RESEARCH

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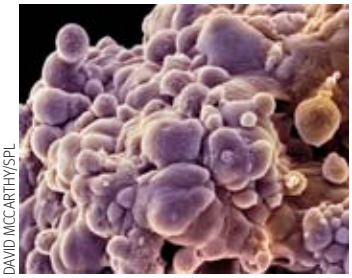


DAVID MCCARTHY/SPL

THIS WEEK'S RESEARCH QUESTIONS

593 What are the benefits and harms of population screening for prostate cancer?

594 What is the relation between a single test for prostate specific antigen at age 60 and subsequent lifetime risk of prostate cancer?

595 Does the novel non-endoscopic device the Cytosponge provide a feasible, acceptable, and accurate way to test for Barrett's oesophagus?

596 Is isoniazid resistance associated with subsequent death in patients being treated for an initial episode of tuberculous meningitis?

Screening for Barrett's oesophagus—a new approach

The usual way to detect Barrett's oesophagus is by using white light gastroscopy and biopsy, but this approach is invasive and expensive. Sudarshan Kadri and colleagues' prospective cohort study suggests that a new device called the Cytosponge, when coupled with a single immunomarker trefoil factor 3, might be a promising new way to screen for Barrett's oesophagus (p 595).

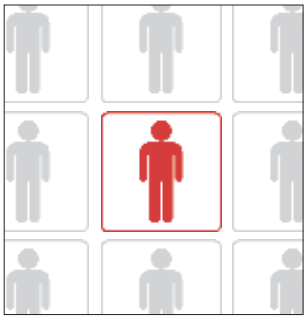
The Cytosponge is an ingestible gelatine capsule that contains a compressed mesh attached to a string. The capsule and string are swallowed with water, where the capsule dissolves in the stomach. The mesh then expands and is withdrawn by pulling on the string, thus obtaining a specimen from the oesophagus that can be examined in the laboratory.

The Press Association reported this story with the headline "'Sponge' could help prevent cancer." As Peter Bampton points out in his linked editorial (p 564), Barrett's oesophagus increases the risk of oesophageal cancer by 30-40-fold. By detecting Barrett's oesophagus early, the Cytosponge could help make sure these patients receive appropriate treatment and don't "convert" to adenocarcinoma. But he warns that this approach does not fulfil the criteria for a population screening programme.

Nearly all (99%) of the patients in this study of diagnostic accuracy were able to swallow the Cytosponge, and most (82%) reported low levels of anxiety before and after the test, indicating that this approach is acceptable to patients. Compared with gastroscopy, the sensitivity and specificity of the test for segments of 1 cm or more were 73.3% and 93.8%, respectively, whereas these values were 90.0% and 93.5% for segments of 2 cm or more.

Elsewhere in the journal, Janusz Jankowski and colleagues discuss the natural history and diagnosis of Barrett's oesophagus in a Clinical Review (p 597). They also cover treatments to prevent progression of Barrett's oesophagus to adenocarcinoma and highlight new NICE guidelines that recommend clinicians consider offering endoscopic ablative therapy as an alternative to oesophagectomy for people with high grade dysplasia and intramucosal cancer.

Screening for prostate cancer



Screening based on prostate specific antigen (PSA) has led to increased rates of diagnosis of prostate cancer, but whether this translates into more lives saved has been in doubt. Mia Djulbegovic and colleagues aimed to clarify the matter with a systematic review which identified six randomised controlled trials (387 286 participants) for meta-analysis (p 593). Their results confirmed that screening increased the probability of being diagnosed with prostate cancer—although the quality of evidence was low—but they showed no effect on overall or disease specific mortality, based on moderate quality evidence. Little information was available about the potential harms of screening. The authors conclude that we don't have enough good evidence to justify routine population screening at present.

As editorialist Gerald Andriole Jr points out (p 563) another concern is the substantial human and economic cost associated with screening—largely down to overdiagnosis. Andrew Vickers and colleagues investigated an approach that might help to limit "overscreening" by identifying men who are most at risk (p 594). Their case-control study looked at the relation between concentration of PSA at age 60 and subsequent diagnosis of clinically relevant prostate cancer in an unscreened population of over 1000 Swedish men. The results indicated that this measure could predict lifetime risk of metastasis and death from prostate cancer. Since the great majority of deaths from prostate cancer were in men who had PSA concentrations in the top quarter at age 60, the authors suggest that screening should focus on this high risk subgroup. These results require further validation, and in the meantime Andriole advises clinicians to individualise their approach to screening on the basis of factors such as age and family history.

LATEST RESEARCH: For this and other new research articles see http://www.bmj.com/channels/research.dtl

DAVID M MARTIN/SPL

Podcast: Barrett's oesophagus
Rebecca Fitzgerald, an author of this week's paper on testing for Barrett's oesophagus, talks to Duncan Jarvies about how improvements in treatment for the disease have spurred on the search for population screening methods, and about how the suitability of the Cytosponge for such a role is being evaluated.

Slideshow: How to get your research published in the *BMJ*
In this slideshow, three of the *BMJ*'s senior research editors give insiders' tips on how to focus your research question, write a great paper, and maximise your chances of getting it published (www.bmj.com/video/how-to-write.dtl).

Screening for prostate cancer: systematic review and meta-analysis of randomised controlled trials

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EDITORIAL by Andriole
RESEARCH p 594

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STUDY QUESTION

What are the benefits and harms of screening for prostate cancer?

SUMMARY ANSWER

Based on moderate quality evidence, population based prostate cancer screening does not have a significant impact on overall mortality or mortality specific to prostate cancer.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Screening for prostate cancer leads to increased diagnosis. Screening does not have a significant impact on overall or disease specific mortality.

Selection criteria for studies

We searched several electronic databases including Medline, Embase, and CENTRAL, as well as abstract proceedings and reference lists up to 13 July 2010 without language restrictions using predefined search terms and inclusion criteria. We sought all randomised controlled trials of prostate cancer screening with the use of prostate specific antigen with or without digital rectal examination compared with no screening. Outcomes of interest included all cause and disease specific mortality, diagnosis of prostate cancer, effect of screening on stage, false positive and false negative results, harms of screening, quality of life, and cost effectiveness.

Primary outcomes

We focused on outcomes important to patients, in particular all cause mortality and death from prostate cancer.

Main results and role of chance

We included six randomised controlled trials in the analysis with a total of 387 286 participants (table). Moderate quality evidence based on four trials showed no effect of prostate cancer screening on all cause mortality. Moderate quality evidence from five trials showed no effect of screening on death from prostate cancer, whereas low quality evidence from five trials showed an increase in the number of diagnoses of prostate cancer associated with screening (relative risk increase 46%, confidence interval 21% to 77%). None of the studies provided data on the effects of screening on patients' quality of life, and little information about potential harms associated with screening was provided. There were limited data on the effect of screening when analyses were stratified by age.

EFFECTS OF SCREENING FOR PROSTATE CANCER

	No of studies	No of participants	Relative risk (95% CI)	Overall quality of studies
All cause mortality	4	256 019	0.99 (0.97 to 1.01)	Moderate
Death from prostate cancer	5	302 500	0.88 (0.71 to 1.09)	Moderate
Prostate cancer diagnosis	5	340 800	1.46 (1.21 to 1.77)	Low

Bias, confounding, and other reasons for caution

The included trials had several methodological limitations, including lack of allocation concealment, failure to report intention to screen analysis, and selective reporting bias. Results for deaths from prostate cancer and diagnosis of prostate cancer were inconsistent across trials. Further limitations were contamination of the non-screening arm as well as the relatively short length of follow-up (range 4-15 years) of the included studies. Though screening probably aids in diagnosis at an earlier stage, this comes with the risk of potential overtreatment and downstream adverse effects that currently cannot be precisely quantified.

Study funding/potential competing interests

This study was funded by the Department of Urology, University of Florida, and the Dennis W Jahnigen Career Development Scholars Award through the American Geriatrics Society.

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Prostate specific antigen concentration at age 60 and death or metastasis from prostate cancer: case-control study

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EDITORIAL by Andriole
RESEARCH p 593

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STUDY QUESTION

What is the relation between a single test for prostate specific antigen at age 60 and subsequent lifetime risk of clinically relevant prostate cancer?

SUMMARY ANSWER

Concentration of prostate specific antigen at age 60 can predict lifetime risk of prostate cancer metastasis and death.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Prostate specific antigen is widely used for the early detection of prostate cancer but is associated with considerable overdiagnosis, and many men must be screened to save one life. As 90% of deaths from prostate cancer occur in men in the top quarter of prostate specific antigen concentrations measured at age 60, screening should focus on this subgroup of men at higher risk.

Participants and setting

Participants in our study were from a population based cohort study of Swedish men aged 60 who had provided blood samples in 1981-2 for a cardiovascular study and were followed to age 85. The rate of prostate specific antigen testing during the course of the study was low.

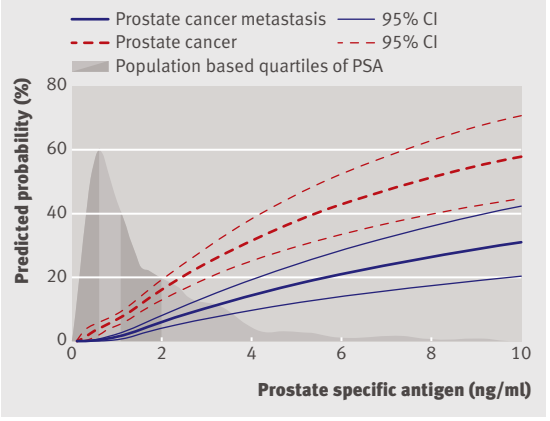
Design, size, and duration

The records of all 1160 men were linked to the Swedish cancer registry update of 31 December 2006 to determine diagnoses of prostate cancer. Metastasis and death from prostate cancer were assessed by review of records. All men in the study were followed until death or age 85.

Main result and the role of chance

There were 43 cases of metastasis and 35 deaths from prostate cancer. Concentration of prostate specific antigen at age 60 was associated with prostate cancer metastasis (area under the curve 0.86, 95% confidence interval 0.79 to 0.92; P<0.001) and death from prostate cancer (0.90, 0.84 to 0.96; P<0.001). The higher the value for the area under the curve (values from 0.5 to 1) the better the test. Of all the deaths from prostate cancer, 90% (78% to 100%) occurred in men in the top quarter of prostate specific antigen concentrations, equivalent to concentrations of about 2 ng/ml or higher (odds ratio 26 for ≥2 ng/ml *v* <2 ng/ml). Conversely, men with concentrations at median or lower (≤1 ng/ml) at age 60 were unlikely to have clinically relevant prostate cancer (0.5% risk of metastasis and 0.2% risk of death from prostate cancer by age 85).

LIFETIME RISK OF PROSTATE CANCER OR METASTASIS BY PSA CONCENTRATION AT AGE 60



Bias, confounding, and other reasons for caution

As we blindly analysed stored blood samples, there is little risk of bias in the study. We could, however, have overestimated the risk of clinically relevant prostate cancer for a contemporary patient. Firstly, men who have undergone prostate specific antigen testing before the age of 60 will, on average, be at lower risk because they would have already had cancer detected had they been at high risk. Secondly, overdetection can occur even in the absence of screening. For example, a man presenting to a urologist with prostate symptoms might have a cancer detected during the clinical investigation that would never have become apparent had the patient not developed concurrent benign disease.

Generalisability to other populations

It is unclear how well our risk estimates apply to men of other races. Incidence of and mortality from prostate cancer are higher in African-Americans and lower in Asians than in white people. Further research could show whether there are also racial differences in the relation between prostate specific antigen at age 60 and future risks of metastases and death.

Study funding/potential competing interests

This work was supported by the National Cancer Institute (grant numbers R21-CA127768-01A1, P50-CA92629); the Swedish Cancer Society (3455); the Swedish Research Council (Medicine) (20095); the Sidney Kimmel Center for Prostate and Urologic Cancers; David H Koch through the Prostate Cancer Foundation; and Fundación Federico SA. HL holds patents for free PSA and hK2 assays.

Acceptability and accuracy of a non-endoscopic screening test for Barrett's oesophagus in primary care: cohort study

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EDITORIAL by Bampton

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STUDY QUESTION How feasible, acceptable, and accurate is screening for Barrett's oesophagus in primary care using a novel non-endoscopic device called a Cytosponge, when coupled with an immunomarker, trefoil factor 3?

SUMMARY ANSWER The test was feasible in primary care and well tolerated. Compared with gastroscopy the sensitivity and specificity of the test was 73.3% (95% confidence interval 44.9% to 92.2%) and 93.8% (91.3% to 95.8%) for 1 cm or more circumferential length and 90.0% (55.5% to 99.7%) and 93.5% (90.9% to 95.5%) for clinically relevant segments of 2 cm or more.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Oesophageal adenocarcinoma is associated with a five year survival of less than 20%; timely diagnosis and treatment of the precursor lesion Barrett's oesophagus may improve survival. The Cytosponge test offers the possibility of a primary care based screening programme for Barrett's oesophagus.

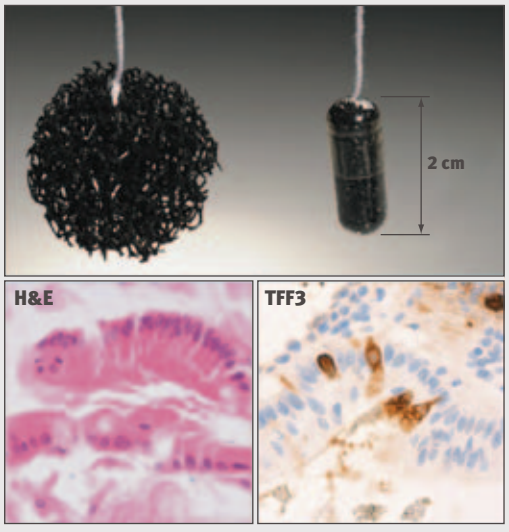
Participants and setting

Overall, 2696 eligible patients were identified from 12 UK general practices in Cambridgeshire (total list size 100 688). Five hundred and four (18.7%) agreed to participate (Cytosponge test and gastroscopy). All endoscopies were done in a single hospital endoscopy unit.

Design, size, and duration

This prospective cohort study used electronic practice records to identify patients with a minimum prescription of acid suppressants for three months in the past five years. All eligible patients were invited for testing with the Cytosponge followed by gastroscopy. We compared the test accuracy of the Cytosponge for detecting Barrett's oesophagus, with respect to segment length, with gastroscopy findings. Participant anxiety and acceptability of the test were assessed before testing and after seven and 90 days using the short form Spielberger state trait anxiety inventory, impact of events scale, and a visual analogue scale.

CYTOSPONGE IN CAPSULE AND EXPANDED. REPRESENTATIVE STAINS FROM PATIENT WITH BARRETT'S OESOPHAGUS (X400)



Main results and the role of chance

Five hundred and one patients (99%) (median age 62, male to female ratio 1:1.2) successfully swallowed the Cytosponge. No serious adverse events occurred. Fifteen (3.0%) patients had an endoscopic diagnosis of Barrett's oesophagus (1 cm or more circumferential length, with intestinal metaplasia) and 10 (2.2%) had 2 cm or more circumferential Barrett's oesophagus and intestinal metaplasia. In this population with a length cut-off point of 1 cm or more the sensitivity and specificity of the test were 73.3% (95% confidence interval 44.9% to 92.2%) and 93.8% (91.3% to 95.8%), respectively, giving a positive predictive value of 26.8% (14.2% to 42.9%) and a negative predictive value of 99.1% (97.8% to 99.8%). For clinically relevant segments of cut-off length 2 cm or more, the sensitivity and specificity were 90.0% (55.5% to 99.7%) and 93.5% (90.9% to 95.5%), respectively. Most patients (355/496, 82%, 95% confidence interval 78.9% to 85.1%) reported low levels of anxiety before the test and scores remained within normal limits at follow-up. Less than 4.5% (2.8% to 6.1%) of participants reported psychological distress (impact of event scale) a week after the procedure.

Bias, confounding, and other reasons for caution

This study involved two procedures (Cytosponge and gastroscopy). In a screening programme, uptake of the test would be expected to be higher than 18.7% as important consumer awareness campaigns would accompany its nationwide implementation.

Generalisability to other populations

The prevalence of Barrett's oesophagus in our study population is in line with other European studies, and the characteristics of the participants were representative of a British population. Therefore the values for accuracy, including positive and negative predictive values, might be generalisable to other British cohorts and possibly to other European cohorts.

Study funding/potential competing interests

This research was supported by the Medical Research Council development gap fund, NIHR School for Primary Care Research, BD Diagnostics, Cambridge Experimental Cancer Medicine Centre, and the National Institute for Health Research Cambridge Biomedical Research Centre.

Isoniazid resistance and death in patients with tuberculous meningitis: retrospective cohort study

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EDITORIAL by Blomberg and Langeland

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STUDY QUESTION

Is initial isoniazid resistance associated with subsequent death among patients being treated for an initial episode of tuberculous meningitis?

SUMMARY ANSWER

In a US national cohort of patients with tuberculous meningitis, isoniazid resistance on initial susceptibility testing was associated with subsequent death among those with positive cerebrospinal fluid cultures for *Mycobacterium tuberculosis*.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Mortality from tuberculous meningitis is greater than that from any other form of tuberculosis, and starting effective anti-tuberculous treatment early is the key to a successful outcome. In areas with a high prevalence of isoniazid resistance among newly diagnosed cases of tuberculosis, treatment strategies other than the standard four drug regimen should be evaluated.

Participants and setting

We analysed data from the National Tuberculosis Surveillance System at the Centers for Disease Control, between 1 January 1993 and 31 December 2005. We selected patients for inclusion if they had a meningeal site of involvement and a positive culture for *M tuberculosis* from any site. We excluded patients with a previous diagnosis of tuberculosis and those with initial resistance to both isoniazid and rifampicin.

Design, size, and duration

We did a retrospective cohort study to examine the association between isoniazid resistance on initial susceptibility testing with the outcome of subsequent death. From a total of 3114 cases of tuberculous meningitis reported during the study period, 1896 cases met the selection criteria and were included in the analysis.

Main results and the role of chance

In 123 (6%) of 1896 patients, isoniazid resistance was present on initial susceptibility testing. The unadjusted association between initial isoniazid resistance and subsequent death among these 1896 patients did not reach statistical significance (odds ratio 1.38, 95% confidence interval 0.94 to 2.02). However, among 1614 patients with cerebrospinal fluid cultures positive for *M tuberculosis*, we found a significant unadjusted association between initial isoniazid resistance and subsequent death (odds ratio 1.61, 1.08 to 2.40). This association increased after adjustment for age, race, sex, and HIV status (odds ratio 2.07, 1.30 to 3.29).

Bias, confounding, and other reasons for caution

Although the exact cause of death is not reported, we believed it to be unlikely that a significant proportion of patients stopping treatment because of death would have died for reasons unrelated to the underlying disease process. Several key variables had various degrees of missing data. We handled missing data by multiple imputation, and in sensitivity analyses we found that the effect of unmeasured confounding due to missing data would be minimal.

Generalisability to other populations

On a global scale, the mortality from tuberculous meningitis attributable to isoniazid resistance will be greater where isoniazid resistance among newly diagnosed cases is more common. In addition, the relation between initial isoniazid resistance and death may be different in settings without readily available neurosurgical services.

Study funding/potential competing interests

The findings and conclusions in this paper are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention. The study had no source of funding.

MULTIVARIATE LOGISTIC REGRESSION MODEL FOR DEATH AMONG 1614 PATIENTS WITH POSITIVE CEREBROSPINALFLUID CULTURES

Characteristic	Odds ratio (95% CI) for death	P value
Isoniazid resistance	2.07 (1.30 to 3.29)	0.002
Age >24 to ≤34	Reference	
Age >34 to ≤44	1.30 (0.87 to 1.92)	0.197
Age >44 to ≤54	1.97 (1.23 to 3.15)	0.005
Age >54 to ≤64	1.83 (1.09 to 3.09)	0.023
Age >64 to ≤74	4.36 (2.48 to 7.67)	<0.001
White, non-Hispanic	Reference	
Black, non-Hispanic	1.44 (1.01 to 2.06)	0.046
HIV positive	3.57 (1.87 to 6.82)	0.002