Evidence on Screening Efficacy in Randomized Trials & Effectiveness in United States Practice

Randomized trials of cancer screening in the general population demand heroic effort: typically recruiting 10,000 or more patients and following them for 10 or more years (the large sample size and lengthy follow-up requirements reflect the rarity of the primary outcome – death from the target cancer – in the general population). Not surprisingly, few have been performed.

The efficacy data from randomized trials are summarized below using two metrics. The first is more familiar: the relative reduction in the risk of death from the target cancer (screened vs. control). The second is less familiar: the absolute reduction in the risk of death: the risk of target cancer death in the control group minus the risk of death in the screened group at 10 years (the typical length of follow-up and the standard time frame for absolute risks throughout medicine, e.g. 10-year risk of cardiovascular disease). This metric provides insight into the actual magnitude of the benefit.

Randomized trials provide data on the efficacy of screening in a well-controlled, idealized setting – effectiveness in clinical practice may differ for a variety of reasons. Treatments may improve, diminishing the benefit of screening. Furthermore, the screening and management processes employed in the trial may not be replicated in clinical practice, fundamentally changing the intervention (e.g. expanded target population, lower diagnostic thresholds, new screening modalities, and more aggressive subsequent testing strategies).

Breast Cancer Screening

Efficacy in Randomized Trials

Meta-analysis of screening mammography 9 trials:

Age Group	Relative Reduction in Breast Cancer Mortality	Absolute Reduction* in Breast Cancer Mortality
39-49	12%	0.4 per 1000
50-59	14%	0.8 per 1000
60-69	33%	2.1 per 1000
70-74	20%	1.3 per 1000

Source: 2016 USPSTF Evidence Synthesis - https://www.ncbi.nlm.nih.gov/books/NBK343819/

* change in the 10-year risk of death

Effectiveness in US Practice

Because the randomized trials of mammography largely precede major advances in breast cancer treatment in the 1990s (adjuvant chemotherapy, hormonal therapy), the forgoing estimates likely exaggerate the current effect of mammography. Breast cancer mortality has declined substantially in the United States since 1990 (≈40%) – a decline observed both in women regularly screened (age 40+) and in those rarely exposed to screening (age < 40) – suggesting that the decline primarily reflects improved treatment, not screening. The advent of screening has had little effect on the incidence of late-stage disease and virtually no effect on the incidence of metastatic disease, suggesting that mammography has limited ability to advance the time of diagnosis of breast cancers destined to present as late-stage.

False positive mammograms are extremely common in US practice: estimates of the 10 year risk exceed 50%. The problem of overdiagnosis is substantial. The National Health Service estimates provides a lower bound estimate from their organized screening program in England: the

probability of overdiagnosis from mammography is 3 times that of avoiding a breast cancer death. Because screening is more intensive here (e.g. lower biopsy thresholds, more ultrasounds and MRIs), colleagues and I have argued that this ratio is closer to 10 to 1 in the United States.

Colorectal Cancer Screening

Efficacy in Randomized Trials

Meta-analysis of various screening modalities in randomized trials:

Modality	Relative Reduction in Colorectal Cancer Mortality	Absolute Reduction* in Colorectal Cancer Mortality
Flexible Sigmoidoscopy (4 trials)	26%	1.2 per 1000†
Fecal Occult Blood (5 trials)	24%	1 per 1000††
Colonoscopy (0 trials)	No RCT	No RCT

Source: 2021 USPSTF Evidence summary
https://uspreventiveservicestaskforce.org/uspstf/document/final-evidence-summary19/colorectal-cancer-screening
* change in the 10-year risk of death
† https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4399600/
†† https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009259.pub2/full

Effectiveness in US Practice

Both the incidence of metastatic colorectal cancer and colorectal cancer mortality have declined substantially in the United States – both have fallen by more than half since 1975 – suggesting a decline in true cancer occurrence. Although screening is typically credited for this decline, much of it precedes the widespread diffusion of screening. So screening can be only part of the explanation.

The most common US screening practice – colonoscopy – is both the least rigorously studied and the most expensive. Randomized trials of colonoscopy vs. FIT testing are ongoing in China, Spain and the US.

While false positive results are identifiable for stool testing, it is not clear what constitutes a false positive colonoscopy since it serves as its own gold standard. It is clear that cancer overdiagnosis is not a substantial problem for colonoscopy, but overdiagnosis of precursor lesions is extraordinarily common – and is, in fact, purposeful given the motivation to reduce incidence.

Prostate Cancer Screening

Efficacy in Randomized Trials:

Trial	Relative Reduction in Prostate Cancer Mortality	Absolute Reduction* in Prostate Cancer Mortality	Note
PLCO (US)	Not significant	Not significant	Because 46% of controls were screened, the PLCO should be viewed as a trial of organized vs. opportunistic screening
ERSPC (Europe)	21%	1.1 per 1000	

Source: 2018 USPSTF Evidence Synthesis - https://www.ncbi.nlm.nih.gov/books/NBK518890/
* change in the 10-year risk of death

Effectiveness in US Practice:
Prostate cancer mortality has declined substantially in the United States – it has fallen by more than one-third from the 1950-1970 baseline. Furthermore metastatic prostate cancer incidence has declined by 60%, suggesting that PSA does advance the time of diagnosis for cancers destined to become metastatic. Concerns about competing causes of death, however, are particularly relevant in prostate cancer as the median age of death (80 years) is 8 years older than in colon cancer (72 years) and 12 years older than in breast cancer (68 years). The combination of a high burden of competing risks for death and high rates of intervention-related complications conspires to limit any reduction in all-cause mortality offered by screening (the RR for death from all-causes was 1.0 in the ERSPC)

Because of PSA screening, the harms of cancer screening became more broadly understood by clinicians and the public. The rapid uptake of PSA ("a simple blood test") and the substantial autopsy reservoir of prostate cancer combined to produce a dramatic spike in prostate cancer incidence – and made the term "overdiagnosis" familiar to both clinicians and their patients. Furthermore, screening sensitized physicians to both the harms of prostate biopsy (bleeding, infection and excess hospitalization) and prostate cancer treatment (impotence, incontinence and radiation proctitis).

Lung Cancer Screening

There have been multiple randomized trials of lung cancer screening, but not in the general population. Instead, lung cancer screening has typically targeted the exceptional high-risk group with a history of heavy cigarette smoking. It is hard to imagine conditions more favorable to screening: lung cancer is the most common cause of cancer death, treatment for late-stage disease is largely ineffective and the portion of the population at substantially elevated risk is easily identifiable.

Screening chest X-rays were found in the 1980s to have no effect – or, in fact, found to be harmful. The two major trials of screening chest CTs found reductions in lung cancer mortality of 15% and 25%.

Other Cancers

Randomized trials of ovarian cancer screening found no effect on ovarian cancer mortality, but substantial increases in the risk of undergoing surgery for a false positive result.

No randomized trials have been performed of screening for thyroid, bladder, skin or cervical cancer (the reduction of cervical cancer mortality observed in countries initiating screening was sufficiently large that randomized trials were never performed). Observational data suggest that the primary effect of early detection in thyroid cancer and melanoma is increased incidence, overdiagnosis, and unchanged mortality.