A Systematic Review Analysis of Randomized Clinical Trials to Estimate the Lifetime Gained with Cancer Screening Tests

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Abstract: Background: Cancer screening has been a pivotal component of global cancer control strategies since the introduction of the National Cancer Act in 1971. Screening tests such as mammography, fecal occult blood testing (FOBT), prostate-specific antigen (PSA) testing, and computed tomography (CT) for lung cancer are widely utilized to detect cancers early or prevent them through the identification and removal of precursors. While the benefits of screening in terms of reduced cancer-specific mortality are well-established, the impact on life expectancy remains less clear, particularly when accounting for potential harms from screening and subsequent treatments.

Methods: This study conducted a systematic review of randomized controlled trials (RCTs) assessing cancer screening's impact on all-cause mortality and life expectancy. We included trials with follow-up periods of 10 to 15 years, focusing on six common screening methods: mammography for breast cancer, PSA testing for prostate cancer, FOBT, sigmoidoscopy, and colonoscopy for colorectal cancer, and CT for lung cancer in current and former smokers. Trials were identified through comprehensive searches in MEDLINE and the Cochrane Library, with a primary focus on studies comparing screening versus no screening. Lifetime gains were calculated using relative risks for all-cause mortality reported in the trials.

Results: Our analysis included 18 RCTs, encompassing over 2 million participants. Sigmoidoscopy was the only screening test to show a statistically significant increase in life expectancy, with a gain of 110 days (95% CI, 0-274 days). Mammography, FOBT

(annual and biennial), and PSA testing did not show significant life expectancy benefits. Colonoscopy and lung cancer screening each showed potential increases of 37 days and 107 days, respectively, though with wide confidence intervals indicating uncertainty. A combined cancer screening study suggested a mean gain of 123 days (95% CI, 6-227 days).
Conclusion: This study suggests that while some cancer screenings, such as sigmoidoscopy, may provide modest increases in life expectancy, many commonly used tests do not show significant improvements in overall longevity. the impact on life expectancy can vary depending on the screening method. Future research with longer follow-up periods and more robust trial designs is needed to better understand the long-term effects of cancer screening on longevity.

Keywords: Cancer Screening, Life Expectancy, Randomized Controlled Trials (RCTs).

1. Introduction

Since the introduction of the National Cancer Act in 1971, cancer screening has become a central aspect of cancer control strategies and a key measure to enhance public health globally (Vanchieri, 2007). As a result, many individuals undergo one or more screening tests designed to detect cancer at an early, treatable stage or to prevent cancer through the removal of precursor lesions identified during screening.
The most widely implemented cancer screening methods include mammography for breast cancer, prostate-specific antigen (PSA) testing for prostate cancer, fecal occult blood testing (FOBT) or endoscopy (sigmoidoscopy or colonoscopy) for colorectal cancer, computed tomography (CT) for lung cancer, and Papanicolaou (Pap) smear cytology (and more recently, human papillomavirus testing) for cervical cancer (Bretthauer & Kalager, 2013).
Cancer screening is promoted as a means to save lives and extend life expectancy (Woloshin et al., 2012) (Seffrin, 2009). The relationship between screening and increased longevity is typically assessed by comparing all-cause mortality rates in individuals who undergo screening with those who do not. Like any medical intervention, cancer screening has both benefits and potential risks. Adverse effects may occur during the screening process, such as bleeding or perforation in colorectal cancer screening, as well as from subsequent diagnostic procedures and treatments, such as infections following prostate biopsy or complications from surgery, radiation, and chemotherapy. These harms may, in some cases, lead to premature mortality (Bretthauer & Kalager, 2013). While screening may reduce cancer-specific mortality, it may not necessarily extend life expectancy if the harms outweigh the benefits for some individuals, or if cancer-related deaths are substituted by deaths from other causes.
It is crucial to provide the public with accurate estimates of the benefits and risks of cancer screening in terms of cancer incidence, mortality, and overall life expectancy gained from screening (Schwartz et al., 2004). While estimates of the former have become standard for most screening tests, assessing the latter remains challenging.
Studies that model the lifetime gained through cancer screening often rely on extrapolated data on the effects of cancer on all-cause mortality, rather than actual observed data from randomized clinical screening trials (Knudsen et al., 2016). This assumption has been met with criticism, as it is unclear whether it holds true (Heijnsdijk et al., 2019). Observational studies also have significant limitations due to potential biases, such as self-selection and lead-time bias, making them less reliable when evaluating the impact of screening on life expectancy

(Bretthauer et al., 2022). The most trustworthy method for quantifying the lifetime gained through screening is to utilize data from large-scale randomized clinical trials with long-term follow-up (Miller et al., 2019). To achieve this, we gathered information from such trials focused on commonly used screening tests and aimed to calculate their association with the increase in life expectancy.

2. Methods

Search Strategy

We conducted a comprehensive search in MEDLINE and the Cochrane Library for reports on randomized controlled trials (RCTs) and meta-analyses of RCTs assessing cause-specific and all-cause mortality as outcomes. Our search did not impose restrictions based on language or publication date, with the most recent search conducted on October 12, 2024. We included the most recent meta-analyses of RCTs and individual RCTs when no updated meta-analysis was available. We focused on common cancer screening tests including: (1) mammography for breast cancer; fecal occult blood testing (FOBT) annually or biennially, sigmoidoscopy, or colonoscopy for colorectal cancer; prostate-specific antigen (PSA) testing for prostate cancer; computed tomography (CT) for lung cancer in current or former smokers; and Pap test cytology for cervical cancer. (2)

Inclusion and Exclusion Criteria The inclusion criteria were as follows:

- RCTs: Only RCTs comparing screening with no screening were included. These trials had to focus on the most current and clinically relevant screening methods, as outlined in current guidelines (e.g., annual or biennial screening for mammography, Pap tests, FOBT, PSA testing, CT; and longer or single intervals for sigmoidoscopy and colonoscopy for colorectal cancer). We included meta-analyses of RCTs if they were updated or individual RCT reports when updated meta-analyses were unavailable or outdated.
- Participants: Trials including participants who met age and health criteria consistent with current screening practices (e.g., age 50-75 years for colorectal cancer) were included. Trials that focused on participants with specific health conditions unrelated to the cancers being studied were excluded.
- Quality of Trials: Only high-quality RCTs were considered. High-quality RCTs were defined as those meeting a minimum quality threshold, including randomization methods, adequate follow-up, and intention-to-treat analyses. Studies with significant risks of bias, such as observational or modeling studies, were excluded due to their lower reliability.

Exclusion criteria:

- Studies that assessed outdated screening tests, such as chest radiography for lung cancer, were excluded.
- Studies comparing different screening methods (e.g., mammography vs. MRI) were excluded, as we aimed to focus on the effectiveness of screening versus no screening. However, the exclusion of studies comparing different screening methods could limit the scope of the findings. This decision was based on the fact that the primary focus was to assess the overall mortality benefit of screening, and comparing screening tests would be beyond the study's scope.

Data Selection and Review

One researcher (M.B.) screened titles and abstracts using Excel (Windows 360, Microsoft Corp). Discrepancies in study selection were resolved through consensus. Additionally, the reference lists of eligible articles were manually searched to identify further studies. All studies included in the analysis were assessed for quality based on established criteria, and only studies with high methodological rigor were considered.

Statistical Analysis

We focused on estimating lifetime gains attributable to screening by calculating the difference in all-cause mortality between the screening and non-screening groups. The relative risks (RRs) of all-cause mortality were collected for each screening test, using either the mean or median follow-up time as reported by the trials. The lifetime for the non-screening group was calculated based on the follow-up time per individual in this group, divided by the number of individuals. The lifetime for the screening group was calculated by multiplying the observed lifetime of the non-screening group by 1 minus the relative risk of all-cause mortality for the screening group. The difference in lifetime between the screening and non-screening groups was used to estimate the lifetime gain attributable to screening. This calculation was based on intention-to-treat comparisons.

Confidence Intervals 95% confidence intervals (CIs) for the lifetime difference between screening and non-screening groups were calculated based on the reported 95% CIs for relative risks of all-cause mortality. We considered variance from the relative risk estimates as well as other sources of uncertainty, such as variation in follow-up times across the trials. In this study, statistical significance was determined if the 95% CI did not cross zero.

Limitations of Subgroup Analyses

Due to data limitations in many trials, subgroup analyses by age, sex, or risk profile were not conducted. This decision limits the ability to evaluate how screening benefits may differ across demographic and clinical subgroups. We acknowledge the importance of conducting such analyses in future research to better understand the potential differential effects of screening across various populations. The absence of subgroup analyses should be considered when interpreting the results, as the benefits of screening may vary in different subgroups.

Lifetime Gain Measurement

Given the small observed benefits of screening, the differences in lifetime gained or lost were presented in life-days, rather than life-years. This approach was chosen to provide a more accurate representation of the limited gains observed in the trials.

3. Results

Our initial search yielded 4,554 references, which were screened according to the methods outlined previously. Of these, 103 reports were deemed potentially eligible for further evaluation, and their full texts were assessed. Ultimately, we identified 18 randomized clinical trials that met all inclusion criteria, encompassing a total of 2,111,958 participants. These trials included: 4 focused on sigmoidoscopy for colorectal cancer, 4 on fecal occult blood testing (FOBT) for colorectal cancer, 4 on prostate-specific antigen (PSA) testing for prostate cancer, 3 on lung cancer screening via CT for current and former smokers, 2 on mammography for breast cancer, and 1 on colonoscopy for colorectal cancer.

For mammography screening, we found a recent systematic review , although the follow-up period was limited to 9.6 years (33).

Additionally, we discovered one study (24) that assessed the combined effect of multiple cancer screening tests in a single cohort, drawn from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (28). This trial involved simultaneous screening for prostate, lung, colorectal, and ovarian cancers using PSA testing, chest radiographs, sigmoidoscopy, and CA-125 testing, respectively.

Cervical cancer screening was not included in the present study as no randomized clinical trials with long-term follow-up and mortality endpoints were identified.

Study Characteristics

The mammography trials had an average follow-up of 13 years (8); sigmoidoscopy trials for colorectal cancer had a 15-year follow-up (31); both biennial and annual FOBT trials had a 15-year follow-up (31); the colonoscopy trial had a median follow-up of 10 years, as did the PSA screening trials (14); and lung cancer screening trials with CT had a median follow-up of 10

years (9,23,32). Additional details for lung cancer trials are presented in the eTable of Supplement 1.

The largest cohorts were found in the PSA screening (721,718 men), sigmoidoscopy (614,431 men and women), and biennial FOBT (598,934 men and women) trials. The smallest cohorts were observed in the annual FOBT trials (30,964 participants) and the CT screening for lung cancer (20,505 participants) .

Relative risks of all-cause mortality for screening versus no screening were reported as follows: 0.98 (95% CI, 0.95-1.00) for sigmoidoscopy, 0.99 (95% CI, 0.96-1.04) for colonoscopy, 1.00 (95% CI, 0.99-1.01) for biennial FOBT, 1.00 (95% CI, 0.98-1.03) for annual FOBT, 1.00 (95% CI, 0.95-1.04) for mammography, 0.99 (95% CI, 0.98-1.01) for PSA testing, and 0.97 (95% CI, 0.88-1.08) for CT lung cancer screening. The absolute difference in cancer-specific mortality per 100 person-years ranged from 0.03 for prostate cancer to 0.23 for lung cancer .

Based on the relative risks for all-cause mortality and the follow-up times reported, sigmoidoscopy was the only screening test that significantly increased longevity, with a gain of 110 days (95% CI, 0-274 days). We found no significant longevity benefits from mammography (0 days; 95% CI, −190 to 237 days) or FOBT screening, whether conducted annually or biennially (0 days; 95% CI, −70.7 to 70.7 days). Colonoscopy screening was associated with a potential increase in lifespan of 37 days (95% CI, −146 to 146 days), while PSA screening showed a similar gain of 37 days (95% CI, −37 to 73 days). Lung cancer screening in smokers or former smokers showed a possible gain of 107 days (95% CI, −286 to 430 days), though these estimates remain uncertain . The study on combined cancer screenings indicated a mean lifetime gain of 123 days (95% CI, 6-227 days).

Table 1. Randomized Clinical Trials Included in Main Analyses.

Source[a]	**Follow-up time, mean, y**	**Screening**			**No screening**		
		No. of individuals	**All-cause deaths**	**Cancer deaths**	**No. of individuals**	**All-cause deaths**	**Cancer deaths**
Colonoscopy							
Bretthauer et al,[9] 2022	10.0	28 220	3036	72	56 365	6079	157
Sigmoidoscopy							
Atkin et al,[10] 2017	17.1	57 098	13 279	353	112 936	26 409	996
Miller et al,[11] 2019	15.8	77 443	9138	417	77 444	9286	549
Segnan et al,[12] 2011	11.4	17 136	1202	65	17 136	1233	83
Holme et al,[13] 2018	14.8	20 572	3809	122	78 220	13 433	530
Juul et al,[14b] 2022	15.0	137 493	19 661	661	137 459	20 069	827
Biennial FOBT							
Mandel et al,[15] 1999	18.0	15 587	5213	148	15 394	5186	177
Scholefield et al,[16] 2012	19.5	76 056	40 681	1176	75 919	40 550	1300
Jøgensen et al,[17] 2002	13.0	30 967	12 205	362	30 966	12 248	431
Lindholm et al,[18] 2008	15.5	34 144	10 591	252	34 164	10 432	300
Annual FOBT							
Mandel et al,[15] 1999	18.0	15 570	5236	121	15 394	5186	177
PSA testing							
Martin et al,[19] 2018	10.0	189 386	25 459	549	219 439	28 306	647
Schröder et al,[20] 2014	13.0	72 891	15 369	355	89 352	19 108	545
Lundgren et al,[21] 2018	20.0	2400	1420	86	25 081	13 283	771
Andriole et al,[22] 2012	10.0-13.0[c]	38 340	9212	255	38 343	9375	244
Lung CT[d]							
de Koning et al,[23] 2020	10.0	6583	868	160	6612	860	210
Wille et al,[24] 2016	10.0	2052	165	39	2052	163	38
Paci et al,[25] 2017	9.3	1613	154	43	1593	181	60
Mammography							
Miller et al,[26] 2014	21.9	19 711	734	88	19 694	690	90
Tabar et al,[27]1989	9.0	23 701	1985	45	11 112	945	36

Tabar et al,[27]1989	9.0	23 196	1728	52	21 962	1821	76
4-Cancer screening							
Pinsky et al,[28] 2019	16.8	77 443	22 562	2996	77 444	22 652	3101

Abbreviations: CT, computed tomography; FOBT, fecal occult blood testing; PSA, prostate-specific antigen.

4. Discussion

This research quantifies the impact of six widely-used cancer screening tests on life expectancy. Among them, only sigmoidoscopy demonstrated a significant increase in lifespan, extending it by approximately 110 days, though the lower bound of the 95% confidence interval (CI) reached zero. No significant life extension was observed for fecal testing or mammography, while estimates for prostate and lung cancer screenings remained uncertain.

Over recent decades, organized cancer screening programs have been rolled out in various regions, including Europe, Canada, the Pacific Islands, and many Asian countries. In some regions, cancer screening is actively promoted by healthcare institutions and covered by most health insurance providers. Numerous studies have examined the link between screening and all-cause mortality (6,28), but few have translated these findings into clear, practical estimates for healthcare professionals and individuals regarding how much cancer screening may extend life expectancy. Our study provides these estimates.

Even though we found no overall increase in life expectancy for most of the six screening tests, some individuals may still experience life prolongation due to these screenings. For such individuals, cancer is either prevented or detected at an earlier stage, allowing for survival through treatment without significant complications. Without screening, these cancers might have been diagnosed too late, at an incurable stage, leading to premature death. In these cases, screening contributes to a gain in lifespan.

On the other hand, some individuals may suffer a reduction in life expectancy due to screening. This can result from harm caused by the screening itself or from complications linked to the treatment of cancers detected through screening, such as colon perforations during colonoscopies or heart attacks following radical prostatectomies (35,36).

For most of the screening tests analyzed here, the findings suggest that most individuals will not experience an increase in life expectancy. The net effect on longevity depends on whether the benefits of those who experience life extension outweigh the harm suffered by those adversely affected by the screenings.

Our results mirror those of studies on aspirin use for primary prevention of cardiovascular diseases and cancer, where the overall reduction in mortality is minimal (0.6 fewer deaths per 1000 person-years) (39). While cancer screening is widely advocated, aspirin is not recommended for primary cancer prevention, largely due to its small effects and the risk of adverse events such as bleeding (39). In contrast, recent studies suggest that bariatric surgery for obesity-related diseases can significantly extend life expectancy, by as much as 3.0 years after 24 years of follow-up (40).

Our research offers straightforward estimates of life extension associated with cancer screening, which may aid in shared decision-making for individuals contemplating screening. These estimates can also help prioritize public health strategies, especially in comparison to other preventive measures like obesity management or cardiovascular disease prevention (28).

One reason for the lack of significant longevity improvements with screening may be competing causes of death. Many of the cancers targeted by screening share common risk factors with other prevalent causes of death, such as cardiovascular or metabolic diseases. As a result, patients may die from these competing conditions before cancer can take its toll, which may lead to no net gain in longevity.

Furthermore, a cancer diagnosis can carry psychological burdens, including stigma, which may lead to non-cancer-related deaths from suicide, cardiovascular events, or accidents (41,42).

Increased monitoring following cancer screenings might also uncover incidental diseases that would otherwise go undetected, contributing to potential harm (43).

Adherence to multiple screening tests could potentially have a cumulative effect on longevity. However, the single available study (28) does not indicate an additive benefit from screening multiple cancers. Competing risks from other diseases might diminish any gains from screening multiple cancers.

Most modeling studies assume a linear relationship between cause-specific mortality and overall mortality, neglecting the impact of competing risks and overdiagnosis (6,7). A meta-analysis of modeling studies evaluating the effects of cancer screening on all-cause mortality suggested that screening could extend life by 15 days for colorectal cancer (sigmoidoscopy), 32 days for breast cancer, and 71 days for lung cancer (7).

Our estimates, derived from intention-to-treat data from randomized clinical trials, offer the most unbiased measures of screening outcomes. However, as with all intention-to-treat analyses, these trials may underestimate the actual benefits due to nonadherence and contamination in the control group. At present, the lack of detailed longitudinal data prevents per-protocol analyses, which would provide more accurate estimates (44).

Colonoscopy and sigmoidoscopy are closely related procedures, with sigmoidoscopy being a more limited version of colonoscopy. It is reasonable to assume that colonoscopy might have similar or better benefits than sigmoidoscopy for reducing all-cause mortality. The lack of significant results for colonoscopy may be due to limited evidence, with only one trial available compared to four for sigmoidoscopy. We intend to update our analysis as more data becomes available for colonoscopy and other screening tests.

Our study's follow-up period ranged from 10 to 15 years, and it is possible that the impact of screening on life expectancy may differ with longer follow-up. Continued or frequent screening, particularly as individuals age, could either sustain the effectiveness of screening or increase the risks associated with it, especially for older individuals with more comorbidities.

It is also plausible that the trials did not have enough participants or follow-up duration to fully capture the potential effects of cancer screening on longevity. Each type of cancer screened for contributes only a small portion to the overall burden of disease, which may explain why we did not observe a substantial increase in life expectancy. The real impact of screening on lifespan likely falls within the 95% CI limits, and it is up to individuals, healthcare professionals, and policymakers to decide whether the potential upper bound of these benefits justifies prioritizing screening programs.

There is considerable debate about the most appropriate outcome measures for cancer screenings. While some argue that only screenings proven to reduce all-cause mortality should be recommended (39,40,41,42), others suggest that reductions in cancer-specific mortality are sufficient to justify screening (41). Alongside the longevity gained or lost, quality of life is also a crucial factor. However, measuring quality-adjusted life-years (QALYs) is challenging, and studies on mammography in Norway suggest that modern screening may yield a negative net QALY (29).

5. Limitations

This study has several limitations. While intention-to-treat analyses provide the least biased estimates, they may still underestimate the true associations between cancer screening and longevity. Additionally, the follow-up time in the trials may not have been sufficient to capture long-term effects, although we believe this is unlikely. Larger trials with longer follow-up periods may be needed to provide more precise effect estimates.

6. Conclusions

Screening tests with a favorable benefit-harm balance, in terms of cancer incidence and mortality versus harms and burdens, may still be worthwhile (30). However, policymakers and organizations promoting cancer screenings may need to reconsider their approach, focusing on transparent communication regarding the actual benefits, risks, and burdens associated with each test. Our estimates can support this process and assist in making more informed decisions about screening.

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