Cancer screening in Europe

Rapid review 1

What is the evidence for extending existing screening programmes to lung, prostate, gastric, ovarian and oesophageal cancers?

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Rapid Review 1

What is the evidence for extending existing screening programmes to lung, prostate, gastric, ovarian and oesophageal cancers?

Rapid Review Details

Review conducted by:
A team led by the Specialist Unit for Review Evidence (SURE) for SAPEA (Science Advice for Policy by European Academies).

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Method:
This is one of three rapid reviews - a lighter form of a full systematic review that takes account of time constraints. The top-line results are included in the main SAPEA Evidence Review Report, with cross-referencing between the documents.

The review summarises a valuable subset of the evidence base, emphasising the findings from recent randomised and other controlled clinical trials. To meet deadlines, a pragmatic and precise search strategy was employed; it is possible that further controlled trials would have been identified if there had been time for a detailed and sensitive systematic search. The timeline also precluded any statistical or meta-analysis of findings unless these were available from published systematic reviews. No formal critical appraisal was carried out although information is provided on whether the trial included a power calculation. Data extraction and summary were undertaken by different reviewers and, although reviewed by another author, these have not been independently checked for accuracy and consistency.

Acknowledgements:
The advisory group for the review team, comprising the Chairs of the Expert Workshop, Professor Ole Petersen (Academia Europaea), members of SAPEA, the Group of Chief Scientific Advisors (Advisors) and the SAM Unit. Kate Brain (Professor of Health Psychology, Cardiff University) for reviewing and commenting on the draft pre-publication and Professor Jacek Jassem (Head, Department of Oncology & Radiotherapy, Medical University of Gdańsk).

Disclaimer: The authors of this work declare that they have no conflicts of interest.

What is the evidence for extending existing screening programmes to lung, prostate, gastric, ovarian and oesophageal cancers?

TOPLINE SUMMARY

Who is this summary for?

To support the work of SAPEA in providing evidence to the European Commission's Group of Chief Scientific Advisors on cancer screening in Europe.

Background

This review is one of three rapid reviews conducted on the topic of cancer screening in Europe. It was produced specifically for the expert workshop convened to discuss the scientific basis for extending existing screening programmes to other cancers throughout the EU. This final version has been revised to address feedback received on earlier drafts and supplements the workshop report (available on the SAPEA website).

Aim

To examine the published evidence base for the question, *'Based on findings from controlled clinical and randomised controlled trials on efficacy, harm-benefit and cost effectiveness, what is the evidence for extending existing screening programmes to lung, prostate, gastric, ovarian and oesophageal cancers?'.*

Rapid review method

A literature search was conducted in August 2021 for controlled trials published since 2007, supplemented with studies from published systematic reviews. Trials were included if they examined screening for first diagnosis of lung, gastric, prostate, ovarian or oesophageal cancers and included data on efficacy, harm-benefit or cost-effectiveness.

Key findings

Gastric cancer [2 trials]:

- Detection rates for gastric cancers by endoscopic screening were low. Precursor lesions are also detected
- Compliance rates for endoscopic screening were approximately 45%
- Screening via gastric juice MicroRNAs has not yet been assessed in randomised controlled trials
- Limited data from two trials not identified within this rapid review, but included in an identified systematic review, suggest a 79-80% sensitivity and specificity for cancer identification by breath analysis
- No cost-effectiveness data were identified

Lung cancer [13 trials]:

- Higher lung cancer incidence as well as early-stage disease are found in the screening arm, compared to control
- Reduced lung cancer mortality but not overall mortality is observed in the screening arm, compared to control with mild gender variation: 29% in women and 13% in men
- The harms due to false-positive screening results may be minimal

- There are short-term psychosocial harms observed, due to involvement or suspicious results of screening, but this may resolve in the long run
- Four trials provided data on healthcare costs

Oesophageal cancer [5 trials]:

- Endoscopic screening can improve the detection rate of oesophageal cancer, compared to the control group
- Compliance rates were less than 50%
- A single trial estimated the healthcare costs to detect one cancer/one early-stage cancer
- A trial of biomarker-based screening in higher risk individuals has shown a promising effect on early diagnosis of Barrett's Oesophagus and subsequent cancer development

Ovarian cancer [5 trials]:

- No improvement of cancer mortality is observed in the screening arm compared to the control arm
- The psychosocial harms are minor for screening *per se,* unless high-level repeat screenings are required
- A single trial provided data on healthcare costs

Prostate cancer [8 trials]:

- Screening via low threshold prostate specific antigen (PSA) results in a small absolute reduction in prostate cancer/any cause mortality (one death fewer per 1000 men screened over 10 years)
- Any mortality benefit tends to be balanced against overdiagnosis and overtreatment of low-risk disease
- Longer follow-up is required to fully evaluate real-world costs
- One trial suggests that using MRI scanning to indicate biopsy may reduce the risk of overdiagnosis in men with abnormal PSA

Strength of evidence

No formal critical appraisal was carried out within this rapid review but the evidence is from randomised and other controlled clinical trials, with the least theoretical potential for bias. Clinically important inconsistency across trials reduces the level of confidence for some findings.

Full report

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1. Background

This Rapid Review is one of three reviews being conducted to support the work of Expert Groups convened to assist the European Commission Scientific Advice Mechanism (SAM) in developing policy guidance in relation to cancer screening. As described in the Scoping Paper[1], this review supported the first of the Expert Group workshops convened to discuss the question, **"What is the scientific basis of extending such screening programmes to other cancers e.g. lung, prostate and gastric cancers, and ensuring their feasibility throughout the EU?"**

An advisory group was formed to provide guidance to the review team, comprising the Chairs, Professor Ole Petersen (Academia Europaea), members of SAPEA, the Group of Chief Scientific Advisors and the SAM Unit.

1.1 Purpose of this review

Following detailed discussions with the advisory group, the question for the rapid review to inform the first workshop was:

"Based on findings from controlled clinical and randomised controlled trials on efficacy, harm-benefit and cost effectiveness, what is the evidence for extending existing screening programmes to lung, prostate, gastric, ovarian and oesophageal cancers?"

1.2 Research question

Rapid Review Question
Based on findings from controlled clinical and randomised controlled trials on efficacy, harm-benefit and cost effectiveness, what is the evidence for extending existing screening programmes to lung, prostate, gastric, ovarian and oesophageal cancers?

2. Results

2.1 Summary of the evidence base

In all, 84 trial reports have been summarised. We provide a narrative overview of the identified evidence below. A summary of each included trial is provided in Section 2.2.

Gastric cancer

Trial data about gastric cancer screening are scarce.

[1] Scientific Advice Mechanism. European Commission's Group of Chief Scientific Advisors. Scoping Paper: Cancer Screening. 22 April 2021

Efficacy

GC detection rates in the two available reports on endoscopic screening (Zeng et al, 2020; Xiao et al, 2020) were low (0.04% and 0.4%): equivalent rates for pre-cursor lesions (2.22% and 0.3%) and low-grade benign lesions (7.9%). Detection of early-stage lesions was higher in high-risk areas and in males aged 60 to 69.

Gastric cancer-specific mortality: Mortality data are not available from existing preliminary trial data (after one-off screening). Case-control data has indicated organised endoscopic screening may plausibly reduce gastric cancer-specific mortality[2] but this has not been tested in rigorous RCT. The detection rates of low-grade, high-grade pre-cursor lesions and low-grade dysplasia in the current trial data (Zeng et al, 2020; Xiao et al, 2020) suggest potential for reduced GC incidence/mortality reduction.

Harm-benefit

Screening compliance rates of approximately 45% in the two reports could be indicative of an unacceptably invasive procedure. The low endoscopy complication rate (0.3 per 1000 screened) can be balanced against the 0.4% detection rate for cancerous lesions and 0.3% rate for pre-cursor precancerous lesions (Zeng et al. 2020). The complication rate was lower in high-risk areas.

Cost-effectiveness

Healthcare costs of screening are not reported in the trial data. The low compliance and gastric cancer detection rates/prevalence suggest that endoscopy is unlikely to be a cost-effective mass screening tool. More targeted approaches, e.g. older men, precision medicine, or novel pre-endoscopic screening tests may be indicated.

Novel pre-endoscopic screening tests excluded from review

A non-systematic review summarises four studies exploring gastric juice MicroRNAs as potential biomarkers of gastric cancer (Virgilio et al. 2018). This body of evidence has been excluded as no component study is a controlled clinical trial.

A systematic review summarises 24 studies of breath analysis as a novel pre-endoscopic screening test (Haddad et al. 2020). None of the component studies were identified by our rapid review search strategy; most were case-control variants, though design reporting is often superficial. Summary information is included here from two controlled trials that reported quantitative results on efficacy.

- The predictive probabilities of a set of volatile organic compounds tested in a sample of 335 generated an area under the ROC curve of 0.85: 80% sensitivity and 81% specificity for the diagnosis of OGC oesophagogastric cancer (Markar et al. 2018).
- A breath-based algorithm correctly classified three patients with gastric cancer and 570 of the 723 cancer-free screened participants : 100% sensitivity, 79% specificity, and 79% accuracy (Broza et al. 2019).

Lung cancer

13 lung cancer trials were included. Most trials took place in Europe (DANTE, Depiscan, DLCST, ITALUNG, LungSEARCH, LUSI, MILD, NELSON, UKLS), three in the United States (LSS, NLST and PLCO) and one in China (ChiCTR-Shanghai). The sample size ranged from 765 to 53,542 participants, with the majority male. Most of the RCTs recruited former and current smokers whilst only 3 trials (CHiCTR-Shanghai, PLCO and UKLS)

[2] Jun et al (2017). A case control study that does not meet the inclusion criteria for this review. http://dx.doi.org/ doi: 10.1053/j.gastro.2017.01.029

included passive or non-smokers. Three trials (Depiscan, NLST and LSS) compared LDCT screening with CXR screening, instead of a non-screening group. One trial (PLCO) compared CXR screening to a non-screening group. UKLS did not reveal data specifically in the control group.

Efficacy

Lung cancer Incidence: By pooling data from 9 RTCs (DANTE, Depiscan, DLCST, ITALUNG, LUSI, MILD, NELSON, LSS and NLST), the overall lung cancer incidence was higher in the LDCT screening group compared to the control group (RR 1.26; 95%CI 1.10-1.45). Around 22.4% lung cancer cases in the screening arm were non-screening detected (SD 17%). There is a consistent trend across different trials that more stage I cancers (mean 44% vs 26%) and less stage IV diseases (29% vs 43%) were detected in the screening arm than in the control arm (Hunger et al., 2021). The most extreme ratio among RCTs covered by this review was reported in the ChiCTR-Shanghai trial, where 94.1% lung cancers detected in the screening arm were stage I disease compared to 20% in the non-screening control (Yang et al., 2018). In PLCO where CXR screening was used to compare to the non-screening group, the lung cancer incidence was similar between the two arms (RR 1.06; 95%CI 0.99-1.13; P = 0.09) (Paul Flores et al., 2018). The certainty of the evidence is moderate to high that the lung cancer incidence is higher in the screening arm (especially the incidence of early-stage disease) compared to the control arm.

Lung cancer and overall mortality: A meta-analysis study pooling data from 8 RTCs (DANTE, DLCST, ITALUNG, LUSI, MILD, NELSON, LSS and NLST) revealed that among 44,299 LDCT screening participants, a total of 1549 lung cancer deaths were observed, while 1705 lung cancer deaths were observed in 43,579 participants of control group. The RR was calculated 0.88 (95%CI 0.79-0.97), suggesting a 12% reduction of lung cancer mortality in the LDCT screening arm compared to the control arm. A further analysis excluded LSS and NLST, where CXR was utilised as control arm, and the RR was estimated at 0.80 (95% CI 0.70-0.92). A gender variation was also observed, as the RR was 0.71 (95%CI 0.60-0.86) for women and 0.87 (95%CI 0.77-0.97) for men (Hunger et al., 2021). The PLCO trial, where the CXR screening arm was compared to the non-screening control arm, provided slightly different results. The overall mortality rate after a 17-year follow-up was 0.966 for men (RR; 95%CI 0.943-0.989; P=0.004) and 1.002 for women (Pinsky et al., 2019). Across RCTs covered by the current review, there was no statistically significant difference found regarding the all-cause mortality (Hunger et al., 2021; Pinsky et al., 2019). One study evaluated the impact of screening intensity on the mortality rate by comparing the biennial screening protocol with the annual protocol in the MILD trial. There was no statistically significant difference found in terms of overall mortality (HR 0.8; 95%CI 0.57-1.12) and lung cancer mortality (HR 1.10; 95%CI 0.59-2.05) (Pastorino, Sverzellati, et al., 2019). Altogether, the evidence is moderate in terms of the lung cancer and all-cause mortality.

Lung cancer detection rate and sensitivity/specificity: A meta-analysis of 9 RTCs (DANTE, Depiscan, DLCST, ITALUNG, LSS, LUSI, MILD, NELSON and NLST) found that the positive or indeterminate scan results were ranging from 3.6% to 24.2%, with most of them (84% to 96%) being false positive. As a result, some false positive cases underwent invasive workups, yet the complication rates associated with them were low (0.2-1.7%) (Hunger et al., 2021). Another study pooled cumulative data on screening arms from 5 UK-based lung cancer screening programmes including UKLS, Lung Screen Uptake Trial, Manchester Lung Health Checks, Liverpool Healthy Lung Project and Nottingham Lung Health MOT (Balata et al., 2021). In total, 11,815 LDCT screenings were performed across 5 programmes between 2016 and 2020, among which 85.5% were categorised as negative, 10.5% as indeterminate and 4% as positive. The overall detection rate of lung cancer was 2.1% (range 1.7-4.4% across 5 sites) while the FPR was 1.9% (219 of 11,815 scans). Invasive investigation and surgical resection for benign disease were 0.5% (61 of 11,815) and 0.07% (8 of 11,815), respectively, with no major complications or deaths reported. These studies provide moderate evidence suggesting that harms from false positive results may be minimised.

In terms of screening sensitivity and specificity, the ChiCTR-Shanghai trial reported an overall sensitivity of 98.1%, specificity of 78.2% with PPV 6.3% and NPV 99.9% (Yang et al., 2018). The sensitivity in the LUSI trial was estimated was estimated at 83-91% without data on the specificity (Becker et al., 2020).

Two studies provided evidence on screening intervals versus lung cancer detection and predictive rates. Performance between annual and biennial screening protocols in MILD were comparable with the overall detection rate of lung cancer, both 0.56%, as well as the specificity (99.2% in both arms), sensitivity (73.5% in biennial arm vs 68.5% in annual arm, P = 0.62), PPV (42.4% in biennial arm vs 40.6% in annual arm, P = 0.83) and NPV (99.8% in biennial arm vs 99.7% in annual arm, P = 0.71) (Sverzellati et al., 2016). Likewise, the final screening round of the NELSON trial (with a 2.5-year interval) also demonstrated similar lung cancer detection rate and PPV compared to former rounds (with 1- or 2-year interval) (Yousaf-Khan et al., 2017).

The accuracy of using serial LDCT (n = 161, as standard protocol) or PET-CTB (n = 100) as following workups was evaluated in the DANTE trial. The diagnostic accuracy was 91% for the LDCT arm with sensitivity 100%, specificity 91%, PPV 26% and NPV 100%. On the other hand, the accuracy was 90% for PET-CTB with sensitivity 98%, specificity 81%, PPV 85% and NPV 97% (Lopci et al., 2019).

In summary, the evidence is low to moderate because of consistency across RCTs, despite a lack of meta-analysis involving several trials.

Harm-benefit

Risk of radiation: The risk of screening-related radiation was analysed and reported in two controlled trials (ITALUNG and NLST). Based on the NLST screening settings and an average effective dose of 1.5mSv, it was estimated the lung cancer excess risk due to LDCT screening was 0.07-0.23% for men and 0.14-0.85% for women depending on models used for estimation (Pinsky, 2014). One analysis evaluated the risk of X-ray exposure between multi-detector CT and single-detector CT scanners using the ITALUNG settings. The cumulative effective dose to the screening arm was 3.35 Sv per 1000 subjects over 4 years with the multi-detector CT and 5.87-7.12 Sv, using the single-detector CT. The risk of lifetime fatal cancers associated with the screening intervention was 11.7 per 100,000 using the multi-detector CT and 20.5-24.9 per 100,000 using the single-detector CT. Assuming a 10% screening efficacy, the risk-benefit ratio was estimated between 0.32 and 0.02 depending on different settings (Mascalchi et al., 2006). In summary, the evidence regarding the risk of radiation is low to moderate as analyses were performed in RCTs with multi-round screenings yet settings or equipment might be distinct.

Risk of overdiagnosis and incurred harm: The highest overdiagnosis rate was reported in the DLCST trial after ≥ 4 years of follow-up post-last screening, which was 69.1% (Hunger et al., 2021), whereas the risk of overdiagnosis after longer follow-up (≥ 11-year) was 8.9% in NELSON (Paci et al., 2020) and 3.1% in NLST (Team, 2019). The risk of overdiagnosis can be quantified as the excess of cumulative incidence of lung cancer in the screening arm, which was reported as 0.89 (RR; 95%CI 0.67-1.18) in the ITALUNG trial (Paci et al., 2020) and 25.4% (95%CI -11.3-64.3) in the LUSI trial (Gonzalez-Maldonado et al., 2020). In general, the estimated overdiagnosis rate across other trials ranges from 0% to 67.2% (Jonas et al., 2021). The evidence regarding the risk of overdiagnosis is low, due to huge variation and varied follow-up periods across different trials.

Psychosocial harms: Studies linked to seven RCTs (DANTE, DLCST, ITALUNG, MILD, NELSON, NLST and UKLS) offered data on the influence of screening on the health-related quality of life. The participation of trials might have little negative psychosocial consequences for both screening and control arms (Hunger et al., 2021) while the trial allocation might lead to short-term distress of participants in the screening arm with overall scores of distress, anxiety and depression within the normal range (Field et al., 2016). A positive or

indeterminate screening result also led to short-term distress and anxiety especially in individuals who were referred to MDT (close to clinical threshold). Yet no long-term adverse effect was observed (Field et al., 2016). Analyses across several trails reported that patient anxiety may come along with false-positive results where indeterminate results led to the distress of patients due to potential lung cancer diagnosis in the short-term; such anxiety or distress, however, may be resolved in the long run (Jonas et al., 2021; Pinsky, 2014). In summary, the evidence regarding the health-related quality of life, anxiety or distress is moderate because of consistency across different RCTs.

Change of smoking behaviours: A recent systemic review examined studies across 4 RCT trials (DLCST, LSS, NELSON and NLST) and 3 cohort studies (not included in this current rapid review) and found no obvious smoking cessation or abstinence between screening and control groups (Jonas et al., 2021). A positive or indeterminant LDCT result may increase the rate of smoking cessation and continued abstinence (Hunger et al., 2021). Altogether there is limited evidence to conclude the influence of screening on a change of smoking behaviours.

Cost-effectiveness

There are four studies reporting the cost-effectiveness of the screening programmes (DANTE, DLCST, NLST and UKLS). Two of them provide details of costs incurred under corresponding protocols.

In the DANTE trial, a retrospective analysis was carried out to evaluate the cost-effectiveness between 2 nodule work-ups: serial LDCT (n = 161, as standard protocol) and PET-CTB (n = 100). Based on the Italian National Health Service, the average inpatient's costs for both protocols were €12,121 while the average outpatient's costs were €694 and €1,462 for LDCT and PET-CTB, respectively. Hence, the general effective costs in the outpatient settings were 94 % for LDCT and 90% for PET-CTB. When it comes to diagnostics of nodules ≥ 9 mm, the effective costs in the outpatient settings would be 74 % for LDCT and 90% for PET-CTB ($P = 0.018$). Under inpatient conditions, the effective costs were 17% for LDCT and 84% for PET-CTB ($P < 0.001$) (Lopci et al., 2019).

A simulation analysis based on the UKLS trial also revealed information of screening-related health economics. With UKLS protocol, the mean gross current costs were £687,617 (95% CI £479,173-£899,794), consisting of £282,490 for CT scans; £72,592 for the MDT work-up and £332,534 for cancer treatments. An additional 10% of gross cost may incur for the screening invitation and selection, rendering the costs to £754,877 (95%CI £544,824 to £966,304). The gross cost avoided for cancer management when presented symptomatically was estimated at £213,658, around 28% of the management costs after screen detection. Altogether the ICER was estimated at £8466 per QALY gained (95%CI £5516 to £12634) while the QALYs gained per person screened was 0.03 (Field et al., 2016). Despite similar QALYs gained per person in NLST (0.0201, 95%CI 0.0088 to 0.0314), the mean ICER was $81,000 per QALY gained with wide variations (95%CI 52,000 to 186,000) due to distinct screening implementations (Black et al. 2014).

A report related to the DLCST trial demonstrated a 60% increase of total annual healthcare cost for LDCT screening, among which 12% could be attributed to more lung cancer cases detected. For the control arm, a 48% increase of costs was estimated as the lung function tests and smoking counselling were provided instead (Jensen et al., 2020). Altogether the evidence of cost-effectiveness is low due to different implementations and following work-ups across RCTs.

Oesophageal cancer

Limited data from four controlled trial studies was available to evaluate the efficacy of endoscopic screening for oesophageal cancers. All reports are from China, with questionable generalisability to typical disease prevalence in European settings. Only preliminary post-screening data is available. Datasets range

from 20 to 150,000 participants, with study regions being dichotomised as being high-risk/non-high-risk in some cluster trials. In addition to cancer detection, a protein biomarker trefoil factor 3 (TFF3) used together with a special specimen collection device – Cytosponge® – has shown promising effect on early diagnosis of Barrett's oesophagus in higher risk individuals, in the UK primary care setting, and consequent development of adenocarcinoma (Fitzgerald et al., 2020a; Fitzgerald et al., 2020b; Swart et al., 2021).

Efficacy

Based on three study findings (He et al. 2019, Xiao et al. 2020, Zeng et al. 2020), the detection rate of high-grade lesions is in the range 0.7– 0.3%. Squamous cell carcinoma accounted for between 0.13 and 0.22 of cases, with the remainder being in-situ disease and pre-cancerous lesions. [moderate confidence as consistent findings but risk of bias]. An early-stage detection rate of about 70% was achieved [moderate confidence], with data suggesting a trend for earlier stage disease in a screened relative to control group (Chen-Tao Guan 2018) [low confidence: single study, risk of bias, publication bias risk]. Detection rates were unsurprisingly higher in 'high-risk' areas. Individual risk factors associated with high-grade lesions were age, male gender and family history of OC.

No follow-up reports are available to evaluate effect on mortality. Baseline data suggest that the endoscopic excision of early-stage cancer, detected cancer precursor lesions, plus surveillance and management of low-grade lesions have some potential to reduce OC-specific mortality as follow-up accrues.

Harm-benefit

The absence of mortality data limits an evaluation of harms/benefit. Compliance rates from those invited to screening were less than 50% across trials. This high proportion of non-enrolled target population would dilute any beneficial effect of organised screening.

The age-specific prevalence of high-grade oesophageal lesions detected was 744 per 100,000 in ESECC trial (He et al. 2019). This rate increased to 902 when all detected upper gastrointestinal lesions were included i.e. other UGI high-grade lesions were usefully detected. The equivalent rate for serious complication from endoscopy was 30 per 100,000. Trials used endoscopy plus Lugol staining as the standard detection protocol. A small RCT of the novel detection method of narrow band imaging has demonstrated potential to reduce the number of biopsies per patient to detect high-grade dysplasia and improve patient tolerance compared to standard staining (Chaber-Ciopinska et al. 2018).

Cost-effectiveness

A single trial report estimates the healthcare cost to detect one OC and one early-stage OC at $26,347 and $37,687, respectively (at 2018 costs) (Li et al. 2019). These costs would likely reduce significantly if protocol-driven costs were stripped out and initial costs were amortised in a real-world programme. The cost of one oesophageal cancer detection was approximately nine times lower than for gastric cancer, due to higher prevalence. The cost of oesophageal screening will be relatively higher in low-risk regions. Economic analysis from the Barrett's oesophagus trial 3 (Swart et al., 2021) estimated a 97% probability of Cytosponge®-TFF3 being more cost-effective than usual care of endoscopy on GP advice.

Ovarian cancer

There were 14 studies and 2 systematic reviews identified according to the searching criteria and the information across 5 RCTs was extracted. The size of RCTs ranges from 592 (QUEST) to 202,638 (UKCTOCS) women with one taking place in Japan (SCSOCS), two in the US (PLCO and QUEST) and two in the UK (UKCTOCS and UK Pilot). Most RCTs used both CA125 blood test and TVS as screening methods (mostly sequentially except for the USS group in UKCTOCS) while the UK Pilot trial only used CA125 test for screening.

Efficacy

Cancer incidence and detection efficiency

The incidence of ovarian cancer was reported in 4 RCTs and no statistically significant difference was found between the screening group and non-screening group (Henderson et al., 2018; Kobayashi et al., 2008; Menon et al., 2021; Prorok et al., 2018). There was indeed a trend of more early-stage (I/II) diseases and less late-stage (III/IV) diseases found in the screening arm compared to the control arm (Kalsi et al., 2021; Lai et al., 2016; Menon et al., 2021).

In general, the sensitivity and PPV of using TSV alone for ovarian cancer detection was lower than the sequential method of CA125 + TSV (sensitivity 61.5-74% vs 89.4-89.5%; PPV 8.3-11.8% vs 23.3-35.1%) while the specificity was comparably high (99.9% vs 99.8%) (Buhling et al., 2017; Kalsi et al., 2021).

Survival, cancer and all-cause mortality

One study reported an improved survival of patients diagnosed with ovarian cancer in the screening arm compared to the control arm of the PLCO trial (RR 0.66; 95%CI 0.47-0.93) (Lai et al., 2016). Yet no improvement in terms of ovarian cancer or all-cause mortality was observed across all RCTs examined, regardless of the screening protocols (Henderson et al., 2018).

The evidence on cancer incidence, detection efficiency, cancer and all-cause mortality is moderate to strong because of consistency across different RCTs.

Harm-benefit

Risk of overdiagnosis and complications

The risk of overdiagnosis was evaluated in two RCTs (PLCO and UKCTOCS) and found that there might be a possible risk of overdiagnosis (Gentry-Maharaj et al., 2015; Prorok et al., 2018).

The FPR was ranging from 4.2% to 44.2% for CA125 screening with minor complications incurred, while the FPR was reported 10-12% for TUV or combined screening with higher complications occurring in women receiving false-positive surgery due to CA125 test + TVU examination (Henderson et al., 2018).

The evidence on the risk of overdiagnosis is moderate while the evidence for FPR and complications was low to moderate due to heterogenicity across different RCT settings.

Psychosocial harms

Psychosocial harms were evaluated in terms of mental and physical health, cancer worry, sexual activity and functioning. In QUEST, which was designed specifically for this purpose, and another independent study, no psychosocial morbidity difference was found between the screening and control arms. There was a higher level of cancer worry/anxiety observed in women who required repeat screenings (Andersen et al., 2007; Barrett et al., 2014). Similarly, the ovarian cancer screening per se did not affect sexual activity and

functioning unless repeated screens were required due to positive/indeterminate results (Fallowfield et al., 2017).

The evidence on psychosocial harms is low to moderate because data were only available for 2 RCTs.

Cost-effectiveness

The cost-effectiveness analysis was only reported in UKCTOCS, the largest RCT for ovarian cancer screening available. One study reported an ICER between $106,187 and $155,256 when women started screening at the age of 50 (Moss 2018). The other reported that the USS vs non-screening returned an ICER of £625,801 per LYG while the MMS vs non-screening returned an ICER of £91,452 per LYG with CA125-ROCA cost of £20. Provided CA125-ROCA cost of £15, the predictive extrapolation over the expected lifetime of women in the UKCTOCS-MMS protocol estimated an ICER of £30,033 per LYG whilst the Markov model estimated an extrapolated QALY of 0.0581 and the ICER of £46,922 per QALY, approaching the NICE (National Institute for Health and Care Excellence, UK) threshold for cost-effectiveness (Menon et al., 2017).

The evidence on cost-effectiveness is limited because only data from a single, though largest, RCT is available.

Prostate cancer

Efficacy

Meta-analysis of five RCTs powered for the primary endpoint of **PCa-specific mortality** concluded that screening has a very small reduction in PCa mortality at 10 years (IRR 0.96, 95% CI 0.85–1.08) (Ilic et al. 2018); [low confidence, inconsistency, risk of bias] This equates to one PCa death fewer per 1000 men screened over 10 years[3].

A pooled IRR of 0.99 (95% CI 0.98–1.01) and consistent trial results (Hugosson et al. 2017, Martin et al. 2018, Pinksy et al 2019b, van Leeuwen et al. 2013) demonstrate no effect on **all-cause mortality** [moderate certainty, risk of bias] although statistical power to detect differences in all-cause mortality is uncertain. One fewer death from any cause would occur per 1000 men screened over 10 years (95% CI -3 to +1).

The main evidence for PCa-specific mortality is from three large RCTs including over 300,000 screened men with 10 to 17 years median follow-up:

- The multi-national European ERSPC reported 20% reduction in PCa mortality at 16-years; RR between screened and non-screened groups = 0.80 [95% CI, 0.72–0.89] P <.001) (Hugosson et al. 2019;
- US PLCO (RR = 0.93 [95% CI, 0.81–1.08] P= .38) Pinksy et al 2019a and UK CAP (RR = 0.96 [95% CI, 0.85–1.08] P= .50) (Martin et al. 2018) at 17 and 10 years follow-up, respectively.

The positive ERSPC trial used quadrennial screening (in most centres), an optimal PSA threshold for detection of localised/high-risk disease biopsy (3ng/mL) and long follow-up period (16 years). The effect size of screening in PLCO is likely to be reduced by a high prevalence of contamination (opportunistic screening) in the control group (Pinksy et al 2019b). A modelling paper argues that screening has lowered the expected risk of PCa mortality in both PLCO arms, consistent with ESPRC, after controlling for US contexts (Tsodikov et al 2017). Simulation of respective trial parameters and contexts were found to

[3] This review was criticised post-publication on the basis that it compared five incompatible trials. See Carlsson SV in Responses: http://dx.doi.org/10.1136/bmj.k3519

account for the discrepancy in mortality findings between the two trials (de Koning et al. 2018). The group equivalence reported in the large UK CAP trial of one-time screening may be biased by 40% screen adherence and a median follow up of 10 years. (Martin et al. 2018)

Harm-benefit

Any mortality *benefit* from low PSA threshold screening is balanced against **overdiagnosis** and overtreatment of low-risk disease.

Screening consistently increased PCa incidence of early, and at a lower rate, advanced and metastatic disease (Osses et al. 2018) [moderate confidence, risk of bias]: meta-analysis of major trials estimates seven more diagnoses of prostate cancer (95% CI +1 to 15) per 1000 men screened (Ilic et al 2018). Excess PCa incidence persisted in all trials (range 10% to 60%) despite substantial control group contamination and long follow-up e.g. 41% at 16 year ESRPC follow-up Hugosson et al. 2019. Earlier diagnosis in screened men needs to be accounted for, as the RR between groups fell from 1.91 at 9 years to 1·57 at 13 years (Schroder et al. 2014).

For every single PCa death saved by screening 1000 men over 10 years, approximately 1, 3, and 25 more men will experience biopsy- and treatment-related sepsis, urinary incontinence, and erectile dysfunction, respectively (Ilic et al. 2018).

Low specificity of PSA results in false-positive rates up to 80% (Prorok et al 2021). False-negative rates are scarce but may be in the order of 15% for all grades and 2% for high-grade disease (Ilic et al. 2018). HRQOL at 15 year follow-up was similar between screened and non-screened men with PCa in FinRSPC (Talala et al. 2020). Risk -based screening (e.g. Stockholm3 test) can stratify an MRI-targeted biopsy approach to detect clinically significant disease and reduce overdiagnosis (Nordström et al. 2021).

Cost-effectiveness

Limited published evidence is available on the impact of organised PCa screening on healthcare costs. Longer follow-up is required to fully evaluate cumulative real-world costs.

A simulation based on ERSPC data screening every four years in men aged 55 to 69 years estimates an increase of 652 life-years and 366 QALYs per 10,000 men screened. A cost of €54,918 cost per QALY gained. (Karlsson et al 2021). Modelling of ESPRC data evaluated the optimal parameters to be biennial screening within the age range 55–59 years, which generated an incremental cost-effectiveness ratio of $73,000 per QALY gained. (Heijnsdijk et al 2021).

An individual registry-based analysis found little difference in healthcare costs between FinRSPC arms of ERSPC with slightly lower mean overall costs and slightly higher prostate-cancer-specific costs in the screened group [low confidence, due to low statistical power and control group contamination] Booth et al 2018.

2.1 Summary of the evidence base [table]

Gastric cancer

Trial	Trial Details	Participants	Outcomes	Results	Notes
Screening of GC in China **Zeng et al. 2020**	Cluster RCT China 2015-2017 In I group, participants from high-risk areas screening by endoscopy. High-risk participants in non-high-risk areas advised for endoscopy One-off	N = 149,956* I = 75,421 C = 74,535 S = 37,922 *from 3 high-risk areas and 4 non-high-risk areas across China (risk category based on crude mortality rate of GC during 1973–1975) 40–69 yrs Plus No personal history of cancer no endoscopy in previous 3 years Report after screening baseline complete	1. Detection rate Early detection rate (proportion of stage 0/I among all positive cases). i.e. includes high-grade dysplasia/in-situ disease and stage I invasive GC 2. Compliance rate	**Uptake:** 152,172 (66.0%) of 230,583 invited attended the baseline survey. **Compliance:** Overall compliance rate was 43.8%: • *High-risk areas:* 27,111 in I group and 32,893 in C group. Compliance rate = 42.2% (26,633/63,123 eligible individuals invited had endoscopy). • *Non-high-risk areas:* 48,310 in I group and 41,642 in C group: 23,532/48,310 identified as high-risk for further endoscopy 48.0% (11,289/23,532 invited had endoscopy) **Outcomes:** - **GC incidence/detection rate:** Among 37,922 subjects who underwent endoscopy, overall gastric detection (rate) for combined pre- and malignant lesions was 284 (0.8%); 0.9% vs 0.3% in high- and low-risk areas, respectively. Older age group (OR = 8.7, 95%CI 5.8–13.2), male (3.0, 95%CI 2.3–3.9) and high-risk areas (3.4, 95%CI 2.4–4.8) were risk factors for positive detection.	Power calculation: Y Trial of endoscopic cancer screening of whole oesophagus and stomach cancer and gastric cancer High-risk participants in non-high-risk areas categorised based on bespoke questionnaire

				- **Stage:** 117 (0.3%) of cases were high-grade dysplasia and 167 (0.4%) GC, with 2977 (7.9%) cases of intestinal metaplasia/low-grade dysplasia. 214 (75.4%) and 70 (24.6%) were early stage vs. advanced stage disease. In high risk areas, 81.5% of detection was early stage vs 33.3% in non-high-risk areas. - **Cancer-specific mortality:** NR - **Sensitivity/Specificity:** NR - **Harms:** overall, 0.3 per 1000 screened had complications from endoscopy (8 cases with bleeding, 2 oesophageal perforation, 1 gastric perforation, 1 gastro-spasm).	
Screening of GC in non-high-risk areas **<u>Xiao et al. 2020</u>**	Cluster RCT China 2015-2017 Upper endoscopic screening with biopsy of suspicious lesions One-off	N =19,981* I = 10,416 C = 9565 S = 2388 *across non-high incidence areas i.e. urban settings 40–69 years Plus No personal history of cancer no endoscopy in previous 3 years	1. UGC mortality 2. UGC detection rate Incidence rate Survival rate Stage at diagnosis Feasibility	**Uptake:** 20,156 (74.3%) of 27,116 subjects contacted consented to participate. **Compliance:** 5242 (50.3%) of I group were estimated to be high-risk (based on bespoke questionnaire). 2388 (45.6%) underwent endoscopic screening. Older age and higher household income were positively associated with compliance. **Outcomes:** - **Incidence/detection rate:** 1276/1488 pathologies detected were not cancerous or pre-cancerous. One stage I gastric cancer (0.04%), and 53 (2.22%) pre-cancerous gastric lesions were detected.	Power calculation: Y Trial of endoscopic cancer screening of whole oesophagus and stomach cancer and gastric cancer Study conducted in one of non-high-risk centres in the national screening of upper gastrointestinal cancer in China study

		Report after screening baseline complete		- **Stage:** Older age (OR= 1.04,; 95% CI 1.01–1.08) and male gender (OR = 2.34, 95% CI 1.33–4.17) correlated with a higher risk of gastric precancerous lesions. - **Cancer-specific mortality:** NR - **Sensitivity/Specificity:** NR	

	Uptake: **Percentage of invited population agreeing to participate in the trial** ***Compliance:*** **Percentage of trial population completing the baseline screening** **N=Total number in trial; I=in intervention group(s); C= in control group; S=No. screened**
UGC	Upper gastrointestinal cancer

Lung Cancer

Trial	Trial Details	Participants	Outcomes/Results	Notes
ChiCTR-Shanghai **(Qian et al., 2017; Wang et al., 2017; Yang et al., 2018)**	China 2013-2014 1) Biennial LDCT screening for 3 rounds (I) 2) Unscreened control (C) Criteria: D ≥ 4 mm	N = 6717 I = 3512 C = 3145 S = 3473* Mean age 59.8 y (45-70 y) 46.8% Male ≥ 5 y follow-up **Population:** general	**Uptake:** NR **Compliance:** The compliance rate was 98.9% at the baseline. **Outcomes:** - **Lung cancer incidence:** Within the 2-year follow-up, a total of 51 lung cancer cases were confirmed (1.5%) of which 10 cases were in the non-screening group (0.3%). - **Detection rate:** Among 3512 LDCT participants, 804 were positive of screening results (22.9%).	Power calculation: NR NLST eligible criteria shows poor performance in Chinese population, where the detection rate of lung was 1.4% (45/3256). Low tobacco use among Chinese women (2.4%) might be the cause of under-including candidates with high risks.

		Baseline smoking status: 10.3% former smoker [a]; 21.3% current [b] smoker; 23.5% passive [c] smoker *Interpreted from the given compliance rate	- **Stage:** Early-stage lung cancer detection is 94.1% in LDCT group versus 20% in control group (stage I: 48 vs 2; stage II-IV or limited stage: 3 vs 8). - **Lung cancer and all-cause mortality:** NR - **Sensitivity/Specificity:** Among 52 participants in the LDCT group confirmed with lung cancer, one of them was with negative screening result, based on which the LDCT screening sensitivity was 98.1% (51/52, 95%CI = 88.4-99.9), the specificity 78.2% (2707/3460, 95%CI = 76.8-79.6), PPV 6.3% (51/804, 95%CI = 4.8-8.3), and NPV 99.9% (2707/2708, 95%CI = 99.8-99.9).	
DANTE **(Hunger et al., 2021; Infante et al., 2017; Lopci et al., 2019)**	Italy 2001-2006 1) Annual LDCT screening for 5 y (I) 2) Unscreened control (C) Criteria: all solid, non-smooth	N = 2450 I = 1264 C = 1186 S = NR Mean age 65 y (60-74 y) 100% Male Median follow-up 8.4 y **Population:** former or current smokers Baseline smoking status: 43% former smoker [d]; 57% current smoker [b]	**Uptake:** NR **Compliance:** NR **Outcomes:** - **Lung cancer incidence:** The number of diagnosed lung cancers in screening and control arms were 104 (8.2%) and 72 (6.1%), respectively. - **Detection rate:** Among the 104 confirmed cases in the screening arm, 38 (37%) were not picked up via screening. Considering a total of 6482 LDCT scans performed, the recall rate across all screening rounds was 28.1% whereas the lung cancer detection rate was 5.3%. - **Stage:** NR - **Lung cancer and all-cause mortality:** NR - **Sensitivity/Specificity:** Among patients with ≥ 1 indeterminate nodule detected through screenings (217 patients with 261 lung nodules), a retrospective analysis was carried out to evaluate the accuracy and cost-	Power calculation: NR The cost-effectiveness analysis was based on the costs of Italian National Health Service and showed in Euro. Errors in Table 2 and inconsistency in text from Lopci et al. made it difficult for judging the accurate information. Hence, cost-effectiveness data in Table 3 was extracted instead.

			effectiveness of the 2 nodule workups: serial LDCT (n = 161, as standard protocol) and PET-CTB (n = 100). The diagnostic accuracy was 91% for LDCT arm with sensitivity 100%, specificity 91%, PPV 26% and NPV 100%. The accuracy was 90% for PET-CTB with sensitivity 98%, specificity 81%, PPV 85% and NPV 97%. - **Cost effectiveness:** The average inpatient's costs for both protocols were €12,121 while the average outpatient's costs were €694 and €1,462 for LDCT and PET-CTB, respectively. Hence, the general effective costs in the outpatient settings were 94 % for LDCT and 90% for PET-CTB. Considering diagnostics of nodules ≥ 9 mm, the effective costs in the outpatient settings would be 74 % for LDCT and 90% for PET-CTB (*P* = 0.018). Under inpatient conditions, the effective costs were 17% for LDCT and 84% for PET-CTB (*P* < 0.001).	
Depiscan **(Hunger et al., 2021)**	France 2002-2004 1) Annual LDCT screening for 3 y (I) 2) Annual CXR screening for 3 y (C) Criteria: D > 5 mm	N = 765 I = 385 C = 380 S = NR Mean age 56 (50-75 y) 71% Male Median follow-up NR **Population:** former [a] or current [j] smokers	**Uptake:** NR **Compliance:** 144 subjects withdrew consent after enrolment. Baseline data available for 621 (81%) of 765 subjects enrolled **Outcomes:** - **Lung cancer incidence:** Baseline results were reported where 2.1% of LDCT screening participants were diagnosed with lung cancer compared to 0.3% in the CXR screening arm. - **Detection rate:** An independent meta-analysis showed that, considering a total of 336 LDCT scans performed with 81 (24.1%) positive or indetermined findings in	Power calculation: NR Depiscan compared LDCT screening to screening with chest radiography (CXR) as control.

			Depiscan, the recall rate and lung cancer detection rate were 24% and 2.4%, respectively. - **Stage:** NR - **Lung cancer and all-cause mortality:** NR - **Sensitivity/Specificity:** NR	
DLCST **(Hunger et al., 2021; Jensen et al., 2020; Wille et al., 2016)**	Denmark 2004-2006 1) Annual LDCT screening for 5 y (I) 2) Unscreened control (C) Criteria: D ≥ 5 mm	N = 4104 I = 2052 C = 2052 S = 1960* Mean age 58 y (50-70 y) 56% Male Median follow-up 9.8 y **Population:** former or current smokers Baseline smoking status: 24% former smoker [e]; 76% current smoker [b] *Interpreted from the given compliance rate	**Uptake:** NR **Compliance:** The mean annual participation rates were 95.5% and 93.0% in the screening group and control group, respectively. **Outcomes:** - **Lung cancer incidence:** There were more lung cancer cases found in the screening arm (100 of 2052) compared to the control arm (53 of 2052, *P* < 0.001), especially the adenocarcinomas (58 vs 18, respectively, *P* < 0.001). - **Detection rate:** Meta-analysis of efficiency showed that, within 9800 LDCT scans performed, 512 (5.2%) were positive/indeterminate. The recall rate and lung cancer detection rate were 7.6% (baseline) and 0.7% (overall), respectively. - **Stage:** A trend of more early-stage cancers in the screening group than control group was observed (stage I and II, 54 vs 10, respectively; *P* < 0.001). More highest-stage disease (T4N3M1) were found in the control (21 of 53) than in screening arm (8 of 100, *P* = 0.025). - **Lung cancer & all-cause mortality:** The overall mortality rate (HR 1.02; 95%CI 0.82-1.27; *P* = 0.867) and lung cancer mortality rate (HR 1.03; 95%CI 0.66-1.6; *P* = 0.888) were comparable in both arms.	Power calculation: Y

			- **Sensitivity/Specificity:** NR - **Cost effectiveness:** A 60% increase of total annual healthcare cost was reported for LDCT screening, among which 12% could be attributed to more lung cancer cases detected. For the control arm, a 48% increase of costs was estimated as the lung function tests and smoking counselling were provided. - **Risk of overdiagnosis:** After ≥ 4 years of follow-up post-last screening, the overdiagnosis rate was 69.1% in DLCST. - **Psychosocial harms:** Participation in trial might have little negative psychosocial consequences for both screening and control arms. High motivation of smoking cessation and a positive baseline LDCT result might increase the quitting rate.	
ITALUNG **(Hunger et al., 2021; Jonas et al., 2021; Mascalchi et al., 2006; Paci et al., 2020; Paci et al., 2017)**	Italy 2004-2006 1) Annual LDCT screening for 4 y (I) 2) Unscreened control (C) Criteria: D > 5 mm	N = 3206 I = 1613 C = 1593 S = NR Mean age 61 y (55-69 y) 65% Male Median follow-up 11.3 y **Population:** former or current smokers Baseline smoking status: 35% former	**Uptake:** 17,055 (24%) responses to questionnaire in 71,232 invitation letters. **Compliance:** 1,406 (87%) of 1,613 in I group performed the baseline scan **Outcomes:** - **Lung cancer incidence:** The incidence rates of lung cancer were 52.8 and 59.4 (per 10,000 person-year) in the screening and control arms, respectively (RR 0.89; 95%CI 0.67-1.18). Among 91 confirmed cases in the screening group, 38 cases (42%) were screen-detected. - **Detection rate:** A total of 5333 LDCT scans were performed with 1044 (19.6%) positive/indeterminate findings. The recall rate and lung cancer detection rate	Power calculation: Y

		smoker; 65% current smoker[f]	throughout all screening rounds were estimated 52.7% and 0.5%, respectively. - **Stage:** The resected rate of screen-detected cases was 82% where 61% were stage I, compared to the control arm where 28% were resected with 12% stage I (*P* < 0.001). - **Lung cancer & all-cause mortality:** After a median of 9.3-year of follow-up, all-cause mortality was comparable between screening arm (105.1) and control arm (127 per 10,000 person-years, *P* = 0.08). - **Sensitivity/Specificity:** NR - **Survival rate:** The 3-year lung cancer survival rate was 44% for the screening arm and 25% for the control arm after a median of 9.3-year of follow-up (*P* = 0.07). After 11-year follow-up, with 38% "resected and early" cases in the screening arm compared to 19% in the control arm (*P* = 0.003), the 10-year survival rates were similar (64% vs 60%; *P* = 0.689). For "unresected and late" cases, the 5-year survival rates were 10% and 7% in the screening and control arms, respectively (*P* = 0.679). - **Risk of overdiagnosis:** The risk of overdiagnosis was quantified as the excess of cumulative incidence of lung cancer in the careening arm, which was estimated 0.89 (RR; 95%CI 0.67-1.18). - **Risk of radiation:** Analysis evaluating the risk of X-ray exposure between multi-detector CT and single-detector CT scanners demonstrated the cumulative effective dose to the screening arm was 3.35 Sv per 1000 subjects over 4 years using the former setting and 5.87-7.12 Sv using the latter. The risk of lifetime fatal cancers associated with the	

			screening intervention was 11.7 per 100,000 using the former and 20.5-24.9 per 100,000 using the latter settings. Assuming a 10% screening efficacy, the risk-benefit ratio was estimated between 0.32 and 0.02 depending different settings. - **Adverse events:** The death rates within 60 days post-surgery were 1.2 and 1.3 per 1000 in the screening and control arms, respectively (*P* = 0.99). The death rates within 60 days post-invasive diagnostic procedure were 3.7 for the former and 3.8 for the latter (per 1000, *P* = 0.98).	
LSS **(Hunger et al., 2021; Jonas et al., 2021)**	US 2000-2001 1) Annual LDCT screening for 2 y (I) 2) Annual CXR screening for 2 y (C) Criteria: D > 3 mm for baseline; D > 4 mm for others	N = 3318 I = 1660 C = 1658 S = NR Mean age NR (55-74 y) 59% Male Median follow-up 5.2 y **Population:** former or current smokers Baseline smoking status: 42% former smoker [d]; 58% current smoker [g]	**Uptake:** 12,270 responses (1.9%) to 653,417 information packages. 4,828 found to be eligible. (Gohagan 2004 https://doi.org/10.1378/chest.126.1.114) **Compliance:** NR **Outcomes:** - **Lung cancer incidence:** The number of lung cancer detected were 40 (2.4%) in the LDCT group and 20 (1.2%) in the CXR group. - **Detection rate:** In total, 2984 LDCT scans were performed, among which 655 (22%) were positive/indeterminate findings. The overall recall rate was 34.5% whereas the lung cancer detection rate was 0.57%. Around 5% of lung cancer cases not picked up by screening. - **Stage:** NR - **Lung cancer & all-cause mortality:** The overall mortality rates were 1667 and 1384 per 100,000 in the LDCT arm	Power calculation: NR LSS is a feasibility pilot study comparing LDCT screening to screening with CXR.

			and CXR arm, respectively (IRR 1.2; 95%CI 0.94-1.53) while the corresponding lung cancer mortality were 383 and 310 per 100,000 (IRR 1.24; 95%CI 0.74-2.07). - **Sensitivity/Specificity:** NR	
LungSEARCH **(Spiro et al., 2019)**	UK 2007-2011 1) Annual sputum screening for 5 y (I) 2) Unscreened control (C) Criteria of LDCT: D ≥ 9 mm	N = 1568 I = 785 C = 783 S = 669 Mean age 63 y 52% Male Median follow-up 5 y **Population:** former or current smokers with COPD Baseline smoking status: 44% former smoker; 56% current smoker	**Uptake:** From Centres collecting this data, 3,099 (39%) of 7,998 contacted by telephone accepted the invitation to attend pre-trial assessment; of which 42% (1313/3099) were randomised. **Compliance:** The baseline compliance with the sputum sampling with evaluable samples was 85.2%. The ratio of providing evaluable samples dropped to 53.9% by year 5. The overall compliance with AFB and LDCT was 72.0% and 91.6%, respectively. **Outcomes:** - **Lung cancer incidence:** A total of 78 lung cancers were confirmed with 36 in the control arm and 42 in the screening arm. - **Detection rate:** Among participants provided adequate sputum samples, 19% were abnormal for cytology or cytometry. - **Stage:** The ratio of disease diagnosed at early stage was 45.2% and 54.8% in control and screening arm, respectively. - **Lung cancer & all-cause mortality:** NR - **Sensitivity/Specificity:** Among the 42 confirmed cases in the screening group, 44.7% had an abnormal sputum	Power calculation: Y Participants were subjected to AFB and LDCT provided sputum cytology or cytometry showed abnormalities (sequential screening approach).

			sample, thereby led to the overall sensitivity of 40.5% and FPR of 32.8% for sputum.	
LUSI **(Becker et al., 2020; Gonzalez-Maldonado et al., 2020; Hunger et al., 2021)**	Germany 2007-2011 1) Annual LDCT screening for 5 y (I) 2) Unscreened control I Criteria: D ≥ 5 mm or VDT = 400-600 days and D < 7.5 mm	N = 4052 I = 2029 C = 2023 S = 2028* Mean age NR (50-69 y) 65% Male Median follow-up 9.8 y **Population:** former or current smokers Baseline smoking status: 38% former smoker [d]; 62% current smoker [h] *Baseline screening round; the number screened declined with each round: 2000, 1978, 1954, and 1925 for 2nd-5th rounds, respectively	**Uptake:** NR **Compliance:** There was over 90% of attendance for each screening round. In total 84% of participants completed all 5 screenings. **Outcomes:** - **Lung cancer incidence:** There were 4.2% (85 of 2029) and 3.3% (67/2023) lung cancer cases diagnosed in the screening and control arm, respectively. Around 7% (6 of 85) cases were not detected via screening. Within 5-year post-randomisation, an increased number of lung cancer diagnosis was observed in the screening arm compared to control arm (HR 1.76; 95%CI 1.17-2.66; *P* < 0.01). - **Detection rate:** In total, 9405 LDCT scans were performed with 816 (8.7%) positive/indeterminate findings. The overall recall rate was 22.2% while the lung cancer detection rate was 1.1%. - **Stage:** NR - **Lung cancer & all-cause mortality:** The overall mortality rates were similar between screening and control arm (HR 0.99; 95%CI 0.79-1.25; *P* = 0.95). The lung cancer mortality rates were reduced in screened women (HR 0.31; 95%CI 0.1-0.96; *P* = 0.04) but not in men (HR 0.99; 95%CI 0.79-1.25; *P* = 0.95) compared to control counterparts. - **Sensitivity/Specificity:** The LDCT sensitivity was estimated 83-91%.	Power calculation: Y

			- **Risk of overdiagnosis:** The excess cumulative incidence was 25.4% (95%CI -11.3-64.3) in the screening arm (assessed 5.73 years since last screening).	
MILD **(Hunger et al., 2021; Infante et al., 2017; Pastorino, Silva, et al., 2019; Pastorino, Sverzellati, et al., 2019; Sverzellati et al., 2016)**	Italy 2005-2011 1) Annual LDCT screening for 7 rounds (I_1) 2) Biennial LDCT screening for 4 rounds (I_2) 3) Unscreened control Criteria: D ≥ 5 mm or V ≥ 60 mm^3	N = 4099 I_1 = 1190 I_2 = 1186 C = 1723 S = 2303 Median age 58 y (49-75 y) 68.4% Male Median follow-up 10 y **Population:** former [d] or current [b] smokers	**Uptake:** NR **Compliance:** The overall participation in screening was 96.9% (2303 of 2376). **Outcomes:** - **Lang cancer incidence:** Lung cancer cases confirmed was 98 (4.1%) in the screening arm (both annual and biennial) and 60 (3.5%) in the control arm. There were 27.6% lung cancer patients not detected via screening. - **Detection rate:** Both annual and biennial screening protocols conferred a lung cancer detection rate of 0.56%. - **Stage:** Among lung cancer staged, half of cases in the screening arm were early stage while 21.7% were stage I in the control arm. In contrast, most cancer cases in control arm were stage IV (53.3%) whilst late-stage cases accounted for 29.6% in the screening arm (*P* = 0.0004). - **Lung cancer & all-cause mortality:** The overall mortality rates were 593.5 and 653.9 per 100,000 in screening arm and control arm, respectively. Mortality due to lung cancer were estimated 173.3 per 100,000 for the screening arm and 246.8 for the control arm. The landmark analysis beyond 5 years showed a reduced mortality risk in the screening arm compared to control arm (HR 0.68; 95%CI 0.49-0.94; *P* = 0.01). In terms of lung cancer mortality, screening group demonstrated 58% risk	Power calculation: Y

			reduction than the control group (HR 0.42; 95%CI 0.22-0.79; *P* = 0.0037). The impact of screening intensity on the long-term mortality, which was assessed by comparing the biennial with the annual protocols, was reported to be mild as the overall mortality (HR 0.8; 95%CI 0.57-1.12) and lung cancer mortality (HR 1.10; 95%CI 0.59-2.05) were similar between two protocols. - **Sensitivity/Specificity:** Both screening protocols showed similar specificity (99.2% in both arms), sensitivity (73.5% in biennial arm vs 68.5% in annual arm, *P* = 0.62), PPV (42.4% in biennial arm vs 40.6% in annual arm, *P* = 0.83) and NPV (99.8% in biennial arm vs 99.7% in annual arm, *P* = 0.71). A total of 7369 LDCT scans were performed in the annual arm with 268 (3.6%) positive/indeterminate findings, resulting in a recall rate 5.81%. For the biennial arm, 5006 LDCT scans were performed with 217 (4.3%) positive/indeterminate findings, leading to a recall rate of 6.97%.	
NELSON **(de Koning et al., 2020; Hunger et al., 2021; Jonas et al., 2021; Paci et al., 2020; Walter et al., 2018; Yousaf-Khan et al., 2017)**	The Netherlands and Belgium 2003-2006 1) Four LDCT screenings in year 0, 1, 3 and 5.5 (I) 2) Unscreened control(C)	N = 15,792 I = 7915 C = 7877 S = 6309* Median age 58 y (50-74 y) 84% Male Median follow-up 10 y **Population:**	**Uptake:** 150,920 (25%) of 606,409 responded to a questionnaire. 30,959 were eligible and 15,822 of these (51%) provided written informed consent. **Compliance:** The overall screening compliance was 90.0% (95%CI 76.9-95.8%) among male participants. **Outcomes:** - **Lung cancer incidence:** Around 4.3% (344 of 7915) and 3.8% (304 of 7877) participants were diagnosed with lung cancer in the screening arm and control arm, respectively.	Power calculation: Y Volume-based nodule-management protocol

	Criteria: D > 5 mm or V > 50 mm^3 or VDT = 400-600 days	former or current smokers Baseline smoking status: 45% former smoker [d]; 55% current smoker [i] *Number of men screened at the baseline; number of women NR	- **Detection rate:** Cases missed by the LDCT screening was 41%. Among the 22,600 LDCT scans performed, 2536 (11.3%) were positive or indeterminate. The baseline recall rate was 20.4% whilst the overall lung cancer detection rate was estimated 3.2%. - **Stage:** The rate of screening-detected lung cancer was 59% (203 of 344) in the screening arm, most of which were in stage IA or IB (58.6%). In contrast, only 14,2% and 13.5% of non-screening detected lung cancers were diagnosed in stage IA or IB in the screening arm and control arm, respectively. Only 9.4% of the screening-detected lung cancer were diagnosed stage IV whilst 51.8% and 45.7% of non-screening detected lung cancers were stage IV in the screening arm and control arm, respectively. - **Lung cancer mortality:** After 10-yr follow-up, the lung cancer mortality rate in men was 2.5 deaths versus 3.3 deaths per 1000 person-year in the screening arm compared to control arm (RR 0.76, 95%CI 0.61-0.94; *P* = 0.01). Analysis of women (much smaller sample size) revealed an RR of 0.67 (95%CI 0.38-1.14) at 10 years; RR 0.52 (95%CI 0.28-0.94) at 9 years; RR 0.42 (95%CI 0.19-0.84) at 8 years. - **Sensitivity/Specificity:** A final of 2.1% (467 of 22,600 scans) were test-positive after 10-yr follow-up and required further workup, which ended up with 203 screening-detected lung cancer cases. The overall PPV was 43.5% with the FPR 1.2%.	

			- **Risk of overdiagnosis:** The risk of overdiagnosis was estimated 8.9% (95%CI -18.2-32.4) after 11-year follow-up of screen-detected cases. - **Impact of various screening intervals:** Longer screening and follow-up intervals (<10 m; 10-14 m; 15-21 m; 22-26 m and >26 m) helped discriminate between benign and malignant; however, the lung cancer proportion also increased with longer intervals (2%, 3%, 3%, 7%, 11%, respectively, *P* = 0.001). The analysis of the final screening round (with 2.5-year interval) showed similar lung cancer detection rate and PPV compared to former rounds. A higher proportion of later stage lung cancer was observed in the final round (17.3% compared to 6.8% in former rounds, *P* = 0.02) and more interval cancers found in the 2.5-year interval than 1-year and 2-year intervals (28 vs 5 and 19, respectively).	
NLST **(Black 2014; Hunger et al., 2021; Jonas et al., 2021; Pinsky, 2014; Pinsky et al., 2018; Pinsky et al., 2015; Team, 2011, 2013, 2019)**	US 2002-2004 1) Annual LDCT screening for 3 y (I) 2) Annual CXR screening for 3 y (C) Criteria: D > 4 mm	N = 53,452 I = 26,722 C = 26,730 S = 52,344* Mean age 61 y (55-74 y) 59% Male Median follow-up 11.3 y for incidence; 12.3 y for mortality **Population:**	**Uptake:** NR **Compliance:** The baseline compliance was 98.5% for LDCT and 97.4% for CXR, which decreased slightly at year 3 where the compliance rate was 90.2% for LDCT and 87.3% for CXR. **Outcomes:** - **Lung cancer incidence:** The confirmed number of lung cancer cases were comparable between LDCT arm (6.4%, 1701 of 26,722) and CXR arm (6.3%, 1681 of 26,730), giving an RR of 1.01 (95%CI 0.95-1.09). - **Detection rate:** Considering a total of 75,126 LDCT scans performed with 18,146 (24.2%) positive/indeterminate	Power calculation: Y NLST compared LDCT screening to screening with CXR as control Diameter-based nodule-management protocol

		former [d] or current [b] smokers Baseline smoking status: 52% former smoker [a]; 48% current smoker [g] *Baseline screening round	findings, the overall recall rate and lung cancer detection rate were 24.2% and 1.1%, respectively. - **Stage:** Compared to the CXR arm, there was a higher proportion of lung cancer cases diagnosed stage I in the LDCT arm (27.5% vs 39.6%; *P* < 0.0001). - **Lung cancer mortality:** The lung cancer mortality was 42.9 per 1000 subjects in the LDCT arm versus 46.2 per 1000 in the CXR arm with the RR estimated 0.92 (95%CI 0.85-1.00; *P* = 0.05). With adjusted analysis, the lung cancer mortality RR was 0.89 (95%CI 0.8-0.997). - **Sensitivity/Specificity:** The sensitivity and specificity for LDCT were 93.8% (95%CI 90.6-96.3) and 73.4% (95%CI 72.8-73.9) whilst 73.5% (95%CI 67.2-79.8) and 91.3% – 95%CI 91.0 - 91.6) for CXR. The overall PPV for LDCT arm was 3.8% (270 of 7181) and 5.7% (136 of 2379) for the CXR arm. The FPR was 23% in each of the three screening rounds, which led to costs for further workups including other diagnostic procedure (90.4%) and imaging (81%). Around 2.7% of false-positive cases were subjected to invasive diagnostic procedures. - **Risk of overdiagnosis:** An analysis published after extended follow-up (11.3 years) revealed a minimal excess of cumulative incidence of lung cancer in the careening arm (RR 1.01; 95%CI 0.95-1.09) and estimated 3.1% risk of overdiagnosis. - **Risk of radiation:** Considering an average effective dose of 1.5mSv, the lung cancer excess risk due to LDCT was estimated 0.23% for men and 0.85% for women. Using a multiplicative model, the lung cancer excess risk due to LDCT was 0.07% for men and 0.14% for women.	

			- **Cost effectiveness:** The average annual cost of LDCT screening would be $241 per person. The cost of preventing one lung cancer death was estimated $240,000. The cost per life-year saved would be below $19,000. With QALYs being 0.0201 (95%CI 0.0088 to 0.0314), the mean ICER was $81,000 per QALY gained (95%CI 52,000 to 186,000).	
PLCO **(Paul Flores et al., 2018; Pinsky et al., 2019; Prorok et al., 2018)**	US 1993-2001 1) Annual CXR screenings for 3 y (never smoker) or 4 y (I) 2) Unscreened control (C) Criteria: one or more of the following: nodule, mass, hilar or mediastinal lymph node enlargement, infiltrate, consolidation, or alveolar opacity	N = 154,887 I = 77,443 C = 77,444 S = NR Median age NR (55-74 y) Median follow-up 17 y 49.5% Male **Population:** general Current, former, never smokers or unknown	**Uptake:** NR **Compliance:** NR **Outcomes:** - **Lung cancer incidence:** After 13 years of follow-up, 1838 and 1737 lung cancer cases were confirmed in the screening and control arm, respectively (RR 1.06; 95%CI 0.99-1.13; *P* = 0.09). - **Detection rate:** Instead of lung cancer-specific analysis, only the overall PPV was reported as 4.2% with 96% FPR. The overall cancer detection rate was 3.38 per 1000 screened. - **Stage:** NR - **Lung cancer & all-cause mortality:** The overall mortality rate after 17-year follow-up was 0.966 for men (RR; 95%CI 0.943-0.989; *P* = 0.004) and 1.002 for women in the screening arm compared to control arm. The number of death due to lung cancer was comparable in both arms (16.2% for both; RR 1.008; 95%CI 0.947-1.07; *P* = 0.80). - **Sensitivity/Specificity:** NR	PLCO trial was designed to evaluate screening modalities for prostate, lung, colorectal and ovarian cancers. Power calculation: Y Lung cancer screening was evaluated by comparing CXR screening group with non-screening control.

UKLS **(Balata et al., 2021; Field et al., 2016)**	UK 2011-2013 1) Single LDCT screening (I) 2) Unscreened control (C) Criteria: D ≥ 3 mm or V ≥ 15 mm^3	N = 4055 I = 2028 C = 2027 S = 1994 Mean age 67.1 y (50-75 y) 74.9% Male ≥10 y follow-up **Population:** general Baseline smoking status (screening arm): 61.6% former smoker; 38.3% current smoker; 0.1% never smoker	**Uptake:** 75,958 (30.7%) of 247,354 contacted were positive responders. 4061 individuals (5.3% of all positive responders and 46.5% of all high-risk positive responders) consented and were recruited into the RCT. 4055 randomised. **Compliance:** Among the 2028 participants, 1994 individuals completed the baseline scan (98.3%). **Outcomes:** - **Lung cancer incidence:** Among 1994 individuals completing the baseline scan, 1015 (50.9%) individuals were recommended for repeat scans. A total of 114 individuals (5.7%) were referred to the MDT, among which 42 were diagnosed with lung cancer (2.1%). - **Detection rate:** NR - **Stage:** Most participants diagnosed with lung cancer underwent surgery (83.3%), reflecting the high proportion of disease detected at early stages (I and II). - **Lung cancer & all-cause mortality:** NR - **Sensitivity/Specificity:** FPR was calculated as 3.6% (72/1994). - **Cost effectiveness:** Under the protocol of UKLS trial, a total of 3363 CT scans were required (single area, no contrast, mean unit cost £84). After the baseline scans, 114 individuals were referred to the MDT for further work-ups, where an additional 122 CT scans (≤ 3 area, with contrast, mean unit cost £135), 20 guided needle biopsies (mean unit cost £863), 50 PET scans (mean unit cost £425) and 4 endobronchial ultrasound biopsies	Power calculation: NR Follow-up CT scans in suspicious cases; further referral to multidisciplinary team (MDT) clinics based on nodule size criteria

			(mean unit cost £1461) were requested. Regarding the treatment of 42 diagnosed lung cancer cases, 35 surgeries (mean unit cost £7502), 5 radiotherapies (mean unit cost £3039) and 11 chemotherapies (mean unit cost £3883) were undertaken. Furthermore, 4 patients received surgical biopsies/resection (mean unit cost £4295) for benign disease while 2 patients received palliative care (mean unit cost £340). Altogether, the mean gross current costs were £687,617, consisting of £282,490 for CT scans; £72,592 for the MDT work-up and £332,534 for cancer treatments. Considering the cost range per procedure, an estimated cost would have a 95% CI between £479,173 and £899,794. An additional 10% of gross cost may incur for the screening invitation and selection, rendering the costs to £754,877 (95%CI £544,824 to £966,304). The gross cost avoided for cancer management when presented symptomatically was estimated £213,658 (28% of the management costs after screen detection). The ICER was estimated £8466 per QALY gained (95%CI £5516 to £12634) while the QALYs gained per person screened was 0.03. - **Psychosocial harms:** The trial allocation led to a short-term (2-4 weeks) distress of participants in the screening arm; yet the overall scores on measures of distress, anxiety and depression were within the normal range. Within the screening arm, the baseline screening results caused short-term cancer distress in participants required a repeat scan or referred to MDT (due to suspected lung abnormalities). The MDT group reported higher distress than other groups with levels close to clinical threshold.	

			Anxiety levels, but not depression, were reported among participants in the screening arm with higher levels of short-term anxiety in the MDT group, yet scores within the normal range. Long-term adverse effects were not observed.	

[a] ≤ 15 y since quitting
[b] ≥ 20 pack-y
[c] > 2 h-day for at least 10 y
[d] ≤ 10 y since quitting
[e] quit after age 50 and < 10 y since quitting
[f] ≥ 20 pack-y in the last 10 y or quit < 10 y
[g] ≥ 30 pack-y
[h] 15 cigarettes/d for ≥ 25 y or 10 cigarettes/d for ≥ 30 y
[i] 15 cigarettes/d for >25 y or 10 cigarettes/d for > 30 y
[j] ≥ 15 cigarettes/d for ≥ 20 y

	Uptake: **Percentage of invited population agreeing to participate in the trial** ***Compliance:*** **Percentage of trial population completing the baseline screening** **N=Total number in trial; I=in intervention group(s); C= in control group; S=No. screened**
AFB	Autofluorescence bronchoscopy
COPD	Chronic obstructive pulmonary disease
CXR	Chest radiography
D	Diameter
DANTE	Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays
DLCST	Danish Lung Cancer Screening Trial
FPR	False-positive rate
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IRR	Incidence rate ratio
ITALUNG	Italian Lung Cancer Screening Trial

LDCT	Low-dose computed tomography
LSS	Lung Screening Study
LUSI	The German Lung Cancer Screening Intervention Trial
MDT	Multidisciplinary team
NELSON	Nederlands-Leuvens Longkanker Screenings Onderzoek
NLST	National Lung Screening Trial
NPV	Negative predictive value
NR	Not reported
PET	Positron emission tomography
PET-CTB	Positron emission tomography-computed tomography-guided core biopsy
PLCO	The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial
PPV	Positive predictive value
RCT	Randomised clinical trial
RR	Rate ratio
SD	Standard deviation
UKLS	The UK lung Cancer Screening
QALY	Quality-adjusted life-years
V	Volume
VDT	Volume doubling time
Y	Year

Oesophageal cancer

Trial	Trial Details	Participants	Outcomes	Results	Notes
BEST3 **Fitzgerald et al., 2020a; Fitzgerald et**	RCT UK 2017–2019	**Total number** N = 13,514 (enrich) I = 6983 C = 6531	1. Diagnosis of BO at 12 mo in I vs C groups 2. Uptake of	**Uptake:** In I group, 39% (2679/6983) expressed interest in taking Cytosponge®-TFF3.	Power calculation: Y Subsequent upper endoscopy offered when TFF3-positive

al., 2020b; Swart et al., 2021	Usual care of GP advised endoscopy vs usual care + offer of Cytosponge®-TFF3 procedure One off	S = 1654 Mean FU 12 mo **Population:** ≥ 50yrs with > 6m treatment of gastro-oesophageal reflux. No endoscopy with 5 yrs	Cytosponge®-TFF3 procedure; Number of cases of BO with dysplasia and intestinal metaplasia-associated cancer, by stage at diagnosis; PPV of Cytosponge®-TFF3 test, in subset of patients with subsequent endoscopy after +ve TFF3; Acceptability and safety of Cytosponge®-TFF3 test.	**Compliance** 65% of I group (1750/2679) met eligibility criteria and received the procedure, 95% (1654/1750) of whom successfully swallowed the Cytosponge® for sample production: an overall uptake of 24%. **Outcomes:** - **Cancer/BO incidence:** 2% (140 /834) participants in I group vs <1% (13/6388) in C group were diagnosed with BO (RR 10.6, 95%CI 6.0–18.8; *P* < 0.0001). Nine cases with early-stage neoplasia were diagnosed in I group vs none in C group. - **Detection rate:** Among participants taking Cytosponge®-TFF3 procedure, 13% (221/1654) underwent endoscopy due to positive TTF3, 59% (131/221) of whom were diagnosed with BO or OAC. - **Stage:** Of the 9 neoplasia cases diagnosed in I group, 4 were dysplastic BO and 5 were stage I oesophago-gastric cancer. - **Cancer-specific and all-cause mortality:** NR - **Sensitivity/Specificity:** Estimated specificity of the Cytosponge®-TFF3 procedure for detection of BO, dysplasia, or cancer was 94%.	cells identified in I group

				- **Harms:** One case required endoscopic removal of detached Cytosponge. 4% of participants reported a sore throat **Cost-effectiveness:** An additional 0.015 QALYs per patients was generated with one-off Cytosponge®-TFF3 screening, rendering an ICER of £5500 per QALY gained. The probabilistic sensitivity analysis revealed an incremental cost of £78 and 0.015 QALYs for Cytosponge®-TFF3 screening compared to usual care, giving an ICER of £5405 (95%CI -6791 to 17,600). Considering the willingness-to-pay threshold at £20,000 per QALY, there was a 97% probability of Cytosponge®-TFF3 being more cost-effective than usual care. The total budget impact, including screening plus incurred treatment and palliative care for identified BO/OAC was evaluated using the additional cost-per-patient of £82 for one round of Cytosponge®-TFF3 screening, which would cost a total of £21,636,235 spreading over 29 years at an annual cost of £746,077 in UK settings.	
Endoscopic Screening for OC in China **<u>Zeng et al. 2020</u>**	Cluster RCT China 2015-2017 All I group participants from high-risk areas	N = 149,956* I = 75,421 C = 74,535 S = 37,922 *from 3 high-risk areas and 4 non-high-risk areas (risk category based on	1. OC detection rate Early detection rate (proportion of stage 0/I among all positive cases). i.e. includes oesophageal squamous severe dysplasia, OCIS and stage I invasive OC	**Uptake:** 152,172 (66%) attended the baseline survey from 230,583 invitations. **Compliance:** Overall **compliance rate** was 43.8% • *High-risk areas:* 27,111 in I group and 32,893 in C group. Compliance rate = 42.2% (26,633/63,123 eligible individuals invited had endoscopy).	Power calculation: Y Trial of upper endoscopic cancer screening of whole oesophagus and

	screened by upper endoscopy. High-risk participants in non-high-risk areas advised for endoscopy One-off	crude mortality rate of OC during 1973–1975) 40–69 years plus No history of cancer No endoscopy in previous 3 years Report after screening baseline complete	2. Screening compliance rate	• *Non-high-risk areas:* 48,310 in I group and 41,642 in C group: 23,532/48,310 identified as high-risk for further endoscopy Compliance rate = 48.0% (11,289/23,532 invited had endoscopy) **Outcomes:** - **Detection rate:** Among 37,922 subjects undergoing endoscopy, oesophageal detection (rate) for combined pre- and malignant lesions was 254 (0.7%): 0.9% vs 0.1% in high- and non-high-risk areas, respectively. Older age group (OR = 25.6, 95%CI 13.5–48.4), male (1.6, 95%CI 1.3–2.1) and high-risk areas (8.2, 95%CI 4.9–13.9) were risk factors for positive detection. - **Stage:** 230 (90.6%) and 24 (9.4%) were early stage vs. advanced stage disease. In high risk areas, 92.9% of detection was early stage vs 53.3% in non-high-risk areas. 195 (0.5%) of cases were severe dysplasia/OCIS and 59 (0.2%) were OC. Additional cases detected were 1692 (4.5%) mild/moderate dysplasia and 4349 (11.5%) oesophagitis. - **Cancer-specific & all-cause mortality:** NR	stomach cancer and gastric cancer High-risk participants in non-high-risk areas categorised based on bespoke questionnaire

				- **Sensitivity/Specificity:** NR - **Harms:** overall, 0.3 per 1000 screened had complications from endoscopy (8 cases with bleeding, 2 oesophageal perforation, 1 gastric perforation, 1 gastro-spasm).	
Upper GI screening in non-high risk areas **Xiao et al. 2020**	Cluster RCT China 2015-2017 Upper endoscopic screening with biopsy of suspicious lesions One-off	N =19,981* I = 10,416 C = 9565 S = 2388 *across non-high incidence areas i.e. urban settings 40–69 yrs Plus No personal history of cancer no endoscopy in previous 3 yrs Report after screening baseline	1. UGC mortality 2. OC detection rate Incidence rate Survival rate Stage at diagnosis Feasibility	**Uptake:** 20,156 (74%) consented to participate of 27,116 individuals contacted. **Compliance:** 5242 (50.3%) of I group were estimated to be high-risk (based on bespoke questionnaire). 2388 (45.6%) underwent endoscopic screening. Older age and higher household income were positively associated with compliance. **Outcomes:** - **Incidence/Detection rate:** Three OC (0.13%) were detected (one stage Ib SCC and two severe hyperplasia). 1276/1488 pathologies detected were not cancerous or pre-cancerous. - **Stage:** 29 (1.21%) pre-cancerous oesophageal lesions were detected (two moderate and 27 mild dysplasia). 152 low-grade lesions were detected (141 mild oesophagitis, 8 acanthosis, 2 basal cell hyperplasia, 1 moderate oesophagitis.) Older age (OR= 1.07, 95% CI 1.02–1.13), male gender (OR = 2.42, 95% CI 1.11–5.27), and family cancer history (OR = 2.62, 95% CI 1.23–	Power calculation: Y Trial of endoscopic cancer screening of whole oesophagus and stomach cancer and gastric cancer Study conducted in one of non-high-risk centres in the National screening of upper gastrointestinal cancer in China study

				5.57 correlated with a higher risk of oesophageal precancerous lesions. - **Cancer-specific & all-cause mortality:** NR - **Sensitivity/Specificity:** NR	
Effect of screening on OC stage **Chen-Tao Guan 2018**	Population based cluster randomised control study 2012-2016	N = 39,494 I = 18,316 C = 21,178 S ~ 6410 FU - NR	1. TNM disease stage 2. Mortality	**Uptake:** NR **Compliance:** Compliance rate was 35% in I group vs. 50% in C group **Outcomes:** - **Incidence/ OC detection rate:** was 199 and 141 in I and C groups, respectively. - **Stage:** Proportion of cases with TNM stage from I to IV were 43.56%, 34.65%, 20.79%, and 0.99% in I group vs. 32.35%, 41.18%, 22.06%, and 4.41% in C group (P=.28). - **Cancer-specific & all-cause mortality:** NR - **Sensitivity/Specificity:** NR	Underlying risk of OC in the two study areas is not clear. Only ~ 50% of cases had TNM data available
ESECC **He et al. 2019** **Li et al. 2019**	Cluster RCT China 2012-2016 Screening by endoscopy with biopsy of all lesions One-off	N = 33,948 I = 17,151 C = 16,797 S = 15,299 45–69 years plus No history of cancer No endoscopy in previous 5 years	1. OC-specific mortality 2. All-cause mortality Incidence of advanced OC Cost per QALY - NR	**Uptake:** NR **Compliance:** 15,299/17,151 allocated to I group completed UCI endoscopy (89%) **Outcomes:** - **Incidence:** - **Detection rate/Stage:** High-grade lesions: 15,188 had at least one biopsy from which 113 (0.74%) high-grade lesions were detected: 34 (0.22%)	Power calculation: Y

				cases were OC. Pre-malignant lesions accounted for 79/113 (69.9%): 63 (0.41%) severe dysplasia, 16 (0.11%) OCIS. 24 high-grade lesions in other UGI sites were also found incidentally. - Low-grade lesions: Mild and moderate dysplasia was detected in 473 (3.11%) and 87 (0.57%) of cases, respectively. Acanthosis, oesophagitis or basal cell hyperplasia was diagnosed in 14.0%, 14.97% and 18.93% of cases, respectively. Truncated prevalence (aged 45–69 years) of high-grade oesophageal lesions and overall UGI lesions was ~ 744.0/100,000 and 902.0/100,000, respectively. He et al. 2019 - **Cancer-specific & all-cause mortality:** NR - **Sensitivity/Specificity:** NR - **Cost-effectiveness:** Cost per valid endoscopy was $196. Costs for detecting one OC and one early-stage OC were $26,347 and $37,687, respectively ($18,074, and $25,853 after exclusion of protocol-driven costs.) In a simulated screening programme, annual costs decreased by 40%+ at 10-years. Li et al. 2019	Costs adjusted to US $ rate for 2018

	Uptake: **Percentage of invited population agreeing to participate in the trial** ***Compliance:*** **Percentage of trial population completing the baseline screening**

	N=Total number in trial; I=in intervention group(s); C= in control group; S=No. screened
BEST3	Barrett's OESophagus Trial 3
BO	Barrett's Oesophagus
C [group]	Control/unscreened group
ESECC	Endoscopic Screening for Oesophageal Cancer in China
FU	Follow up
I [group]	Intervention group(s)
NR	Not reported
OC	Oesophageal adenocarcinoma
OCIS	Oesophageal cancer in-situ
QALY	Quality adjusted life years
RCT	Randomised controlled trial
SCC	Squamous cell carcinoma
TFF3	Trefoil factor 3
UGI	Upper gastrointestinal
UGC	Upper gastrointestinal cancer

Ovarian Cancer

Trial	Trial details	Participants	Outcomes/Results	Notes
PLCO **(Buhling et al., 2017; Buys et al., 2011; Doroudi et al., 2017; Henderson et al., 2018; Lai et al., 2016; Pinsky et al.,**	US 1993-2001 1) Annual CA-125 blood test for 6 y and annual TVS for 4 y (I)	N = 78,216 I = 39,105 C = 39,111 S = 34,253 Median age 62.8 y (55-74 y) Median follow-up 17 y **Population:** general	**Uptake:** NR **Compliance:** Compliance rate at baseline was 85% for CA-125 and 84% for TVS. These rates reduced to 79% and 78% by the 4th screening. **Outcomes:** - **Ovarian cancer incidence:** A total of 239 and 213 ovarian cancer cases were confirmed in the screening	PLCO trial was designed to evaluate screening modalities for prostate, lung, colorectal and ovarian cancers. Power calculation: Y Bimanual examination of the ovaries was originally part of the screening procedures (first

2019; Prorok et al., 2018)	2) Unscreened control (C) Criteria: CA-125 ≥ 35 U/ml TVS results with (1) ovarian V ≥ 10 cm^3; (2) cyst V ≥ 10 cm^3; (3) any solid area or papillary projection extending into the cavity of a cystic ovarian tumor of any size; and (4) any mixed (solid and cystic) component within a cystic ovarian tumour.		group and control group, respectively. The incidence rate was 1.13 (RR; 95%CI 0.94-1.36). - **Detection rate:** Instead of ovarian cancer-specific analysis, only the overall PPV was reported as 4.2% with FPR 96%. The overall cancer detection rate was 3.38 per 1000 screened. - **Stage:** The patients diagnosed with stage I or II disease was 29% and 17% in the screening group and control group, respectively (*P* = 0.085). Patients with stage IIIC and IV disease was 52% in the screening group while 75% in the control group (*P* = 0.031). - **Ovarian cancer & all-cause mortality:** The number of ovarian cancer death was 250 (246 with ovaries) and 219 (209 with ovaries) in the screening and control group, respectively, leading to an ovarian cancer mortality of 1.10 (RR; 95%CI 0.86-1.40) or 1.18 in women with ovaries (RR; 95%CI 0.98-1.42). The number of all-cause deaths among the whole women participants was 8953 in the screening arm versus 8810 in the control arm, leading to the all-cause mortality of 1.002 in women (RR; 95%CI 0.973-1.031). The mortality analysis targeting the subgroup of participants with family histories of ovarian (22,355 participants; 28,6%) or breast cancer (2708 participants; 3.5%) was reported. The ovarian cancer and all-cause mortality were 0.99 (RR; 95%CI 0.93-1.06) and 0.66 (RR; 95%CI 0.39-1.12), respectively. - **Sensitivity/Specificity:** NR - **Survival:** There was an improved survival of patients diagnosed with ovarian cancer in the screening arm	4 years) but was discontinued in December 1998 because no cancers were detected solely by ovarian palpation and the sensitivity was 5.1% (2/39) with specificity of 99.0% (49,957/50,459); yet in the control group receiving usual care, a high proportion of women underwent bimanual examination with ovarian palpation. TVS was performed using a 5- to 7.5-MHz transvaginal probe.

			compared to the control arm. (RR 0.66; 95%CI 0.47-0.93). Yet such survival improvement did not translate to mortality reduction. - **Risk of overdiagnosis:** There was a possible risk of overdiagnosis.	
QUEST **(Andersen et al., 2007; Henderson et al., 2018)**	US NR *1) Control with usually care (C)* *2) Risk education (I_1)* *3) Screening with CA-125 & TVS (I_2)* *4) Screening with CA-125 & TVS + risk education (I_3)* Criteria: CA-125 ≥ 35 U/ml for pre-menopausal and > 30 U/ml for post-menopausal women TVS results with (1) enlarged	N = 592 I_1 = 150 I_2 = 140 I_3 = 152 C = 150 S = 236 Median age 44.8-45.8 y (≥ 30 y) Median follow-up 2 y **Population:** general	**Uptake:** NR **Compliance:** The overall compliance rate of screening was 80.8% and 64.5% of women completed all 4 screenings. For women allocated to risk education groups (Group 2 and 4), 73% attended the full 4 workshops. **Outcomes:** - **Ovarian cancer incidence:** NR - **Detection rate:** NR - **Stage:** NR - **Ovarian cancer & all-cause mortality:** NR - **Sensitivity/Specificity:** NR - **Psychosocial harms:** In general, no statistically significant differences were found among four groups in terms of mental and physical health as well as cancer worry scores. Compared to the non-screening control group, participants in the screening arms reported no alterations in the level of cancer worry and QOL. Among women participating in the screening, those with abnormal results (32) reported increased levels of cancer worry compared to those receiving normal screening results (OR 2.8; 95%CI 1.1-7.2).	Power calculation: Y The screening protocol included: CA125 blood test at month 1 & 12; TVS at month 6 & 18 Risk education was provided as four 2-h workshops. No detail of TVS was provided.

	ovaries; (2) abnormal morphology			
SCSOCS **(Buhling et al., 2017; Kobayashi et al., 2008)**	Japan 1985-2002 1) Annual CA-125 blood test and pelvis ultrasound for 5 y (I) 2) Unscreened control (C) Criteria: CA125 ≥ 35 U/ml Ultrasound results with (1) ovarian D ≥ 4 cm; (2) complex cyst morphology	N = 82,487 I = 41,688 C = 40,799 S = 34,184 Median age NR (45-85 y) Median follow-up 9.2 y **Population:** post-menopausal women	**Uptake:** NR **Compliance:** The compliance rate of baseline screening was not reported. The compliance with subsequent screenings was 82% at the 2nd round; 71% at the 3rd round; 67% at the 4th round and 56% at the 5th round. **Outcomes:** - **Ovarian cancer incidence:** A total of 35 ovarian cancer cases were diagnosed in the screening group with 8 of them being interval cases. In the non-screening control, 32 participants were diagnosed with ovarian cancer. - **Detection rate:** The cancer detection rate was 0.31 per 1000 at baseline screening and ranged between 0.38 and 0.74 per 1000 in the following screening rounds. - **Stage:** The cases with stage I disease were 63% in the screening arm compared to 38% in the control arm (*P* = 0.2285). - **Ovarian cancer & all-cause mortality:** NR - **Sensitivity/Specificity:** The sensitivity, specificity and PPV of the pelvic ultrasound for ovarian cancer detection was estimated 74%, 99.9% and 23.3%, respectively.	Power calculation: NR In the first 5 years of the trial, ultrasound was performed mainly by the transabdominal method instead of transvaginal method. Yet no detail of the TVS was provided.

UKCTOCS **(Barrett et al., 2014; Buhling et al., 2017; Fallowfield et al., 2017; Gentry-Maharaj et al., 2015; Henderson et al., 2018; Kalsi et al., 2021; Menon et al., 2021; Menon et al., 2017; Moss et al., 2018)**	UK 2001-2014 1) Multimodal screening group (MMS): Annual CA-125 blood test and annual TVS for 11 y (I_1) 2) Ultrasound screening group (USS): Annual TVS for 11 y (I_2) 3) Usual care control (101,359) Criteria: Intermediate risk (≥ 1/1818) or elevated risk (≥ 1/500) based on ROCA; one or both ovaries with complex morphology, simple cysts > 60 cm^3 or ascites	N = 202,638 I_1 = 50,640 I_2 = 50,639 C = 101,359 S = NR Median age 60 y (50-74 y) Median follow-up 16.3 y **Population:** post-menopausal women	**Uptake:** 288,955 (23%) of 1,243,282 women sent an invitation were positive responders. **Compliance:** NR **Outcomes:** - **Ovarian cancer incidence:** USS arm: 960 screen-positive women underwent surgery, and 113 cases were confirmed with ovarian/tubal cancer, in which 80 were invasive epithelial cancers. Among 2055 women diagnosed with ovarian/tubal cancers, 522 (1%) were in the MMS group; 517 (1%) were in the USS group and 1016 (1%) in the unscreened control group. - **Detection rate:** A total of 45 cancer cases (20 borderline) were detected in the USS group while 42 cancer cases (8 borderline) were detected in the MMS group. - **Stage:** Among the 80 invasive epithelial cancers detected in USS arm, 37.5% (95%CI 26.9-49.0) were stage I/II. There were 50 interval invasive epithelial cancer cases where 6% were stage I/II. Among cases detected in MMS arm, there were increased cases with stage I disease (47.2%, 95%CI 19.7-81.1) and decreased cases with stage IV disease (24.5%, 95%CI -41.8 to -2.0) compared to the control arm. - **Ovarian cancer & all-cause mortality:** A total of 1206 women died of ovarian cancer where 296 (0.6%) were in the MMS group; 291 (0.6%) were in the USS group; 619 (0.6%) were in the unscreened control group. The	Power calculation: Y TVS was performed using Mainly Kretz SA9900.

			ovarian cancer mortality was comparable among three groups. - **Sensitivity/Specificity:** The sensitivity, specificity and PPV for detecting ovarian/tubal cancers in the USS arm was estimated 68.5% (95%CI 60.8-75.5), 99.7% (95%CI 99.7-99.7) and 11.8% (95%CI 9.8-14), respectively. The sensitivity, specificity and PPV for detecting invasive epithelial cancers was 61.5% (95%CI 52.6-69.9), 99.7% (95%CI 99.7-99.7) and 8.3% (95%CI 6.7-10.3), respectively. For the MMS arm, the sensitivity, specificity and PPV for detecting ovarian/tubal cancers was estimated 89.4%, 99.8% and 43.3%, respectively. The sensitivity, specificity and PPV for detecting invasive epithelial/tubal cancers was 89.5%, 99.8% and 35.1%, respectively. - **Cost-effectiveness:** An analysis constructed a Markov simulation model to compare MMS with non-screening in the US under the UKCTOCS protocols. Provided screening women starting at the age of 50 with MMS, the cost-effectiveness was estimated 70% under circumstances that decision makers were willing to pay $150,000 per QALY. Screening led to 15% mortality reduction and an ICER between $106,187 (95%CI 97,496-127,793) and $155,256 (95%CI 150,369-198,567). Another study used a Markov model and a predictive extrapolation based on the average life expectancy in the UK to evaluate the with-in trial cost-effectiveness. The USS vs non-screening ICER was estimated £625,801 per LYG (95%CI 620,451-631,245) while the MMS vs	

			non-screening ICER was £91,452 per LYG (95%CI 90.909-92,001) with CA125-ROCA cost of £20. Provided CA125-ROCA cost of £15, the predictive extrapolation over the expected lifetime of women in UKCTOCS estimated an ICER of £ 30,033 per LYG whilst the Markov model estimated an extrapolated QALY of 0.0581 and the ICER of £46,922 per QALY. - **Risk of overdiagnosis:** There were more borderline epithelial ovarian cancers diagnosed in the screening group (97 of 101,279) than control group (62 of 101,359) (*P* = 0.005). Between the two screening arms, there were more screen-detected borderline cancers in the USS arm compared to the MMS arm (92.3% vs 55.6%; *P* < 0.001). - **Psychosocial harms:** The impact of ovarian cancer screening on sexual activity and functioning was evaluated and there was no difference found between screening group (both MMS and USS) and control group in general. Women in the USS group who required further repeated screening reported lower pleasure scores in the questionnaire (mean difference -0.14, *P* = 0.046). Women in both MMS and USS group who had ≥ 2 repeat screens reported decreased pleasure scores compared to their annual scores (mean difference -0.16, *P* = 0.005). The mean pleasure score also decreased when more intensive screens were required (mean difference -0.09, *P* = 0.046). The potential effect of screening on patients' anxiety and psychological morbidity was evaluated in a 7-year follow-up and found that the mean differences of	

			anxiety scores were small, though statistically significant due to large sample size, between all participants at the baseline and women required repeat screens. The overall psychological wellbeing, which was measured using GHQ-12, was not affected by the screening per se. The risk of psychological morbidity was found increased when women required higher level of repeat screens (OR 1.28; 95%CI 1.18-1.39).	
UK Pilot **(Henderson et al., 2018)**	UK 1989-1998 1) Annual CA-125 blood test for 3 y (I) 2) Unscreened control I Criteria: CA125 ≥ 30 U/ml	N = 21,935 I = 10,958 C = 10,977 S = NR Median age NR (≥ 45 y) Median follow-up NR (0-8 y) **Population:** post-menopausal women	**Uptake:** By invitation to 22,000 women who had participated in a previous study [Jacobs et al., 1999 https://doi.org/10.1016/S0140-6736(98)10261-1] **Compliance:** In I group, 6792 (31%) underwent first, 6672 (31%) second and 6455 (30%) third screen. [Jacobs et al., 1999 https://doi.org/10.1016/S0140-6736(98)10261-1] **Outcomes:** - **Ovarian cancer incidence:** In total, 36 patients were diagnosed with ovarian cancers (0.2%). - **Detection rate:** NR - **Stage:** NR - **Ovarian cancer & all-cause mortality:** There were 9 deaths due to ovarian cancer in the screening group (0.08%) while 18 deaths in the non-screening control group (0.16%), leading to a relative risk of 0.50 (95%CI 0.22-1.11). - **Sensitivity/Specificity:** There were 462 women receiving false-positive screening results (4.2%) among	Power calculation: Y Women with elevated CA-125 levels were subjected to follow-up including TVS.

			which 0.2% underwent surgery with no complications reported.	

	Uptake: **Percentage of invited population agreeing to participate in the trial** ***Compliance:*** **Percentage of trial population completing the baseline screening** **N=Total number in trial; I=in intervention group(s); C= in control group; S=No. screened**
CA-125	Cancer antigen 125
D	Diameter
FPR	False-positive rate
GHQ-12	12-item General Health Questionnaire
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IRR	Incidence rate ratio
LYG	Life-year gained
MMS	Multimodal screening group
NPV	Negative predictive value
NR	Not reported
OR	Odds ratio
PLCO	The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial
PPV	Positive predictive value
RCT	Randomised clinical trial
ROCA	Risk of ovarian cancer algorithm
RR	Rate ratio
SCSOCS	Shizuoka Cohort Study of Ovarian Cancer Screening
SD	Standard deviation
TVS	Transvaginal ultrasound
UKCTOCS	UK Collaborative Trial of Ovarian Cancer Screening
USS	Ultrasound screening group
QALY	Quality-adjusted life-years
QOL	Quality of life
QUEST	Quality of Life, Education, and Screening Trial
V	Volume

VDT	volume doubling time

Prostate cancer

Trial	Study Details	Participants	Outcomes	Results	Notes
CAP trial **Martin et al. 2018**	Cluster RCT UK 2001–2009 PSA. Biopsy if ≥3ng/mL One-time screening	N = 419,582 I = 189,386* C = 219,439* S = 67,313 *available for analyses Men aged 50-69 yr Median FU 10yr	1. PCa-specific mortality 2. Disease incidence All-cause mortality Stage Grade (Gleason) HRQoL - NR Cost effectiveness - NR	**Uptake:** Randomisation by GP practice; 73% of the 573 eligible practices agreed to participate. 75,707 (40% of I group) attended for PSA testing. **Compliance:** 67,313 of I group (36%) underwent PSA testing. **Outcomes:** 64,436 had a valid PSA result, of whom 6857 (11%) had a PSA level 3–19.9 ng/mL: 5850/6857 (85%) had a prostate biopsy. - **Incidence/ Detection rate:** Diagnosis of PCa was n = 8054 (4.3%) in I group vs n = 7853 (3.6%) in C group; RR = 1.19 (95% CI, 1.14–1.25). - **Stage/Grade:** More low-risk tumors identified in I group (n = 3263/189,386 [1.7%]) vs C group (n = 2440/219,439 [1.1%]); difference per 1000 men = 6.11 (95% CI, 5.38–6.84), P <.001. - **Cancer-specific & all-cause mortality:** 25,459 deaths in I group vs 28,306 in C group; RR = 0.99 (95% CI, 0.94–1.03); P = .49. PCa-specific mortality was 549 (0.30 per 1000 person-years) in I group vs 647 (0.31 per 1000 person-years) in C group (rate difference,	Power calculation: Y However, a (low) compliance with screening rate (~35%) and a lower than expected number of control arm PCa deaths has raised questions whether the trial was under-powered Trial adopts a less intensive screen frequency to minimize over-diagnosis, however note increased detection rate for low-risk cases, without mortality benefit. The ProtecT trial of treatments for localized PCa was embedded within CAP trial

				−0.013 per 1000 person-years (95% CI, -0.047–0.022); RR = 0.96 (95% CI, 0.85–1.08, P = .50 - **Sensitivity/Specificity:** NR	
ERSPC **Ilic et al. 2018** **Hugosson et_al. 2019** **Osses et al. 2018** **Saarimaki et al. 2017** **Schroder et al. 2012** **Schroder et al. 2014** **Talala et al. 2020** **van Leeuwen et al. 2013** **Kilpelainen et al. 2013** **Walter et al. 2021**	RCT 8 European countries 1993–2003 21 year follow-up PSA ± DRE. Biopsy if ≥3ng/mL Screening every 2-7 yr* *Most centres 4yr with variation eg France 2 yr, Belgium 7yr	N = 162,389* I = 112,553 C = 128,681 S = 72,525 (screened at least once) *'core' age group - Men aged 55-69 yr- is focus of data analysis (some centres included men 50-74) 15.5 yr median FU 16 yr maximum FU	1. PCa-specific mortality 2. All-cause mortality PCa incidence Stage HRQoL – only Finnish centre, based on a random sample of participants (n=1088) from both trial groups excluding men with a subsequent diagnosis of prostate cancer. Harms from PCa screening	**Uptake:** Recruitment processes differed across participating countries; some from population registries while others required consent. Of 112,553 allocated to I group, 72,525 (64%) were screened at least once. **Compliance:** Mean (SD) screens-per-man was 2.1 (1.1). **Outcomes:** - **Incidence/Detection rate:** RR for PCa incidence between I and C groups = 1·91 (95% CI, 1·83–1·99) at 9 years (1·64 [1·58–1·69] including France data), 1·66 (1·60–1·73) at 11 years, and 1·57 (1·51–1·62) at 13 years. Schroder et al. 2012; Schroder et al. 2014 - **Stage:** NR - **Cancer-specific & all-cause mortality:** Absolute RR in excess mortality = 0.08 per 1000 person-years. Overall *all-cause mortality* not significantly different between I and C groups: RR 0.99 (95% CI 0.96–1.01). van Leeuwen et al. 2013. Pooled data from four largest ESPRC centres (N = 141,578) at median FU 9 yr reported excess mortality among men with PCa = 0.29 per 1000 person-years in I group vs 0.37 per 1000 person-years in C group; RR = 0.77 (95% CI, 0.55–1.08). Data from FinRSPC, the	Power calculation: Y Minor protocol variations across 8 European centres • Belgium • Netherlands • Finland • Italy • Spain • Sweden • Switzerland • France* *French data excluded from some analyses as failed to comply with screening criterion

Karlsson et al 2021 **Booth et al 2018** **Heijnsdijk et al 2021**				largest ERSPC centre (31,866 and 48,278 men in I and C groups, respectively) reported 6618 deaths in the I group (cumulative mortality = 20.8%) vs 10,079 deaths (20.9%), in C group at median 12 yr FU. HR for all-cause mortality = 0.99 (95% CI, 0.96–1.02); P = .69). Kilpelainen et al. 2013 21% reduction in *PCa specific mortality* at 16 yr FU; RR between I and C groups = 0.80 (95% CI, 0.72–0.89, P <0.001. No significant change in RR from 9,11 & 13 yr FU. Absolute group difference in PCa mortality increased from 0.14% at 13 yr to 0.18% at 16 yr. Equates to NNI of 742 vs 570 and NND of 26 vs 18, at respective time points. PCa-specific survival for cases detected at screening round 1 significantly worse compared with diagnosis at subsequent screening rounds (HR = 1.86, p<0.001). The pattern of PCa mortality reduction variation across centres, RR range = 0.91–0.63, suggests increased screening intensity may correlate positively to mortality reduction. Hugosson et al. 2019 In FinRSPC (N = 31,866) the largest mortality reduction was in men screened three times (HR 0.17; 95% CI, 0.09–0.33). Pakarainen et al 2019. However, differences in FinRSPC (screening interval of 2 yr; PSA cut-off of 3.0 ng/ml) and Swedish (N = 5901: screening	

				interval 4 yr; PSA cut-off 4.0 ng/ml) protocols 'unlikely to explain the differences in mortality' at 13 yr and 16 yr FU. Saarimaki et al. 2017 Rotterdam pilot 1 study cohort (N = 1134) reported RR of metastatic (M+) disease and of PCa mortality were 0.46 (95% CI, 0.19–1.11) and 0.48 (95% CI, 0.17–1.36), respectively, in favour of screening at 19 yr FU. Osses et al. 2018 - **Sensitivity/Specificity:** >20,000 biopsies were performed to detect ~ 5000 cancers, corresponding to PPV of 24%. A quarter of participants were biopsied at least once, demonstrating low specificity of PSA (with cut-off values of 3–10 ng/mL) as a screening test. Hugosson et al. 2019 - **Overdiagnosis:** The excess PCa incidence in I group was 41% at 16 yr FU) and NND was 18. Hugosson et al. 2019. FinRSPC data (N = 80,149) estimated overdiagnosis in I group as 30%. Kilpelainen et al. 2013. This compares to ~ 60% in overall ERSPC analysis Schroder et al. 2012. A later FinRSPC analysis estimates an overdiagnosis rate between 2.3% and 15.4%, with equivalent results for T1c tumours as a proxy of early-stage screen-detected disease. Walter et al. 2021 - **HRQoL:** 15 yr FU of FinRSPC (N = 80,458) revealed generic HRQOL measures were comparable between I and C groups. PCa	Cost-effectiveness analysis across ERSPC dataset, uses

				specific HRQOL measures were 'slightly higher' in I group vs C group. The only statistically significant difference was for 'urinary bother': (UCLA-PCI score 77.9; 95% CI 75.2–80.5 vs 70.9; 95% 66.8–74.9, P=.005). Talala et al. 2020 - **Cost-effectiveness:** 71 fewer deaths per 10,000 men corresponds with an increase of 652 life-years and 366 QALYs per 10,000 men. PSA screening associated with increased costs for screening (€214/man), diagnostics (€290/man), treatment for localised prostate cancer (€294/man) and productivity losses (€77/man), with lower costs for treatment for advanced prostate cancer (-€306/man). Discounting at 3% per annum, the ICER from a societal perspective was €54,918/ per QALY gained. Karlsson et al 2021 Modelling the effect of screening interval and upper age on mortality (Heijnsdijk et al 2021), predicted a 33% overdiagnosis rate of screen-detected cancers and ICER of $73,000 per QALY gained, with a simulated two-year interval with an age range of 55–59. 20 year FinRSPC data showed cumulative all-cause cost estimates for all men in the trial were equivalent across groups (p =0.64). Mean all-cause costs and PCa-related costs for *diagnosed men* were respectively ~1% (€700) and ~10% *lower* (€1100) in I group. Mean all-cause costs and PCa-related costs for *men*	a microsimulation model, from a lifetime societal perspective Discounted costs, quality-adjusted life-years (QALYs) and incremental cost-effectiveness ratios (ICERs) were calculated Findings are of low certainty due to low statistical power and substantial contamination in C group

				dying from PCa were ~10% (€5100) and ~1% *higher* (€1700) in I group. Booth et al 2018	
Göteborg-1 PCa screening trial **Arnsrud Godtman et al 2015** **Franlund et al 2018** **Hugosson et al 2017** **Carlsson et al 2017b**	RCT 1995–2014 Biennial PSA testing ± DRE	N = 20,000 I = 9950 C = 9949 S = 7647 Men aged 50-69 yr 20yr FU	1. Absolute and relative risk reduction in PC mortality 2. Attendance PCa incidence PCa mortality rate and RR in sociodemographic subgroups	**Uptake:** All 20,000 men in a population registry were randomised into the trial. **In I group,** n = 5855/9950 (59%) attended the first screening round. **Compliance:** Of 5855 attending the first screening round, 661 (11%) had a PSA ≥ 3 ng/mL threshold for biopsy. 77% (7647/9950) attended screening at least once; 74% of study population attended all study invitations. **Outcomes:** - **Incidence/Detection rate:** IRR for PCa incidence at 18 years = 9.7% [95% CI 9.2–10.2] per 1000 person-years in I group vs 6.5% (95% CI 6.1–6.9) per 1000 person-years in C group. The HR for PCa incidence in I vs C group was 5.2, 1.9 & 1.1 at 1, 5 and 15 yrs. Hugosson et al 2017 754/ 5174 (14.6%) men with PSA level **<**3 ng/mL at initial screen were diagnosed with PCa during a median FU of 18.9 years. Cumulative PCa incidence was 17.2%: 7.9% for PSA levels <0.99ng/mL; 26.0% for 1–1.99 ng/mL; 40.3% for 2–2.99 ng/mL (p<0.001). Franlund et al 2018 - **Stage/Grade:** Of 1396 (14%) PCa cases in I group, 7.0%, 4.7%, 1.4% and 0.7% were low	Power calculation: Y The Goteborg Randomized Population-Based Prostate Cancer Screening Trial started in 1995. Since 1996, the trial has constituted the Swedish arm of the ERSPC.

				risk, intermediate risk, high risk and advanced, respectively. - **Cancer-specific & all-cause mortality:** 2844/9950 (28.6%) **died of all causes** in I group vs 2857/9,949 (28.7%) in C group, at 18 yr. Hugosson et al 2017 At 18 yr, cumulative **PCa-specific mortality** was 0.98% (95% CI 0.78–1.22%) in I group vs 1.50% (95% CI 1.26–1.79%) in C group: an absolute reduction of 0.52% (95% CI 0.17–0.87%). RR for PCa death was 0.65 (95% CI 0.49–0.87). NNI = 231 and NND = 10 to prevent one PCa death. Absolute risk reduction for PCa mortality was improved at 20-yr FU compared to 14-yr FU (0.52 vs 0.40), NNI (231 vs 293) and NND (10 vs 12). However, relative risk reduction decreased (RR 0.56 vs 0.65) Arnsrud Godtman et al 2015 Greater benefit for PCa mortality was demonstrated for all men starting screening at 55–59 years (RR = 0.47, 95% CI 0.29–0.78) and for men with low education (RR = 0.49, 95% CI 0.31–0.78) Hugosson et al 2017 A nested cohort study (to evaluate effect of age at start screening on PCa-specific mortality) compared 3479 men aged 50–54 yr in I group vs 4060 aged 51–55 yr in C group. At 17 yr FU, PCa death (IRR = 0.29, 95% CI 0.11–0.67) and the risk of metastases (IRR = 0.43, 95% CI 0.22–0.79) were lower in I group: 57	

				fewer PCa deaths per 10 000 men (95% CI 22–92); NNI = 176 and NND =16, respectively. Carlsson et al 2017b, - **Sensitivity/Specificity:** NR	
Norrköping PCa screening trial **Sandblom et al 2011** **van Leeuwen et al 2012**	Quasi-randomised CT (random allocation of every 6th man). Sweden 1987–1996 Every third year Screening DRE only for first 2 rounds. From 1993, +PSA with 4 µg/L cut-off.	N = 9026 I = 1494 C = 7532 S = 1161 50-69 yr 20 yr FU	1. PCa-specific mortality 2. PCa incidence Tumour stage Tumour grade Treatments	**Uptake:** Identification of sample via National Population Register. Attendance was 1161/1492 (78%) at round one. **Compliance:** Attendance was 957/1363 (70%), 895/1210 (74%), and 446/606 (74%), at rounds two to four respectively. **Outcomes:** - **Incidence/Detection rate:** PCa incidence was = 85/1494 (5.7%) and 292/7532 (3.9%) in I and C groups, respectively. Sandblom et al 2011 - **Stage:** Percentage of localised tumours (T1-2,N0,M0) was significantly higher in I group (56.5%) vs C group (26.7%, P<0.001): Non-localised tumour incidence was 2.5% in I group vs 2.8% in C group (P=0.44). Sandblom et al 2011 - **Cancer-specific & all-cause mortality:** RR for PCa mortality in I group = 1.16 (95% CI 0.78–1.73). PCa-specific survival favoured the C group, HR = 1.23 (95% CI 0.94– 1.62) P=0.13. PCa specific survival adjusted for age-at-study-entry = HR 1.58 (95% CI 1.06– 2.36), P=0.024. In a survival analysis adjusted for age comparing PCa-specific survival in C group with	Power calculation: Y Due to change of protocol, many men did not receive PSA test, some men only received one PSA test and none received more than two PSA tests.

				I group, the age adjusted HR = 1.23 (0.94–1.62; P=0.13). van Leeuwen et al 2012 - **Sensitivity/Specificity:** NR	
PLCO trial **Ilic et al 2018** **Andriole et al 2012** **Pierre-Victor et al 2021** **Pinksy et al 2017** **Pinksy et al 2019a** **Pinksy et al 2019b** **Prorok et al 2021** **Tsodikov et al 2017**	RCT US 1993–-2001 Annual screening with PSA for 6 yrs, + DRE for 4 years	N = 76,685 I = 38,340 C = 38,343 S = ? Men aged 55–74 yr Median 16.9 yr FU for I group	1. PCa-specific mortality 2. All-cause mortality PCa incidence Tumour stage Tumour grade (by Gleason category) Harms of screening	**Uptake:** NR **Compliance:** Approximately 92% of the study participants were followed to 10 years and 57% to 13 years. At transition to centralised FU (end of 2011), 11.2% of patients in I group vs 15.2% in C group refused further FU. **Outcomes:** - **Incidence/Detection rate: PCa incidence:** Overall 20-yr cumulative PCa incidence was 26.4% (95% CI, 24.8–28.1); RR = 1.05 (95% CI, 1.01–1.09). RRs by Gleason category were 1.17 (95% CI, 1.11–1.23) for Gleason 2–6 disease, 1.00 (95% CI, 0.93–1.07) for Gleason 7 and 0.89 (95% CI 0.80–0.99) for Gleason 8–10. During screening phase (i.e. first 6 years), 13% of I group PCa cases vs 27% of C group cases were symptomatic; post-screening, percentages were 18% in each group. Pinksy et al 2019a - **Stage:** Of 4250 I group prostate cancers diagnosed through 13 years, 15.8%, 54.7%, 8.6%, and 1.0% were stage I to IV respectively at diagnosis. Andriole et al 2012 - **Cancer-specific & all-cause mortality:** Overall cumulative mortality rates were 1.2% (95% CI, 0.9–1.7). RR for *all-cause mortality* was 0.977 (95% CI, 0.950–1.004) in PCa cases. In men	PLCO trial evaluates screening modalities for prostate, lung, colorectal and ovarian cancers. Power calculation: Y A critique of the PLCO prostate trial has been that the original (and a revised) power estimate was too high because it was based on both higher levels of contamination and lower numbers of events than predicted. With extended follow-up and approximately 65% more prostate cancer deaths in the current analysis, the second factor has been mitigated to some extent.

				overall (i.e. Prostate Lung Colorectal screening combined) there was a significant reduction in overall mortality in the I versus C group: (RR = 0.966; 95% CI, 0.943–0.989; p = 0.004) Pinksy et al 2019b. Data from a cohort of men (N = 2855) with a positive PSA (> 4 ng/mL) or DRE screen followed by a negative biopsy within one year. showed HRs for PCa mortality increased significantly with increasing PSA. Pierre-Victor et al 2021. **PCa-specific mortality** at 16.9 yrs was 333 (5.5 per 10,000 person-years) in I group vs 352 (5.9 per 10,000 person-years) in C group; RR = 0.93 (95% CI, 0.81–1.08), P= .38. Pinksy et al 2019a HR = 0.93 (95% CI, 0.80–1.08) Pinksy et al 2019b At 15 yrs, approximately 60% of PCa deaths in each group still occurred in cases diagnosed during the first 6 years of the trial. Pinksy et al 2017 No significant interaction was found between comorbidity status and PCa mortality (RR = 0.99 and RR = 1.06 in 'no comorbidity' and 'comorbidity' groups, respectively) Andriole et al 2012 Analyses to reconcile contradictory PCa-mortality results from EESPC and PLCO trials modelled effects of screening on PCa mortality controlling for differences in screening	

				intensity in S and C groups of ERSPC and PLCO trials. Mean lead time (MLT) analysis showed no significant differences in ERSPC and PLCO I groups, but longer MLT in the PLCO vs ERSPC C groups. Screening benefit increased with MLT (P=0.0027–0.0032). Screening confers an estimated 7–9% reduction in PC death per year of MLT. This translates into an estimated 25–31% and 27–32% lower risk of PC death under screening as performed in the ERSPC and PLCO I groups, respectively, relative to C groups. Tsodikov et al 2017 - **Sensitivity/Specificity:** 14,662 +ve PSA results from 177,275 screens, gives an overall +ve rate of 8.27%. 4707 (32.1%) of the 14,662 +ve screens prompted a biopsy and 1793 cancers were detected. (For positive screens, where the cancer was not identified , a repeat test was used about 60–70% of the time across screening rounds.) The overall PPV was 12.23% and the cancer detection rate was 10.11 per 1000 screens. The PCa false +ve rate was over 80% across study waves. Prorok et al 2021	
STHLM3-MRI trial **Eklund et al 2021**	Non-inferiority RCT Sweden 2018–2020	N = 2293 I = 1372 C = 921 S = 1184	1. Probability of detection of clinically significant PCa 2. proportions of benign biopsies and	**Uptake:** 12,750 (26%) of 49,118 invited consented to screening and provided blood samples for PSA testing. **Compliance:** 1372 high risk men were allocated to I group. 1184 had the assigned intervention. **Outcomes:**	Power calculation: Y In experimental group, MRI was followed by standard biopsy where MRI indicated presence of PCa

Nordström et al 2021	MRI + targeted biopsy vs standard biospy	Men aged 50–74 yr Higher risk participants based on PSA (≥3 ng OR Stockholm3 test (≥11%)* FU after screening complete	clinically insignificant cancer Serious adverse events 30 days after biopsy	- **Incidence/Detection rate:** 233 vs 179 PCa cases were detected in I vs C groups. biopsy group, as compared with 106 men (18%) in the standard biopsy The percentage of clinically insignificant cancers was lower in the experimental biopsy group than in the standard biopsy group (4% [41 participants] vs. 12% [73 participants]; difference, −8 percentage points; 95% CI, - **Stage/Grade:** Clinically-significant cancer was diagnosed in 192/929 (21%) vs 106/603 (18%) in I and C groups respectively (3% difference; 95%CI −1 to 7). Clinically-insignificant cancer was diagnosed in 4% vs 12% in I and C groups respectively (8% difference; 95%CI −11 to -5) - **Cancer-specific & all-cause mortality:** NR - **Sensitivity/Specificity:** NR - **Harms/benefits:** I group had a lower incidence of prescription of antibiotics for infection (1·8% vs 4·4%) and admission to hospital (1·2% vs 3·4%) than C group.	* Stockholm3 test is a risk prediction model based on clinical variables (age, first-degree family history of prostate cancer, and previous biopsy), blood biomarkers (total PSA, free PSA, ratio of free PSA to total PSA, human kallikrein 2, macrophage inhibitory cytokine-1, and MSMB), and a polygenic risk score for predicting the risk of prostate cancer with a Gleason score of 7 or higher.
Stockholm trial **<u>Lundgren et al 2018</u>**	RCT Screening v background population Sweden 1988–2003	N = 27,464 (source population) I = 2400 C1 = 621 invited but declined C2 = 25,685 not invited S = 1779	1. PCa-specific mortality 2. All-cause mortality PCa incidence	**Uptake/Compliance:** Random selection of 2,400 from a population of 27,464 men. 1779/2400 (74%) accepted screening. **Outcomes:** - **Incidence/Detection rate:** Cumulative PCa incidence at 20 yr was 13.3% (RR = 1.22 [95% CI 1.08–1.38]), 9.0% (RR = 0.83 [95% CI 0.64–1.07]), and 10.9% (RR =1) in I vs C1 and source	Power calculation: Y Statistical power was limited in retrospective calculation

	PSA, DRE, TRUS. Biopsy on PSA >10ng/mL and DRE & TRUS One-time screening	Men aged 55-70 years 20 yr FU		populations, respectively. PCa incidence remained higher in I population throughout FU. - **Stage:** - **Cancer-specific & all-cause mortality:** All-cause mortality at 20 years was 972 (54.6%) for I group (IRR = 0.92 [95% CI, 0.86-0.98]) vs 448 (72.1%) in C1 group (IRR = 1.25 [95% CI, 1.14-1.37]), and 14,703 (58.6%) in source population. I group participants had decreased overall mortality rate compared to source population (IRR = 0.93, [95% CI, 0.86-0.98]) vs CI (IRR = 1.25, [95% CI 1.14-1.37]). PCa incidence in screening arm represents an overdiagnosis rate of 16.5–32.3%. *PCa mortality* in I group was 59 (3.3%) (IRR 95% CI = 0.97 [0.71-1.23]) vs 27 (4.4%) (IRR = 1.24 [0.86-1.63] in C1 group and 857 (3.4%) in source population. - **Sensitivity/Specificity:** NR	
'US clinical trial' **<u>Catalona et al 2017</u>**	Multicentre CT US ≥ 50 yrs PSA and DRE Biosy if PSA > 4/g/L and/or suspicious DRE	N = 6630 I = 6630 S = 6630 Comparison groups based on screen method -PSA ± DRE	Comparison of efficacy of PSA and DRE to detect: • PCa • Localised disease	**Uptake:** NR **Compliance:** All participants underwent PSA and DRE. 15% had PSA >4 µg/l and 1167 had a biopsy. **Outcomes:** - **Incidence:** Of 160 patients who underwent radical prostatectomy and pathological staging 114 (71%) had organ confined cancer: PSA detected 85 (75%) of this localised disease vs DRE detected 64 (56%), p = 0.003.	Power calculation: NR

		1991–1992 20 y FU		- **Detection rate:** PCa detection rate was 3.2% for DRE, 4.6% for PSA and 5.8% for the methods combined. PSA detected 216/ 264 cancers (82%,) vs DRE 146/ 264 (55%) , p = 0.001. PPV was 32% for PSA and 21% for DRE . - **Stage:** 261/264 men had organ localised cancer and the remaining 3 (1%) had advanced disease. - **Cancer-specific & all-cause mortality:** NR - **Sensitivity/Specificity:** NR	

	Uptake: **Percentage of invited population agreeing to participate in the trial** ***Compliance:*** **Percentage of trial population completing the baseline screening** **N=Total number in trial; I=in intervention group(s); C= in control group; S=No. screened**
C [group]	Control/non-screened group
CAP	Cluster Randomised Trial of PSA Testing for Prostate Cancer
DRE	Digital rectal examination
ERSPC	European Randomized Study of Screening for Prostate Cancer
FinRSPC	Finnish Randomized Study of Screening for Prostate Cancer
FPR	False-positive rate
FU	Follow up
HR	Hazard ratio
HRQOL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IRR	Incidence rate ratio
MLT	Mean lead time [the average time by which diagnosis is advanced by screening relative to the date of diagnosis without screening]
NND	Number needed to invite to diagnose to prevent one prostate cancer death
NNI	Number needed to invite to screening to prevent one prostate cancer death
NPV	Negative predictive value
NR	Not reported

PCa	Prostate cancer
PLCO	Prostate, Lung, Colorectal & Ovarian Cancer Screening trial
PPV	Positive predictive value
PSA	Prostate-specific antigen
QALY	Quality-adjusted life-years
RCT	Randomised controlled trial
RR	Rate ratio
TRUS	Transrectal ultrasound

2.2 Bottom line results

Based on data from the 84 controlled trials included in the rapid review (many of which were randomised controlled trials) the evidence on efficacy, harm-benefit and cost-effectiveness may be summarised as follows.

Gastric cancer:

Two trials were identified looking at endoscopic screening for gastric cancer (Zeng et al. 2020; Xiao et al. 2020). Both found that detection rates for gastric cancers were low (0.04% and 0.4%) but precursor lesions were also detected. Compliance rates were approximately 45%. No trial-based mortality or cost-effectiveness data were identified.

Screening via gastric juice MicroRNAs biomarkers is being explored (Virgilio et al. 2018) but has not yet been assessed in controlled trials so was outside the scope of the review.

Limited data from two trials, not identified within this rapid review but included in an identified systematic review (Haddad et al. 2020), suggest a 79-80% sensitivity and specificity for cancer detection by breath analysis.

The eradication of Helicobacter pylori as an alternative 'screen and treat' strategy for prevention of gastric cancer was outside the scope of this review of cancer screening methods but the authors are aware of ongoing trials (see discussion).

Lung cancer:

Data from 13 published trials found higher lung cancer incidence as well as early-stage disease in the screening arm, compared to control. A review pooling data from 9 randomised controlled trials (RCTs) found that the overall lung cancer incidence was higher in the low-dose CT scan (LDCT) screening group compared to the control group (RR 1.26; 95%CI 1.10-1.45) (Hunger et al. 2021).

Reduced lung cancer mortality but not overall mortality was observed in the screening arm, compared to control with mild gender variation: 29% reduction in women and 13% reduction in men. A meta-analysis pooling data from 8 RCTs calculated a relative risk of 0.88 (95%CI 0.79-0.97), suggesting a 12% reduction of lung cancer mortality in the screening versus control arm (Hunger et al, 2021).

The harms due to false-positive screening results may be minimal with some invasive investigations for benign disease but low complication rates (Balata et al. 2021; Hunger et al. 2020).

There are short-term psychosocial harms observed, due to involvement or suspicious results of screening, but these may resolve in the long run (Field et al. 2016; Hunger et al. 2020; Jonas et al. 2021; Pinsky 2014).

Four trials provided data on healthcare costs and estimates vary widely. Two trial-data based studies estimated costs per quality adjusted life year as £8,466 (95%CI £5516 to £12634) (Field et al. 2016) and $81,000 (95%CI $52,000 to $186,000) (Black et al. 2014).

Oesophageal cancer:

Four controlled trials based in China, found that endoscopic screening can improve the detection rate of oesophageal cancer, compared to the control group. Based on three study findings (He et al. 2019; Xiao et al. 2020; Zeng et al. 2020), the detection rate of high-grade lesions is in the range 0.7–0.3%. No data on mortality were identified.

Compliance rates were less than 50% across the four trials (Chen-Tao Guan 2018; He et al. 2019; Xiao et al. 2020; Zeng et al. 2020)

A single trial estimated the healthcare costs to detect one cancer/one early-stage cancer at $26,347 and $37,687 respectively (Li et al. 2019).

A single trial of biomarker-based screening in higher risk individuals in the United Kingdom has shown a promising effect on early diagnosis of Barrett's Oesophagus and subsequent cancer development (Fitzgerald et al., 2020a; Fitzgerald et al., 2020b; Swart et al., 2021).

Ovarian cancer:

No improvement of cancer mortality is observed in the screening arm compared to the control arm of trials overall. One study reported an improved survival of patients diagnosed with ovarian cancer in the screening arm compared to the control arm of the PLCO trial (RR 0.66; 95% CI 0.47-0.93) (Lai et al., 2016). However, no improvement in terms of ovarian cancer or all-cause mortality was observed across all RCTs examined, regardless of the screening protocols (Henderson et al., 2018). The false positive rate ranges from psychosocial harms are minor for screening *per se,* unless high-level repeat screenings are required (Andersen et al. 2007; Barrett et al. 2014; Fallowfield et al. 2017).

A single trial provided data on healthcare costs with an estimate of £46,922 per QALY (Menon et al. 2017).

Prostate cancer:

Screening via low threshold prostate specific antigen (PSA) results in a small reduction in prostate cancer/all-cause mortality. A meta-analysis of five RCTs estimated an incidence rate ratio of 0.96 (95% CI 0.85–1.08) at 10 years (Ilic et al. 2018). This equates to one prostate cancer death fewer per 1000 men screened over 10 years.

Any mortality benefit tends to be balanced against overdiagnosis and overtreatment of low-risk disease. One study estimated that for every prostate cancer death saved by screening 1000 men over 10 years, approximately 1, 3, and 25 more men would experience biopsy- and treatment-related sepsis, urinary incontinence, and erectile dysfunction, respectively (Ilic et al. 2018).

Longer follow-up is required to fully evaluate real-world costs. Two trial-based studies modelled costs of €54,918 (Karlsson et al. 2021) and $73,000 (Heijnsdijk et al. 2021) per QALY gained.

One trial suggests that using MRI scanning to indicate biopsy may reduce the risk of overdiagnosis in men with abnormal PSA (Nordström et al. 2021) and the authors are aware that trials are ongoing to look at risk adapted screening with MRI.[4]

3. Discussion

3.1 Summary

This rapid review provides evidence for the efficacy of a number of screening regimens, based on the findings of controlled trials (Section 2.2).

Although not within the remit of this review, since no controlled trial evidence was identified, we are aware that a number of related strategies are being considered within the research community. Firstly, the eradication of Helicobacter pylori as an alternative 'screen and treat' strategy for prevention of gastric cancer. This is currently the subject of at least two randomised controlled trials (see Annex A). Secondly, the use of risk stratification algorithms as a way of refining prostate cancer PSA screening to reduce potential harms. These are both discussed in the workshop report (available on SAPEA website).

It is of interest to note the recommendations of guidance documents published this year on lung and prostate cancer screening:
The US Preventive Services Task Force (USPSTF) recommendation statement for 2021 states that *"The USPSTF recommends annual screening for lung cancer with LDCT in adults aged 50 to 80 years who have a 20 pack-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued once a person has not smoked for 15 years"*.[5]

Authors of this review are aware of a number of trials in Europe, the USA, UK, China and Iraq are ongoing to explore a more personalised approach to lung cancer screening[6].

The European Association of Urology (EAU) position and recommendations for 2021 states that "*The EAU has developed a risk-adapted early prostate cancer detection strategy for well-informed men*

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[4] These include: Tampere et al (2022) https://ClinicalTrials.gov/show/NCT03423303; UROONCO [web page 2022] https://prostate.uroonco.uroweb.org/video/barentsz-trial-bi-parametric-mri-versus-multi-parametric-mri-2/

[5] Force, U.P.S.T., *Screening for Lung Cancer. US Preventive Services Task Force Recommendation Statement.* JAMA, 2021. **325**: p. 962-970 DOI: http://dx.doi.org/10.1001/jama.2021.1117

[6] These include: Crosbie et al (2020) http://dx.doi.org/10.1136/bmjopen-2020-037075 ; Hannover et al. (2022)June https://ClinicalTrials.gov/show/NCT04913155; National Jewish Health (2020) https://ClinicalTrials.gov/show/NCT01700257; Oncology Teaching Hospital (2021) https://ClinicalTrials.gov/show/NCT04366661; Changzheng (2021) https://ClinicalTrials.gov/show/NCT03988322; Arnold et al (2016) https://ClinicalTrials.gov/show/NCT00596310; van der Aalst et al (2020) https://doi.org/10.1183/13993003.congress-2020.4171

based on PSA testing, risk calculators, and multiparametric magnetic resonance imaging, which can differentiate significant from insignificant prostate cancer. This approach largely avoids the overdiagnosis/overtreatment of men unlikely to experience disease-related symptoms during their lifetime and facilitates an early diagnosis of men with significant cancer to receive active treatment".[7]

A key issue in relation to the overall reach and impact of screening programmes in the general population is the overall measure of those willing to participate based on the screening offer. Within this rapid review, data giving the reported uptake (the % of the invited population agreeing to participate in the trial) and compliance rates (the % of the trial population screened and/or adherence to multiple screening rounds) are provided within the Evidence Tables (Section 2.1). Information on compliance only may over-estimate the true proportion likely to take up the screening offer in a real-life situation. This appears to be particularly true for lung cancer screening where, in the UKLS and Nelson lung cancer trials, only around 30% of potentially eligible subjects responded to the initial approach from the trial organisers and only around half of those volunteers found to be eligible for the trial agreed to be recruited[8]. Issues relating to screening uptake are discussed in detail in the workshop report (available on the SAPEA website).

3.2 Strengths and limitations of this Rapid Review

3.2.1 Strengths

This review summarises a valuable sub-set of the evidence base. It emphasises the findings from recent randomised and other controlled clinical trials, providing the evidence with the least potential for bias. Despite the very short time-period available for the review, a large number of trial reports have been included.

3.2.2 Limitations

In order to complete the review in a timely fashion a pragmatic and precise search strategy was employed. It is possible that further controlled trials would have been identified should there have been time for a detailed and sensitive systematic search. It is acknowledged that other types of non-trial evidence are relevant to the topic, notably 'real life' screening populations and modelling studies derived from trials and other screening cohorts.

The timeline also precluded any statistical or meta-analysis of findings unless these were available from published systematic reviews. Barriers and facilitators to screening uptake relating to socio-economic factors were not explored. No formal critical appraisal was carried out although information is provided on whether the trial included a power calculation. Data extraction and summary were undertaken by different reviewers and, although reviewed by another author, these have not been independently checked for accuracy and consistency.

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[8] Baldwin DR et al. Participation in lung cancer screening. Translational Lung Cancer Research 2021; 10(2): 1091-1098 http://dx.doi.org/10.21037/tlcr-20-917

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5. Rapid review method

5.1 Eligibility criteria

- Randomised controlled trial (RCT) or controlled clinical trial[9]
- Published during or after 2007
- Screening for first diagnosis of lung, gastric, prostate, ovarian or (o)esophageal cancers
- Inclusion of data on efficacy, harm-benefit or cost-effectiveness
- All locations, all languages

5.2 Literature search strategy

Searches were carried out for publications from 2016 onwards using title and Medical Subject Heading (MeSH) searches of the Cochrane Central Register of Controlled Trials (CCTR). This includes trial data from Medline, Embase and the International Clinical Trials Registry Platform (ICTRP). Supplementary searching of Medline, Embase and the ICTRP was carried out for publications in 2021 that may not yet have been included in the CCTR.

To ensure coverage of trial reports back to 2007, Cochrane Reviews, Health Technology Assessment and the US Preventive Services Taskforce (USPSTF) was searched for systematic reviews on the topics. These were then examined for relevant trial reports.

Text word terms: [lung OR pulmonary OR stomach OR gastric OR prostat* OR ovar* OR esophag* OR oesophag*] *in Record Title* AND [cancer* OR neoplasm*] *in Record Title* AND screen* *in Record Title*

MeSH terms: (exp[10] lung neoplasms OR stomach neoplasms OR exp prostatic neoplasms OR exp ovarian neoplasms OR exp esophageal neoplasms) AND (early detection of cancer)

Additional search methods: The screened results were provided to the co-chairs of the Expert Workshop who were asked to liaise with workshop attendees and the workshop on the topic was attended by one of the review authors to note any additional studies meeting the inclusion criteria.

5.3 Resources list

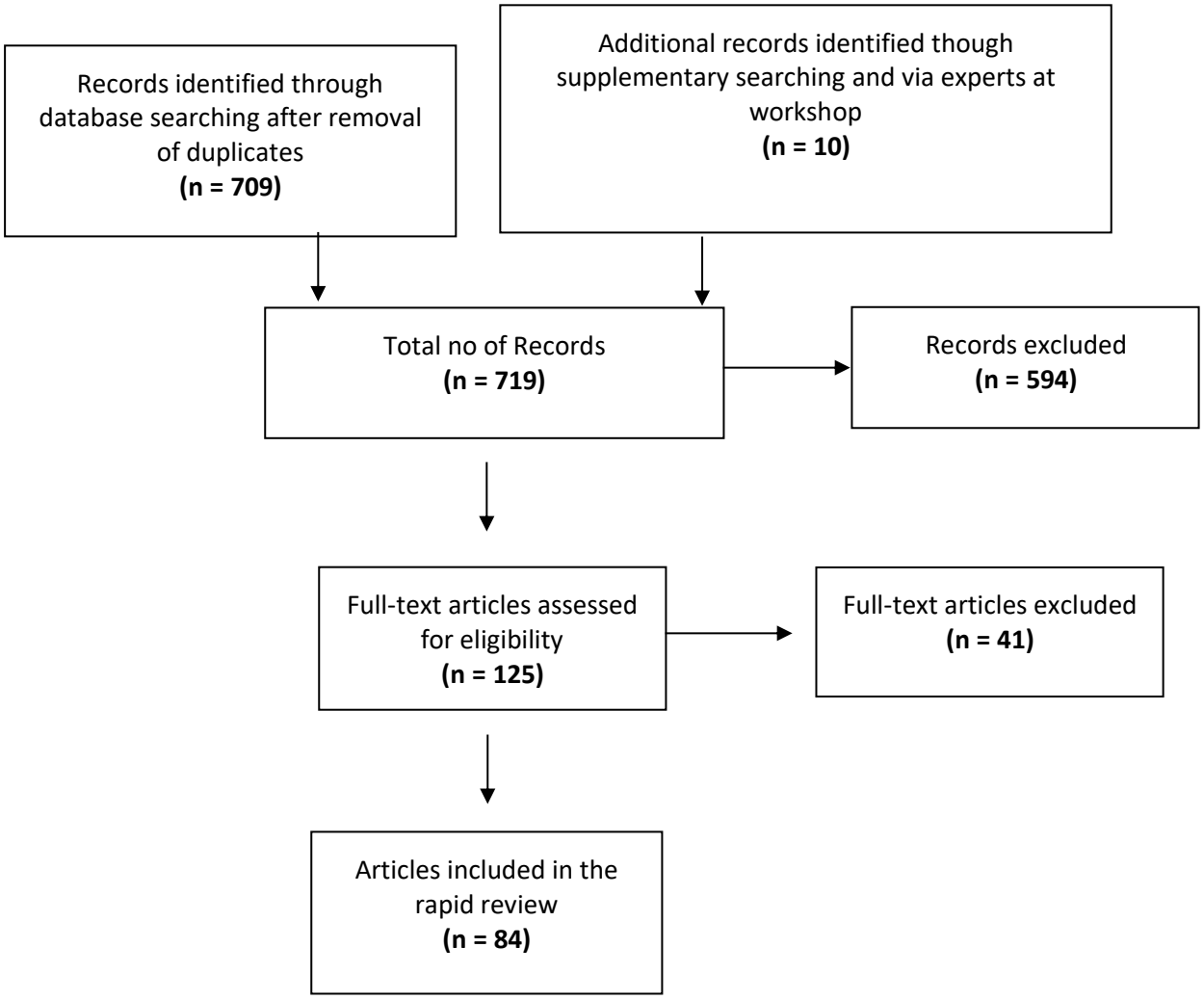
Clinical trials.gov
Cochrane Library [Cochrane Reviews/Cochrane Central Register of Controlled trials]
Health Technology Assessment
Embase
International Clinical Trials Registry Platform (ICTRP)
Medline
US Preventive Services Taskforce (USPSTF)

[9] Quasi-randomised and other controlled trials where randomisation is not explicit, but cannot be ruled out
[10] The exp (explode) function directs the selection of all papers tagged with this heading and any more specific sub-headings.

5.4 Study selection process

Results from the literature searches were imported into EndNote 20, where duplicates were removed. Titles and abstracts were screened for inclusion followed by full text screening. Both screening stages were undertaken by a team of reviewers according to the eligibility criteria in Section 5.1. Identified systematic reviews were examined for trials dating back to 2007.

5.5 Study selection flow chart



5.6 Data extraction

Data from main trial report(s) on efficacy, harm-benefit or cost effectiveness were extracted into a summary table for each cancer by a single reviewer with checking by a second reviewer (Section 2.1).

5.7 Quality appraisal

Each included study was identified as RCT or controlled clinical trial (CCT) according to the study design as provided in the database(s) within the evidence table (Section 2.1) along with a note as to whether a power calculation was included as part of the trial. No other formal critical appraisal was carried out.

5.8 Synthesis

The findings are summarised in a narrative report, drawing from the summary tables with brief findings based on the consensus from the included studies.

6. Additional information

6.1 Conflicts of interest

None

6.2 Acknowledgements

This template is based, with permission, on the rapid review template used within the Palliative Care Evidence Review Service (PaCERS) and the Welsh Covid 19 Evidence Centre.

7. About the review team

The Specialist Unit for Review Evidence (SURE) is a team of experienced systematic reviewers and information specialists at Cardiff University who conduct all forms of systematic and other evidence reviews, and teach evidence review methods. The team work across all topic areas and also specialise in health and social care. Staff have carried out a number of reviews for SAPEA, working closely with Academia Europaea and experienced reviewers within the University's Library Service. Reviews are carried out in close collaboration with subject specialists for each review topic. For these rapid reviews the subject specialists are Dr Hui-Ling Ou (Cambridge University) and Dr Nicholas Courtier (Cardiff University).

8. Brief reference lists on topics related to the rapid review

As agreed within the protocol for Rapid Review 1, some references identified during searching for the review were provided to workshop attendees where they related to additional questions of potential interest to the working group.

A specific search was not undertaken for each of these questions.

An EndNote file with full details of each publication is available from the authors of this rapid review.

A. Ongoing/unpublished clinical trials
B. Trials exploring smoking cessation as part of lung cancer screening programmes
C. Trials exploring decision making tools to assist patients with screening decisions
D. Cost-effectiveness or harm-benefit studies that are not explicitly linked to an included trial
E. Evidence-based screening guidelines published since 2016
F. Systematic reviews published since 2016 on implementation issues such as barriers to screening uptake

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