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BMJ (14 July 2018, Vol. 362, No. 8161)

Prenatal biochemical screening and long term risk of maternal cardiovascular disease: Population based cohort study
Joel G Ray, Tianhua Huang, Wendy S Meschino, et al.
BMJ 2018; 362 (Published 11 July 2018)
https://www.bmj.com/content/362/bmj.k2739

Abstract
Objective To examine whether abnormal prenatal biochemical screening results are associated with an increased risk of premature cardiovascular disease after pregnancy.
Design Population based cohort study.
Setting The entire province of Ontario, Canada, where healthcare is universally available.
Participants Women aged 12-55 years, without pre-existing cardiovascular disease, who underwent prenatal screening between 1993 and 2011. One pregnancy per woman was randomly selected.
Exposures Low (≤5th centile multiple of the median) serum total chorionic gonadotropin, unconjugated estriol, and pregnancy associated plasma protein A and high (≥95th centile multiple of the median) alphafetoprotein and dimeric inhibin-A.
Main outcome measures Composite of hospital admission or revascularisation for coronary artery, cerebrovascular, or peripheral arterial disease or hospital admission for heart failure or dysrhythmia at least 365 days after pregnancy.
Results Among 855 536 pregnancies, and after a median of 11.4 (interquartile range 6.8-17.5) years of follow-up, 6209 women developed the main cardiovascular disease outcome. Abnormal results for each of the five prenatal biochemical screening analytes,

especially dimeric inhibin-A, were associated with a higher risk of cardiovascular disease. Women with an abnormally high dimeric inhibin-A (≥95th centile) had the highest rate of cardiovascular disease (30 events or 8.3 per 10 000 person years versus 251 events or 3.8 per 10 000 person years for those <95th centile; multivariable adjusted hazard ratio 2.0, 95% confidence interval 1.4 to 3.0). Compared with women without any abnormal biochemical measure, the hazard ratio for the cardiovascular disease composite outcome was 1.2-1.3 times higher with one abnormal analyte and 1.5-2.0 times higher with two or more abnormal analytes.
Conclusions Women with abnormal prenatal biochemical screening results, especially for dimeric inhibin-A, may be at higher risk of cardiovascular disease. If these findings are replicated elsewhere, a massive amount of data exists that could aid in identifying women at higher risk of premature cardiovascular disease and that could be conveyed to them or their healthcare providers.

Impact of 2017 ACC/AHA guidelines on prevalence of hypertension and eligibility for antihypertensive treatment in United States and China: Nationally representative cross sectional study

Rohan Khera, Yuan Lu, Jiapeng Lu, et al.
BMJ 2018; 362 (Published 11 July 2018)
https://www.bmj.com/content/362/bmj.k2357

Abstract
Objective To examine the effect of the 2017 American College of Cardiology (ACC)/American Heart Association (AHA) hypertension guidelines on the prevalence of hypertension and eligibility for initiation and intensification of treatment in nationally representative populations from the United States and China.
Design Observational assessment of nationally representative data.
Setting US National Health and Nutrition Examination Survey (NHANES) for the most recent two cycles (2013-14, 2015-16) and China Health and Retirement Longitudinal Study (CHARLS) (2011-12).
Participants All 45-75 year old adults who would have a diagnosis of hypertension and be candidates for treatment on the basis of the ACC/AHA guidelines, compared with current guidelines.
Main outcome measures Diagnosis of hypertension and candidacy for initiation and intensification of antihypertensive treatment.
Results Adoption of the 2017 ACC/AHA hypertension guidelines in the US would label 70.1 (95% confidence interval 64.9 to 75.3) million people in the 45-75 year age group as having hypertension, representing 63% (60.6% to 65.4%) of the population in this age group. Their adoption in China would lead to labeling of 266.9 (252.9 to 280.8) million people or 55% (53.4% to 56.7%) of the same age group as having hypertension. This would represent an increase in prevalence of 26.8% (23.2% to 30.9%) in the US and 45.1% (41.3% to 48.9%) in China. Furthermore, on the basis of treatment patterns and current guidelines, 8.1 (6.5 to 9.7) million Americans with hypertension are untreated, which would be expected to increase to 15.6 (13.6 to 17.7) million after the implementation of the ACC/AHA guidelines. In China, on the basis of current treatment patterns, 74.5 (64.1 to 84.8) million patients with hypertension are untreated, estimated to increase to 129.8 (118.7 to 140.9 million. In addition, the ACC/AHA guidelines would label 8.7 (6.0 to 11.5) million adults in the US and 51 (40.3 to 61.6) million in China as having hypertension that would not require antihypertensive treatment, compared with 1.5 (1.2 to 2.1) million and 23.4 (12.1 to 35.1) million with the current guidelines. Finally, even among people

receiving treatment, the proportion that are candidates for intensification of treatment is estimated to increase by 13.9 (12.2 to 15.6) million (from 24.0% to 54.4% of treated patients) in the US, and 30 (24.3 to 35.7) million (41.4% to 76.2% of treated patients) in China, if the ACC/AHA treatment targets are adopted.
Conclusions If adopted, the 2017 ACC/AHA hypertension guidelines will markedly increase the number of people labeled as having hypertension and treated with drugs in both the US and China, leading to more than half of those aged 45-75 years in both countries being considered hypertensive.

Risks of ovarian, breast, and corpus uteri cancer in women treated with assisted reproductive technology in Great Britain, 1991-2010: Data linkage study including 2.2 million person years of observation

Carrie L Williams, Michael E Jones, Anthony J Swerdlow, et al.
BMJ 2018; 362 (Published 11 July 2018)
https://www.bmj.com/content/362/bmj.k2644

Abstract
Objective To investigate the risks of ovarian, breast, and corpus uteri cancer in women who have had assisted reproduction.
Design Large, population based, data linkage cohort study.
Setting and participants All women who had assisted reproduction in Great Britain, 1991-2010, as recorded by the Human Fertilisation and Embryology Authority (HFEA).
Interventions HFEA fertility records for cohort members were linked to national cancer registrations.
Main outcome measures Observed first diagnosis of ovarian, breast, and corpus uteri cancer in cohort members were compared with age, sex, and period specific expectation. Standardised incidence ratios (SIRs) were calculated by use of age, sex, and period specific national incidence rates.
Results 255 786 women contributed 2 257 789 person years' follow-up. No significant increased risk of corpus uteri cancer (164 cancers observed *v* 146.9 cancers expected; SIR 1.12, 95% confidence interval 0.95 to 1.30) was found during an average of 8.8 years' follow-up. This study found no significantly increased risks of breast cancer overall (2578 *v* 2641.2; SIR 0.98, 0.94 to 1.01) or invasive breast cancer (2272 *v* 2371.4; SIR 0.96, 0.92 to 1.00). An increased risk of in situ breast cancer (291 *v* 253.5; SIR 1.15, 1.02 to 1.29; absolute excess risk (AER) 1.7 cases per 100 000 person years, 95% confidence interval 0.2 to 3.2) was detected, associated with an increasing number of treatment cycles (P=0.03). There was an increased risk of ovarian cancer (405 *v* 291.82; SIR 1.39, 1.26 to 1.53; AER 5.0 cases per 100 000 person years, 3.3 to 6.9), both invasive (264 *v* 188.1; SIR 1.40, 1.24 to 1.58; AER 3.4 cases per 100 000 person years, 2.0 to 4.9) and borderline (141 *v* 103.7; SIR 1.36, 1.15 to 1.60; AER 1.7 cases per 100 000 person years, 0.7 to 2.8). Increased risks of ovarian tumours were limited to women with endometriosis, low parity, or both. This study found no increased risk of any ovarian tumour in women treated because of only male factor or unexplained infertility.
Conclusions No increased risk of corpus uteri or invasive breast cancer was detected in women who had had assisted reproduction, but increased risks of in situ breast cancer and invasive and borderline ovarian tumours were found in this study. Our results suggest that ovarian tumour risks could be due to patient characteristics, rather than assisted reproduction itself, although both surveillance bias and the effect of treatment are also possibilities. Ongoing monitoring of this population is essential.

Reading Mendelian randomisation studies: A guide, glossary, and checklist for clinicians
Neil M Davies, Michael V Holmes, George Davey Smith
BMJ 2018; 362 (Published 12 July 2018)
https://www.bmj.com/content/362/bmj.k601

Summary points

- Mendelian randomisation is a research method that provides evidence about putative causal relations between modifiable risk factors and disease, using genetic variants as natural experiments
- Mendelian randomisation is less likely to be affected by confounding or reverse causation than conventional observational studies
- Like all analytical approaches, however, Mendelian randomisation depends on assumptions, and the plausibility of these assumptions must be assessed
- Moreover, the relevance of the results for clinical decisions should be interpreted in light of other sources of evidence
- We provide a critical appraisal checklist that can be used to assess and interpret Mendelian randomisation studies

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JAMA: Journal of the American Medical Association (17 July 2018, Vol. 320, No. 3)

Effect of a Multifaceted Quality Improvement Intervention on Hospital Personnel Adherence to Performance Measures in Patients With Acute Ischemic Stroke in China: A Randomized Clinical Trial
Yilong Wang, Zixiao Li, Xingquan Zhao, et al
JAMA. 2018; 320 (3): 245-254.
https://jamanetwork.com/journals/jama/fullarticle/2687118

Abstract
Importance In China and other parts of the world, hospital personnel adherence to evidence-based stroke care is limited.
Objective To determine whether a multifaceted quality improvement intervention can improve hospital personnel adherence to evidence-based performance measures in patients with acute ischemic stroke (AIS) in China.
Design, Setting, and Participants A multicenter, cluster-randomized clinical trial among 40 public hospitals in China that enrolled 4800 patients hospitalized with AIS from August 10, 2014, through June 20, 2015, with 12-month follow-up through July 30, 2016.
Interventions Twenty hospitals received a multifaceted quality improvement intervention (intervention group; 2400 patients), including a clinical pathway, care protocols, quality coordinator oversight, and performance measure monitoring and feedback. Twenty hospitals participated in the stroke registry with usual care (control group; 2400 patients.(
Main Outcomes and Measures The primary outcome was hospital personnel adherence to 9 AIS performance measures, with co-primary outcomes of a composite of percentage of performance measures adhered to, and as all-or-none. Secondary outcomes included in-hospital mortality and long-term outcomes (a new vascular event, disability [modified Rankin Scale score, 3-5], and all-cause mortality) at 3, 6, and 12 months.

Results Among 4800 patients with AIS enrolled from 40 hospitals and randomized (mean age, 65 years; women, 1757 [36.6%]), 3980 patients (82.9%) completed the 12-month follow-up of the trial. Patients in intervention group were more likely to receive performance measures than those in the control groups (composite measure, 88.2% vs 84.8%, respectively; absolute difference, 3.54% [95% CI, 0.68% to 6.40% ,[*P* .(02. = The all-or-none measure did not significantly differ between the intervention and control groups (53.8% vs 47.8%, respectively; absolute difference, 6.69% [95% CI, −0.41% to 13.79% ,[*P* .(06. = New clinical vascular events were significantly reduced in the intervention group compared with the control group at 3 months (3.9% vs 5.3%, respectively; difference, −2.03% [95% CI, −3.51% to −0.55% ;[*P* 6 ,(007. = months (6.3% vs 7.8%, respectively; difference, −2.18% [95% CI, −4.0% to −0.35% ;[*P* (02. = and 12 months (9.1% vs 11.8%, respectively; difference, −3.13% [95% CI, −5.28% to −0.97% ;[*P*.(005. =

Conclusions and Relevance Among 40 hospitals in China, a multifaceted quality improvement intervention compared with usual care resulted in a statistically significant but small improvement in hospital personnel adherence to evidence-based performance measures in patients with acute ischemic stroke when assessed as a composite measure, but not as an all-or-none measure. Further research is needed to understand the generalizability of these findings.

Association of Digital Media Use With Subsequent Symptoms of Attention-Deficit/Hyperactivity Disorder Among Adolescents

Chaelin K. Ra, Junhan Cho, Matthew D. Stone, et al

JAMA. 2018; 320 (3): 255-263.
https://jamanetwork.com/journals/jama/article-abstract/2687861

Abstract

Importance Modern digital platforms are easily accessible and intensely stimulating; it is unknown whether frequent use of digital media may be associated with symptoms of attention-deficit/hyperactivity disorder (ADHD).

Objective To determine whether the frequency of using digital media among 15- and 16-year-olds without significant ADHD symptoms is associated with subsequent occurrence of ADHD symptoms during a 24-month follow-up.

Design, Setting, and Participants Longitudinal cohort of students in 10 Los Angeles County, California, high schools recruited through convenience sampling. Baseline and 6-, 12-, 18-, and 24-month follow-up surveys were administered from September 2014 (10th grade) to December 2016 (12th grade). Of 4100 eligible students, 3051 10th-graders (74%) were surveyed at the baseline assessment.

Exposures Self-reported use of 14 different modern digital media activities at a high-frequency rate over the preceding week was defined as many times a day (yes/no) and was summed in a cumulative index (range, 0-14).

Main Outcomes and Measures Self-rated frequency of 18 ADHD symptoms (never/rare, sometimes, often, very often) in the 6 months preceding the survey. The total numbers of 9 inattentive symptoms (range, 0-9) and 9 hyperactive-impulsive symptoms (range, 0-9) that students rated as experiencing often or very often were calculated. Students who had reported experiencing often or very often 6 or more symptoms in either category were classified as being ADHD symptom-positive.

Results Among the 2587 adolescents (63% eligible students; 54.4% girls; mean [SD] age 15.5 years [0.5 years]) who did not have significant symptoms of ADHD at baseline, the median follow-up was 22.6 months (interquartile range [IQR], 21.8-23.0, months). The mean (SD) number of baseline digital media activities used at a high-frequency rate was

3.62 (3.30); 1398 students (54.1%) indicated high frequency of checking social media (95% CI, 52.1%-56.0%), which was the most common media activity. High-frequency engagement in each additional digital media activity at baseline was associated with a significantly higher odds of having symptoms of ADHD across follow-ups (OR, 1.11; 95% CI, 1.06-1.16). This association persisted after covariate adjustment (OR, 1.10; 95% CI, 1.05-1.15). The 495 students who reported no high-frequency media use at baseline had a 4.6% mean rate of having ADHD symptoms across follow-ups vs 9.5% among the 114 who reported 7 high-frequency activities (difference; 4.9%; 95% CI, 2.5%-7.3%) and vs 10.5% among the 51 students who reported 14 high-frequency activities (difference, 5.9%; 95% CI, 2.6%-9.2%).
Conclusions and Relevance Among adolescents followed up over 2 years, there was a statistically significant but modest association between higher frequency of digital media use and subsequent symptoms of ADHD. Further research is needed to determine whether this association is causal.

Site of Death, Place of Care, and Health Care Transitions Among US Medicare Beneficiaries, 2000-2015
Joan M. Teno, Pedro Gozalo, Amal N. Trivedi, et al
JAMA. 2018; 320 (3): 264-271.
https://jamanetwork.com/journals/jama/article-abstract/2686318

Abstract
Importance End-of-life care costs are high and decedents often experience poor quality of care. Numerous factors influence changes in site of death, health care transitions, and burdensome patterns of care.
Objective To describe changes in site of death and patterns of care among Medicare decedents.
Design, Setting, and Participants Retrospective cohort study among a 20% random sample of 1 361 870 decedents who had Medicare fee-for-service (2000, 2005, 2009, 2011, and 2015) and a 100% sample of 871 845 decedents who had Medicare Advantage (2011 and 2015) and received care at an acute care hospital, at home or in the community, at a hospice inpatient care unit, or at a nursing home.
Exposures Secular changes between 2000 and 2015.
Main Outcomes and Measures Medicare administrative data were used to determine site of death, place of care, health care transitions, which are changes in location of care, and burdensome patterns of care. Burdensome patterns of care were based on health care transitions during the last 3 days of life and multiple hospitalizations for infections or dehydration during the last 120 days of life.
Results The site of death and patterns of care were studied among 1 361 870 decedents who had Medicare fee-for-service (mean [SD] age, 82.8 [8.4] years; 58.7% female) and 871 845 decedents who had Medicare Advantage (mean [SD] age, 82.1 [8.5] years; 54.0% female). Among Medicare fee-for-service decedents, the proportion of deaths that occurred in an acute care hospital decreased from 32.6% (95% CI, 32.4%-32.8%) in 2000 to 19.8% (95% CI, 19.6%-20.0%) in 2015, and deaths in a home or community setting that included assisted living facilities increased from 30.7% (95% CI, 30.6%-30.9%) in 2000 to 40.1% (95% CI, 39.9%-30.3%) in 2015. Use of the intensive care unit during the last 30 days of life among Medicare fee-for-service decedents increased from 24.3% (95% CI, 24.1%-24.4%) in 2000 and then stabilized between 2009 and 2015 at 29.0% (95% CI, 28.8%-29.2%). Among Medicare fee-for-service decedents, health care transitions during the last 3 days of life increased from 10.3% (95% CI, 10.1%-10.4%) in 2000 to a high of

14.2% (95% CI, 14.0%-14.3%) in 2009 and then decreased to 10.8% (95% CI, 10.6%-10.9%) in 2015. The number of decedents enrolled in Medicare Advantage during the last 90 days of life increased from 358 600 in 2011 to 513 245 in 2015. Among decedents with Medicare Advantage, similar patterns in the rates for site of death, place of care, and health care transitions were observed.
Conclusions and Relevance Among Medicare fee-for-service beneficiaries who died in 2015 compared with 2000, there was a lower likelihood of dying in an acute care hospital, an increase and then stabilization of intensive care unit use during the last month of life, and an increase and then decline in health care transitions during the last 3 days of life.

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The Lancet (14 July 2018, Vol. 392, No. 10142)

Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): A randomised, open-label, controlled, phase 3 trial

Kohei Shitara, Mustafa Özgüroğlu, Yung-Jue Bang, et al. on behalf of the KEYNOTE-061 investigators

The Lancet: Volume 392, No. 10142, p123–133, 14 July 2018
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)31257-1/fulltext

Summary
Background
Patients with advanced gastric or gastro-oesophageal junction cancer that progresses on chemotherapy have poor outcomes. We compared pembrolizumab with paclitaxel in patients with advanced gastric or gastro-oesophageal junction cancer that progressed on first-line chemotherapy with a platinum and fluoropyrimidine.
Methods
This randomised, open-label, phase 3 study was done at 148 medical centres in 30 countries. Eligible patients were randomised (1:1) in blocks of four per stratum with an interactive voice-response and integrated web-response system to receive either pembrolizumab 200 mg every 3 weeks for up to 2 years or standard-dose paclitaxel. Primary endpoints were overall survival and progression-free survival in patients with a programmed cell death ligand 1 (PD-L1) combined positive score (CPS) of 1 or higher. Safety was assessed in all patients, irrespective of CPS. The significance threshold for overall survival was p=0·0135 (one-sided). This trial is registered at ClinicalTrials.gov, number NCT02370498.
Findings
Between June 4, 2015, and July 26, 2016, 592 patients were enrolled. Of the 395 patients who had a PD-L1 CPS of 1 or higher, 196 patients were assigned to receive pembrolizumab and 199 patients were assigned to receive paclitaxel. As of Oct 26, 2017, 326 patients in the population with CPS of 1 or higher had died (151 [77%] of 196 patients in the pembrolizumab group and 175 [88%] of 199 patients in the paclitaxel group). Median overall survival was 9·1 months (95% CI 6·2–10·7) with pembrolizumab and 8·3 months (7·6–9·0) with paclitaxel (hazard ratio [HR] 0·82, 95% CI 0·66–1·03; one-sided p=0·0421). Median progression-free survival was 1·5 months (95% CI 1·4–2·0) with pembrolizumab and 4·1 months (3·1–4·2) with paclitaxel (HR 1·27, 95% CI 1·03–1·57). In the total population, grade 3–5 treatment-related adverse events occurred in 42 (14%) of the 294

patients treated with pembrolizumab and 96 (35%) of the 276 patients treated with paclitaxel.

Interpretation

Pembrolizumab did not significantly improve overall survival compared with paclitaxel as second-line therapy for advanced gastric or gastro-oesophageal junction cancer with PD-L1 CPS of 1 or higher. Pembrolizumab had a better safety profile than paclitaxel. Additional trials of pembrolizumab in gastric and gastro-oesophageal cancer are ongoing.

Efficacy and safety of continuing versus withdrawing adalimumab therapy in maintaining remission in patients with non-radiographic axial spondyloarthritis (ABILITY-3): A multicentre, randomised, double-blind study

Robert Landewé, Joachim Sieper, Philip Mease, et al.

The Lancet: Volume 392, No. 10142, p134–144, 14 July 2018

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)31362-X/fulltext

Summary

Background

Success of treatment withdrawal in patients with non-radiographic axial spondyloarthritis who are in remission remains unknown. The ABILITY-3 study explored the ability to withdraw adalimumab treatment in patients with non-radiographic axial spondyloarthritis who achieved sustained clinical remission after open-label treatment with adalimumab.

Methods

ABILITY-3 was a multicentre, two-period study done in 107 sites in 20 countries. We enrolled adult patients (≥18 years) diagnosed with non-radiographic axial spondyloarthritis, fulfilling Assessment of SpondyloArthritis international Society classification criteria but not the modified New York radiologic criterion, who had objective evidence of active inflammation, active disease, and inadequate response to at least two non-steroidal anti-inflammatory drugs. Patients who achieved Ankylosing Spondylitis Disease Activity Score (ASDAS) inactive disease (<1·3) with open-label adalimumab (40 mg subcutaneously every other week for 28 weeks) at weeks 16, 20, 24, and 28 were randomly assigned (1:1) using an interactive voice or web response system to 40-week, double-blind treatment with adalimumab (continuation) or placebo (withdrawal). The primary efficacy endpoint was the proportion of patients who did not experience a flare (defined as ASDAS ≥2·1 at two consecutive visits) during the double-blind period. Patients who flared were rescued with open-label adalimumab. This study is registered with ClinicalTrials.gov, number NCT01808118.

Findings

Between June 27, 2013, and October 22, 2015, 673 patients were enrolled to the study. The trial completed on April 14, 2017. Of 673 enrolled patients, 305 (45%) achieved sustained remission and were randomly assigned to double-blind treatment (152 patients to adalimumab and 153 to placebo). A greater proportion of patients continuing adalimumab than those receiving placebo did not experience a flare (107 [70%] of 152 patients *vs* 72 [47%] of 153 patients; p<0·0001) up to and including week 68. Among 673 patients receiving adalimumab at any time, 516 (77%) patients reported an adverse event and 28 (4%) experienced a serious adverse event. The most common adverse events in both the adalimumab and placebo groups were nasopharyngitis (25 [16%] *vs* 20 [13%]), upper respiratory tract infection (20 [13%] *vs* 12 [8%]), and worsening of axial spondyloarthritis (ten [7%] *vs* 21 [14%]).

Interpretation

In patients with active non-radiographic axial spondyloarthritis who achieved sustained remission with adalimumab, continued therapy was associated with significantly fewer patients flaring than was treatment withdrawal.

Causes and incidence of community-acquired serious infections among young children in south Asia (ANISA): An observational cohort study
Samir K Saha, Stephanie J Schrag, Shams El Arifeen, et al.
The Lancet: Volume 392, No. 10142, p145–159, 14 July 2018
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)31127-9/fulltext

Summary
Background
More than 500 000 neonatal deaths per year result from possible serious bacterial infections (pSBIs), but the causes are largely unknown. We investigated the incidence of community-acquired infections caused by specific organisms among neonates in south Asia.
Methods
From 2011 to 2014, we identified babies through population-based pregnancy surveillance at five sites in Bangladesh, India, and Pakistan. Babies were visited at home by community health workers up to ten times from age 0 to 59 days. Illness meeting the WHO definition of pSBI and randomly selected healthy babies were referred to study physicians. The primary objective was to estimate proportions of specific infectious causes by blood culture and Custom TaqMan Array Cards molecular assay (Thermo Fisher, Bartlesville, OK, USA) of blood and respiratory samples.
Findings
6022 pSBI episodes were identified among 63 114 babies (95·4 per 1000 livebirths). Causes were attributed in 28% of episodes (16% bacterial and 12% viral). Mean incidence of bacterial infections was 13·2 (95% credible interval [CrI] 11·2–15·6) per 1000 livebirths and of viral infections was 10·1 (9·4–11·6) per 1000 livebirths. The leading pathogen was respiratory syncytial virus (5·4, 95% CrI 4·8–6·3 episodes per 1000 livebirths), followed by *Ureaplasma* spp (2·4, 1·6–3·2 episodes per 1000 livebirths). Among babies who died, causes were attributed to 46% of pSBI episodes, among which 92% were bacterial. 85 (83%) of 102 blood culture isolates were susceptible to penicillin, ampicillin, gentamicin, or a combination of these drugs.
Interpretation
Non-attribution of a cause in a high proportion of patients suggests that a substantial proportion of pSBI episodes might not have been due to infection. The predominance of bacterial causes among babies who died, however, indicates that appropriate prevention measures and management could substantially affect neonatal mortality. Susceptibility of bacterial isolates to first-line antibiotics emphasises the need for prudent and limited use of newer-generation antibiotics. Furthermore, the predominance of atypical bacteria we found and high incidence of respiratory syncytial virus indicated that changes in management strategies for treatment and prevention are needed. Given the burden of disease, prevention of respiratory syncytial virus would have a notable effect on the overall health system and achievement of Sustainable Development Goal.

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The New England Journal of Medicine (12 July 2018, Vol. 379, No. 2)

Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer
Joseph A. Sparano, Robert J. Gray, Della F. Makower, et al.
N Engl J Med 2018; 379: 111-121 July 12, 2018
https://www.nejm.org/doi/full/10.1056/NEJMoa1804710

Abstract
Background
The recurrence score based on the 21-gene breast cancer assay predicts chemotherapy benefit if it is high and a low risk of recurrence in the absence of chemotherapy if it is low; however, there is uncertainty about the benefit of chemotherapy for most patients, who have a midrange score.
Methods
We performed a prospective trial involving 10,273 women with hormone-receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative, axillary node–negative breast cancer. Of the 9719 eligible patients with follow-up information, 6711 (69%) had a midrange recurrence score of 11 to 25 and were randomly assigned to receive either chemoendocrine therapy or endocrine therapy alone. The trial was designed to show noninferiority of endocrine therapy alone for invasive disease–free survival (defined as freedom from invasive disease recurrence, second primary cancer, or death).
Results
Endocrine therapy was noninferior to chemoendocrine therapy in the analysis of invasive disease–free survival (hazard ratio for invasive disease recurrence, second primary cancer, or death [endocrine vs. chemoendocrine therapy], 1.08; 95% confidence interval, 0.94 to 1.24; P=0.26). At 9 years, the two treatment groups had similar rates of invasive disease–free survival (83.3% in the endocrine-therapy group and 84.3% in the chemoendocrine-therapy group), freedom from disease recurrence at a distant site (94.5% and 95.0%) or at a distant or local–regional site (92.2% and 92.9%), and overall survival (93.9% and 93.8%). The chemotherapy benefit for invasive disease–free survival varied with the combination of recurrence score and age (P=0.004), with some benefit of chemotherapy found in women 50 years of age or younger with a recurrence score of 16 to 25.
Conclusions
Adjuvant endocrine therapy and chemoendocrine therapy had similar efficacy in women with hormone-receptor–positive, HER2-negative, axillary node–negative breast cancer who had a midrange 21-gene recurrence score, although some benefit of chemotherapy was found in some women 50 years of age or younger.

Tailoring Adjuvant Endocrine Therapy for Premenopausal Breast Cancer
Prudence A. Francis, Olivia Pagani, Gini F. Fleming, et al. for the SOFT and TEXT Investigators and the International Breast Cancer Study Group
N Engl J Med 2018; 379: 122-137 July 12, 2018
https://www.nejm.org/doi/full/10.1056/NEJMoa1803164

Abstract
Background
In the Suppression of Ovarian Function Trial (SOFT) and the Tamoxifen and Exemestane Trial (TEXT), the 5-year rates of recurrence of breast cancer were significantly lower among premenopausal women who received the aromatase inhibitor exemestane plus ovarian suppression than among those who received tamoxifen plus ovarian suppression.

The addition of ovarian suppression to tamoxifen did not result in significantly lower recurrence rates than those with tamoxifen alone. Here, we report the updated results from the two trials.

Methods

Premenopausal women were randomly assigned to receive 5 years of tamoxifen, tamoxifen plus ovarian suppression, or exemestane plus ovarian suppression in SOFT and to receive tamoxifen plus ovarian suppression or exemestane plus ovarian suppression in TEXT. Randomization was stratified according to the receipt of chemotherapy.

Results

In SOFT, the 8-year disease-free survival rate was 78.9% with tamoxifen alone, 83.2% with tamoxifen plus ovarian suppression, and 85.9% with exemestane plus ovarian suppression (P=0.009 for tamoxifen alone vs. tamoxifen plus ovarian suppression). The 8-year rate of overall survival was 91.5% with tamoxifen alone, 93.3% with tamoxifen plus ovarian suppression, and 92.1% with exemestane plus ovarian suppression (P=0.01 for tamoxifen alone vs. tamoxifen plus ovarian suppression); among the women who remained premenopausal after chemotherapy, the rates were 85.1%, 89.4%, and 87.2%, respectively. Among the women with cancers that were negative for HER2 who received chemotherapy, the 8-year rate of distant recurrence with exemestane plus ovarian suppression was lower than the rate with tamoxifen plus ovarian suppression (by 7.0 percentage points in SOFT and by 5.0 percentage points in TEXT). Grade 3 or higher adverse events were reported in 24.6% of the tamoxifen-alone group, 31.0% of the tamoxifen–ovarian suppression group, and 32.3% of the exemestane–ovarian suppression group.

Conclusions

Among premenopausal women with breast cancer, the addition of ovarian suppression to tamoxifen resulted in significantly higher 8-year rates of both disease-free and overall survival than tamoxifen alone. The use of exemestane plus ovarian suppression resulted in even higher rates of freedom from recurrence. The frequency of adverse events was higher in the two groups that received ovarian suppression than in the tamoxifen-alone group.

Prevention of M. tuberculosis Infection with H4:IC31 Vaccine or BCG Revaccination

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Abstract

Background

Recent *Mycobacterium tuberculosis* infection confers a predisposition to the development of tuberculosis disease, the leading killer among global infectious diseases. H4:IC31, a candidate subunit vaccine, has shown protection against tuberculosis disease in preclinical models, and observational studies have indicated that primary bacille Calmette–Guérin (BCG) vaccination may offer partial protection against infection.

Methods

In this phase 2 trial, we randomly assigned 990 adolescents in a high-risk setting who had undergone neonatal BCG vaccination to receive the H4:IC31 vaccine, BCG revaccination, or placebo. All the participants had negative results on testing for *M. tuberculosis* infection on the QuantiFERON-TB Gold In-tube assay (QFT) and for the human immunodeficiency virus. The primary outcomes were safety and acquisition of *M. tuberculosis* infection, as defined by initial conversion on QFT that was performed every 6 months during a 2-year

period. Secondary outcomes were immunogenicity and sustained QFT conversion to a positive test without reversion to negative status at 3 months and 6 months after conversion. Estimates of vaccine efficacy are based on hazard ratios from Cox regression models and compare each vaccine with placebo.

Results

Both the BCG and H4:IC31 vaccines were immunogenic. QFT conversion occurred in 44 of 308 participants (14.3%) in the H4:IC31 group and in 41 of 312 participants (13.1%) in the BCG group, as compared with 49 of 310 participants (15.8%) in the placebo group; the rate of sustained conversion was 8.1% in the H4:IC31 group and 6.7% in the BCG group, as compared with 11.6% in the placebo group. Neither the H4:IC31 vaccine nor the BCG vaccine prevented initial QFT conversion, with efficacy point estimates of 9.4% (P=0.63) and 20.1% (P=0.29), respectively. However, the BCG vaccine reduced the rate of sustained QFT conversion, with an efficacy of 45.4% (P=0.03); the efficacy of the H4:IC31 vaccine was 30.5% (P=0.16). There were no clinically significant between-group differences in the rates of serious adverse events, although mild-to-moderate injection-site reactions were more common with BCG revaccination.

Conclusions

In this trial, the rate of sustained QFT conversion, which may reflect sustained *M. tuberculosis* infection, was reduced by vaccination in a high-transmission setting. This finding may inform clinical development of new vaccine candidates.

Recurrent Glioblastoma Treated with Recombinant Poliovirus

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Abstract

Background

The prognosis of patients with recurrent World Health Organization (WHO) grade IV malignant glioma is dismal, and there is currently no effective therapy. We conducted a dose-finding and toxicity study in this population of patients, evaluating convection-enhanced, intratumoral delivery of the recombinant nonpathogenic polio–rhinovirus chimera (PVSRIPO). PVSRIPO recognizes the poliovirus receptor CD155, which is widely expressed in neoplastic cells of solid tumors and in major components of the tumor microenvironment.

Methods

We enrolled consecutive adult patients who had recurrent supratentorial WHO grade IV malignant glioma, confirmed on histopathological testing, with measurable disease (contrast-enhancing tumor of ≥1 cm and ≤5.5 cm in the greatest dimension). The study evaluated seven doses, ranging between 107 and 1010 50% tissue-culture infectious doses (TCID50), first in a dose-escalation phase and then in a dose-expansion phase.

Results

From May 2012 through May 2017, a total of 61 patients were enrolled and received a dose of PVSRIPO. Dose level −1 (5.0×107 TCID50) was identified as the phase 2 dose. One dose-limiting toxic effect was observed; a patient in whom dose level 5 (1010 TCID50) was administered had a grade 4 intracranial hemorrhage immediately after the catheter was removed. To mitigate locoregional inflammation of the infused tumor with prolonged glucocorticoid use, dose level 5 was deescalated to reach the phase 2 dose. In the dose-expansion phase, 19% of the patients had a PVSRIPO-related adverse event of grade 3 or higher. Overall survival among the patients who received PVSRIPO reached a

plateau of 21% (95% confidence interval, 11 to 33) at 24 months that was sustained at 36 months.

Conclusions

Intratumoral infusion of PVSRIPO in patients with recurrent WHO grade IV malignant glioma confirmed the absence of neurovirulent potential. The survival rate among patients who received PVSRIPO immunotherapy was higher at 24 and 36 months than the rate among historical controls.

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Sources

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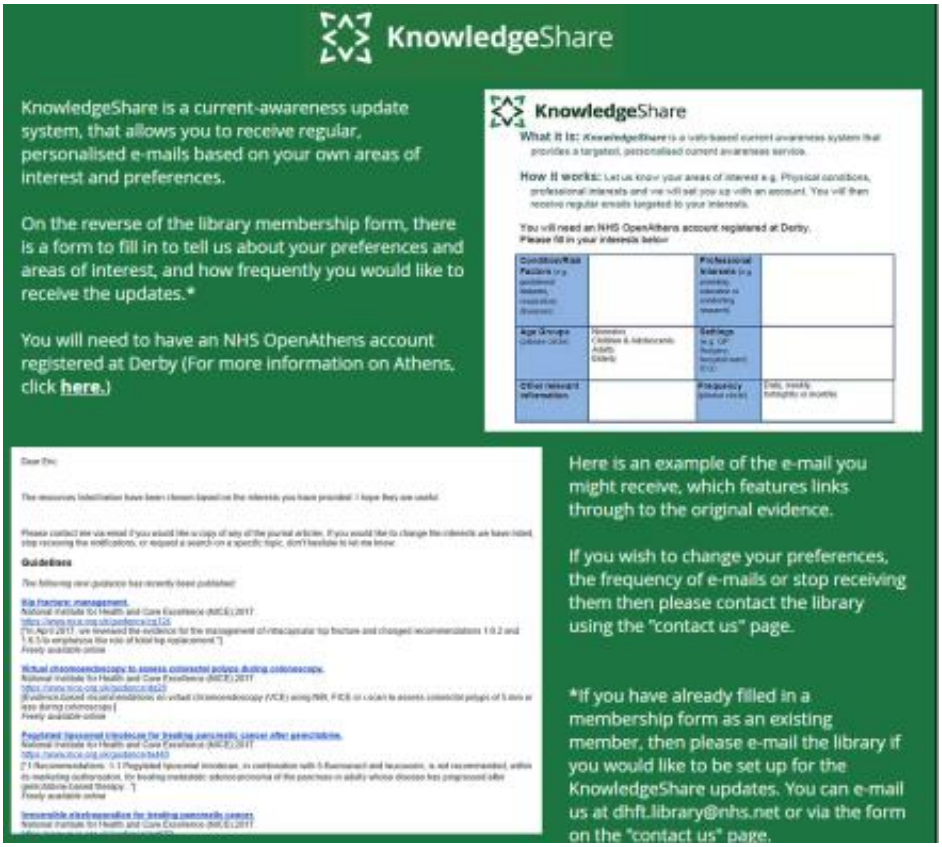

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