference (95% CI)	0.10 (0.07 to 0.12)	0.14 (0.06 to 0.22)		
Pneumonia:				
Preintervention	−0.15	−0.15	−0.04 (−0.11 to 0.04)	0.35
Post-intervention	−0.07	−0.03		
Difference (95% CI)	0.08 (0.05 to 0.10)	0.11 (0.04 to 0.18)		
Non-target conditions†:				
Preintervention	−0.09	−0.06	0.01 (−0.05 to 0.03)	0.61
Post-intervention	−0.02	0.00		
Difference (95% CI)	0.07 (0.06 to 0.08)	0.06 (0.02 to 0.10)		

*Include 44 hospitals from Maryland and 1304 critical access hospitals.
†Include stroke, esophagitis/gastritis, gastrointestinal bleed, urinary tract infection, metabolic disease, arrhythmia, and renal failure.