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Association of Nonadherence to Cancer Screening Examinations With Mortality From Unrelated Causes
A Secondary Analysis of the PLCO Cancer Screening Trial

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Supplemental content

IMPORTANCE Patient nonadherence to chronic disease prevention guidelines is associated with increased mortality. Nonadherence to offered cancer screening tests may be associated with mortality among middle-aged and older adults.

OBJECTIVE To evaluate the association between nonadherence to cancer screening tests and mortality in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening trial, excluding mortality from cancers studied in the trial.

DESIGN, SETTING, AND PARTICIPANTS Randomization at 10 US screening centers occurred from November 8, 1993, to July 2, 2001. Original follow-up was through 13 years or December 31, 2009. Participants were re-consented to further follow-up starting May 18, 2011, and were observed until December 31, 2012. Protocol screening tests for the PLCO Cancer Screening trial intervention arm participants (N = 77 443) included chest radiographs and flexible sigmoidoscopy for both sexes, prostate-specific antigen tests and digital rectal examinations for men, and cancer antigen 125 tests and transvaginal ultrasonography for women. At baseline, participants completed a self-administered questionnaire. The cohort was classified into those receiving all sex-specified PLCO Cancer Screening trial screening tests at baseline (fully adherent), those receiving some but not all baseline tests (partially adherent), and those receiving no baseline tests (nonadherents). Secondary analysis was ad hoc in the original trial protocol. Statistical analysis was conducted from November 24, 2017, to August 29, 2018.

MAIN OUTCOMES AND MEASURES Mortality was ascertained via mailed annual study update questionnaires and searches of the National Death Index. Cox proportional hazards regression was used to analyze the association between mortality and adherence, controlling for various covariates.

RESULTS Of 77 443 participants in the intervention arm, 64 567 (29 537 women and 35 030 men; mean [SD] age, 62.3 [5.3] years) were included in the analysis based on consenting to trial participation before randomization and being eligible for all screening tests. Overall, 55 065 participants (85.3%) were adherent, 2548 (3.9%) were partially adherent, and 6954 (10.8%) were nonadherent with the baseline screening protocol. Within 10 years of follow-up, the hazard ratio of mortality, excluding deaths from cancers studied in the PLCO Cancer Screening trial and controlling only for age, sex, and race/ethnicity (model 1), was 1.73 (95% CI, 1.60-1.89) for nonadherent compared with fully adherent participants and 1.36 (95% CI, 1.19-1.54) for partially compared with fully adherent participants. After adjustment for medical risk factors for mortality and behavioral-related factors (model 2), the hazard ratio decreased to 1.46 (95% CI, 1.34-1.59) for nonadherent compared with fully adherent participants.

CONCLUSIONS AND RELEVANCE Among participants in a screening trial for multiple cancers, a nonadherence behavior profile marked by nonadherence to protocol screenings was associated with higher overall mortality (excluding deaths from cancers studied in the trial). The generalizability of this finding to routine clinical practice should be assessed.

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Chronic disease is the leading cause of death and disability in the United States.[1] Poor nutrition, sedentary lifestyle, tobacco use, and excessive consumption of alcohol are the major modifiable risk factors for chronic diseases.[1] Adherence to chronic disease prevention guidelines for physical activity, obesity, diet, and alcohol consumption is low among Americans. In 2015, more than half of adults did not meet recommendations for physical activity and consumption of fruits and vegetables.[2] Previous studies have shown that nonadherence to chronic disease prevention guidelines for obesity, diet, physical activity, and consumption of alcohol were associated with higher all-cause mortality.[3-5]

Undergoing regular cancer screening and receiving timely treatment reduce cancer mortality,[6] but adherence to cancer screening guidelines are below targets set in the Healthy People 2020 initiative.[7] Nonadherence to chronic disease prevention guidelines has been found to be associated with nonadherence to cancer screening guidelines.[8,9] For example, lower levels of adherence to breast cancer screening guidelines have been reported among current and former smokers[9] as well as among obese women.[10] Moreover, women who did not have a usual source of care[11,12] or who underused preventive health services[8] had lower adherence to cervical cancer screening recommendations. Given the association of nonadherence to disease prevention guidelines and increased all-cause mortality, it is of interest to study the association of adherence to preventive health interventions and mortality.

The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening trial was a large trial of screening for these 4 types of cancers. The objective of this study was to evaluate the association between nonadherence to PLCO Cancer Screening trial tests and mortality, specifically, mortality unrelated to cancers studied in the PLCO Cancer Screening trial. Deaths from cancers studied in the PLCO Cancer Screening trial were excluded because we are trying to ascertain whether nonadherence to medical tests (ie, missing screenings for cancers studied in the trial) is associated with increased mortality from causes unrelated to diseases that the test is assessing. If so, this finding would indicate that there may be a behavioral pattern of nonadherence to medical tests, and possibly medical treatments, that is associated with increased overall mortality.

Key Points

Question Is nonadherence to medical tests, such as cancer screening, associated with mortality from unrelated causes?

Findings In this secondary analysis of 64 567 participants in the Prostate, Lung, Colorectal and Ovarian Cancer Screening trial, higher unrelated mortality was observed among participants who were nonadherent to baseline cancer screening tests. Although trial participants were healthy volunteers, compared with fully adherent participants, nonadherent participants experienced higher rates of mortality from unrelated causes.

Meaning A nonadherence behavior profile, marked by nonadherence to cancer screening tests, was associated with increased mortality among middle-aged and older adults.

Methods

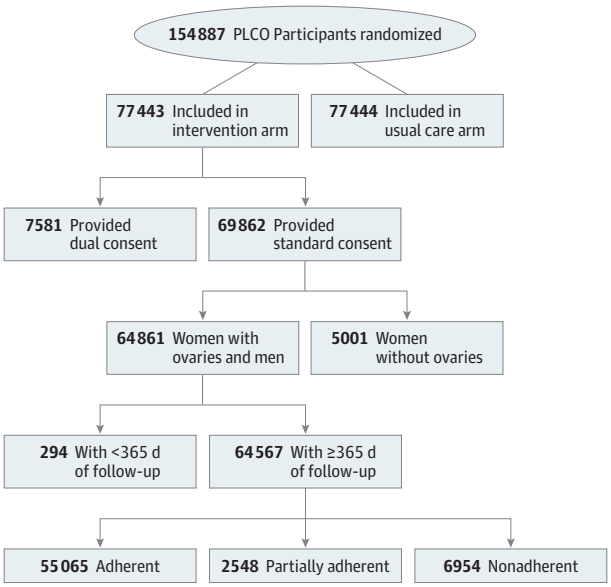
PLCO Cancer Screening Trial Design

The design and methods of the PLCO Cancer Screening trial have been described.[13,14] Briefly, randomization at 10 US screening centers of participants aged 55 to 74 years to either an intervention or control arm occurred from November 8, 1993, to July 2, 2001. Primary exclusion criteria were a history of a cancer being studied in the PLCO Cancer Screening trial, current receipt of cancer treatment, and, beginning in 1995, having had more than 1 prostate-specific antigen test or undergone a lower gastrointestinal tract endoscopy in the prior 3 years. At study entry, participants completed a self-administered baseline questionnaire that included demographics, general risk factors, and screening and medical histories. This secondary analysis of the PLCO Cancer Screening trial was ad hoc in the original trial protocol. The study was approved by the institutional review boards of the University of Alabama at Birmingham, Georgetown University, University of Pittsburgh, Washington University in St Louis, University of Utah, University of Colorado, University of Minnesota, Pacific Health Research and Education Institute, Henry Ford Health System, and Marshfield Clinic Research Foundation. All participants provided written informed consent.

Screening tests included chest radiographs and flexible sigmoidoscopy for both men and women, prostate-specific antigen and digital rectal examination for men, and cancer antigen 125 tests and transvaginal ultrasound for women. All tests except flexible sigmoidoscopy were performed annually, at baseline, and for 3 (transvaginal ultrasound, digital rectal examination, and chest radiographs) or 5 (prostate-specific antigen and cancer antigen 125) more years. Flexible sigmoidoscopy was performed at baseline and year 3 or 5. Participants and their physicians were notified in writing of any suspicious, abnormal results found on screening. The diagnostic process after positive results of the screening was managed by participants' primary care physicians and not dictated by the trial.

The original analysis period for the PLCO Cancer Screening trial was from randomization through 13 years of follow-up or December 31, 2009, whichever came first.[14] For this period, deaths were primarily ascertained through a mailed annual study update questionnaire, with next of kin notifying the trial of deaths, which were verified by obtaining death certificates; searches of the National Death Index were also used to ascertain deaths. Starting May 18, 2011, participants were re-consented to a centralized follow-up process involving mainly passive linkages with cancer registries and the National Death Index.[15] Participants re-consenting to further follow-up were linked to the National Death Index and were followed up for this analysis until December 31, 2012, or date of death, whichever came first. For those refusing further follow-up, because they had to actively refuse and thus were known to be alive at that time (generally from mid-2011 until mid-2012), their end of follow-up was their refusal date or December 31, 2012, whichever came first.

Figure 1. Flowchart of Analysis Cohort



To be included in the analysis cohort, participants had to be in the intervention arm, have provided standard informed consent, have ovaries (if women), and have at least 1 year of follow-up after randomization. Adherent participants underwent all baseline screening tests, partially adherent participants underwent some but not all screening tests, and nonadherent participants underwent no baseline screening tests. PLCO indicates the Prostate, Lung, Colorectal and Ovarian Cancer Screening trial.

Statistical Analysis

Statistical analysis was conducted from November 24, 2017, to August 29, 2018. The purpose of this analysis was to assess the association between adherence to baseline screening and subsequent mortality from causes unrelated to the screening. **Figure 1** shows the analysis cohort for this study. To reduce the likelihood of reverse causation bias, we excluded the minority of participants who had dual, as opposed to standard, consent. In standard consent, participants consented to trial participation and were then randomized. In contrast, in dual consent, participants provided initial consent for only the baseline questionnaire, followed by, for those so consenting, randomization into the trial and subsequent consent for screening. Since participants with dual consent did not initially consent to undergo screening, they could have had a prior condition preventing them from undergoing screening and also predisposing them to mortality, thereby inducing a reverse causation bias. In addition, women with no ovaries were also excluded; they may have had differential mortality owing to their ovary status and additionally differential adherence because they were offered fewer tests (they were not offered screening for ovarian cancer).

The cohort was divided into baseline fully adherent participants (adherents) who received all sex-specified screening tests for the PLCO Cancer Screening trial at baseline, partially adherent participants (partial adherents) who received some but not all baseline tests, and nonadherent participants (nonadherents) who received no tests at baseline.

To further reduce the possibility of reverse causation bias, follow-up for mortality began 1 year from randomization, and participants dying (or becoming lost to follow-up) within 1 year were excluded from the analysis. By definition, all baseline screening examinations had to be performed within 1 year; therefore, follow-up for this analysis began after baseline adherence status was already defined. Deaths from cancers studied in the PLCO Cancer Screening trial (prostate, lung, colorectal, and ovarian cancers) were excluded, with participants censored at the time of such deaths.

Mortality rates were computed as the number of deaths over person-years of follow-up. Cox proportional hazards regression models were used to analyze the association between mortality and adherence status, controlling for covariates. The base model (model 1) included only age (5-year groups), sex, and race/ethnicity (non-Hispanic white vs other) in addition to baseline adherence status. Model 2 included the above variables plus the following factors related to mortality risk or health behavior: cigarette smoking (never, former, or current), body mass index (BMI; calculated as weight in kilograms divided by height in meters squared: <18.5, 18.5-29.9, 30-34.9, and ≥35.0), marital status (married or living as married or not), educational level (college degree or not), and number of major comorbidities (0, 1, or ≥2). Major comorbidities were those included in the PLCO Cancer Screening trial modified Charlson Comorbidity Index score and included coronary heart disease or myocardial infarction, stroke, type 1 or 2 diabetes, history of cancer, chronic obstructive pulmonary disease, and liver disease (cirrhosis or hepatitis).[14] Models were run for various time periods from randomization through 15 years. Dummy variables for the above covariates were used to indicate unknown status. As a sensitivity analysis, a "complete case" analysis was performed in which only participants with no missing covariates were included in the models. To put the effect of adherence status in perspective, we also ran model 1 for a variety of behavioral and health status factors, controlling only for age, sex, and race/ethnicity. To assess whether the effect of adherence status varied by sex or age, we ran stratified analyses and tested for interactions of adherence status with age and sex.

The above models were also run for specific causes of death based on broad *International Classification of Diseases, Ninth Revision* categories. Participants dying of a different cause than the one of interest were censored at their date of death for these analyses. The regression models were created with SAS, version 9.4 (SAS Institute Inc).

Results

Figure 1 shows the eligibility criteria for this analysis, which resulted in 64 567 of 77 443 total intervention arm participants being included. Of the 64 567 participants, 35 030 were men and 29 537 were women, with a mean (SD) age of 62.3 (5.3) years. Demographic and other characteristics of full adherents (55 065 [85.3%]), partial adherents (2548 [3.9%]), and nonadherents (6954 [10.8%]) are shown in **Table 1**. Compared with full adherents, nonadherents were less likely to be male, non-

Table 1. Baseline Characteristics by Baseline Adherence Status[a]

Characteristic	Fully Adherent (n = 55 065)[b]	Partially Adherent (n = 2548)[b]	Nonadherent (n = 6954)[b]
Age, y			
55-59	19 562 (35.5)	884 (34.7)	2704 (38.8)
60-64	16 923 (30.7)	697 (27.4)	1947 (28.0)
65-69	11 874 (21.6)	591 (23.2)	1404 (20.2)
70-74	6706 (12.2)	376 (14.8)	899 (13.0)
Sex			
Male	30 500 (55.4)	1193 (46.8)	3337 (48.0)
Female	24 656 (44.6)	1355 (53.2)	3617 (52.0)
Marital status			
Married	42 651 (77.6)	1868 (74.0)	3664 (68.2)
Not married	12 266 (22.4)	657 (26.0)	1709 (31.8)
Unknown	148 (0.3)	23 (0.9)	1581 (22.7)
Body mass index[c]			
<18.5	333 (0.6)	25 (1.0)	73 (1.4)
18.5-29.9	40 947 (75.2)	1878 (75.1)	3888 (73.7)
30.0-34.9	9447 (17.4)	438 (17.6)	862 (16.3)
≥35.0	3698 (6.8)	158 (6.3)	456 (8.6)
Unknown	640 (1.2)	49 (1.9)	1675 (24.1)
Educational level			
No college degree	34 304 (62.5)	1596 (63.2)	3742 (69.6)
College degree	20 604 (37.5)	931 (36.8)	1631 (30.4)
Unknown	157 (0.3)	21 (0.8)	1581 (22.8)
Smoking			
Current	5631 (10.3)	309 (12.2)	811 (15.0)
Former	24 102 (43.9)	1111 (44.0)	2321 (43.0)
Never	25 228 (45.8)	1109 (43.8)	2226 (42.0)
Unknown	104 (0.2)	19 (0.7)	1556 (22.5)
Race/ethnicity			
Non-Hispanic white	49 971 (90.9)	2166 (85.7)	4575 (84.7)
Non-Hispanic black	2145 (3.9)	150 (5.9)	273 (5.1)
Hispanic	947 (1.7)	72 (2.9)	175 (3.2)
Asian	1516 (2.8)	113 (4.5)	277 (5.1)
Pacific Islander and American Indian	370 (0.7)	25 (1.0)	97 (1.8)
Unknown	116 (0.2)	22 (0.9)	1557 (22.4)
Comorbidities			
0	40 765 (74.1)	1764 (69.8)	3609 (66.7)
1	11 641 (21.2)	592 (23.4)	1383 (25.6)
≥2	2562 (4.7)	173 (6.8)	417 (7.7)
Unknown	97 (0.3)	19 (1.1)	1545 (23.2)

[a] Fully adherent indicates participants who received all sex-specified screening tests for the Prostate, Lung, Colorectal and Ovarian Cancer Screening trial at baseline; partially adherent, received some but not all baseline tests; nonadherent, received no tests at baseline.

[b] Data are given as number (percentage). Percentages for categories other than unknown exclude unknowns in the denominator.

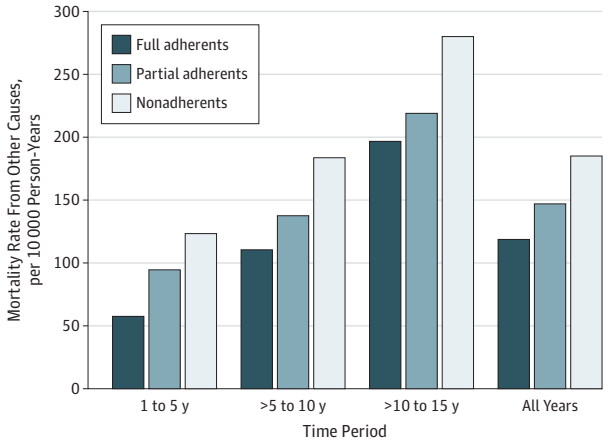
[c] Calculated as weight in kilograms divided by height in meters squared.

Hispanic white, college educated, and married and more likely to be a current smoker. Nonadherents had higher rates of missing covariate data (20%-25%) than the other groups (<2%). The median time from randomization to baseline screening among full adherents was 34 days (25th percentile, 21 days; 75th percentile, 56 days; and maximum, 332 days) and among partial adherents was 41 days (25th percentile, 25 days; 75th percentile, 69 days; and maximum, 330 days). Partial adherents completed a mean of 2.9 of 4 possible tests; 74% of partial adherents missed only sigmoidoscopy.

Through 15 years of follow-up, there were 7966 deaths (excluding those from PLCO Cancer Screening trial cancers) among the full adherents, 449 deaths among the partial adherents, and 1395 deaths among the nonadherents, giving mortality rates (per 10 000 person-years) of 116.3 for full adherents, 145.0 for partial adherents, and 168.3 for nonadherents. **Figure 2** shows mortality rates adjusted for age, sex, and race/ethnicity for these groups over various time periods. For each period, rates were lowest for full adherents and highest for nonadherents, with partial adherents intermediate.

Table 2 shows the results of the Cox proportional hazards regression models. Hazard ratios (HRs) for nonadherents (vs full adherents) were statistically significant at each time period (1-5, 1-10, and 1-15 years) for both model 1 and 2, with HRs

Figure 2. Mortality Rates by Time Period and Baseline Adherence Group



Deaths from cancers studied in the Prostate, Lung, Colorectal and Ovarian Cancer Screening trial are excluded. Rates are adjusted for age (5-year groups), sex, and race/ethnicity (non-Hispanic white vs other) according to the overall cohort distribution.

decreasing in magnitude with longer follow-up periods. Also, for each period, HRs were lower for the fully adjusted model (model 2) than for the base model (model 1, adjusting only for age, sex, and race/ethnicity). A similar pattern was observed for partial adherents, although HRs were uniformly lower. For follow-up through 10 years, the HR for nonadherents (compared with full adherents) was 1.73 (95% CI, 1.60-1.89) for model 1 and 1.46 (95% CI, 1.34-1.59) for model 2; for partial adherents (compared with full adherents), corresponding HRs were 1.36 (95% CI, 1.19-1.54) and 1.26 (95% CI, 1.11-1.46). Through 5, 10, and 15 years, the HR for nonadherents for model 1 decreased from 2.00 (95% CI, 1.74-2.29) to 1.73 (95% CI, 1.60-1.89) to 1.59 (95% CI, 1.49-1.69) and for model 2 decreased from 1.63 (95% CI, 1.41-1.87) to 1.46 (95% CI, 1.34-1.59) to 1.38 (95% CI, 1.30-1.47). Hazard ratios for nonadherents were similar in the complete case analysis: for example, in model 2, the HR for nonadherents at 5 years was 1.64 (95% CI, 1.42-1.90), at 10 years was 1.47 (95% CI, 1.35-1.60), and at 15 years was 1.38 (95% CI, 1.30-1.48).

The analysis of the interaction of nonadherence (vs full adherence) with sex showed no significant interaction for either model 1 or 2 for any time period. Stratified analyses showed generally similar HRs for nonadherence in men and women. For example, at 10 years, model 2 HRs were 1.60 (95% CI, 1.31-1.62) for men and 1.44 (95% CI, 1.25-1.65) for women. Similarly, there was no significant interaction of nonadherence with age. Stratified analyses showed generally similar HRs for nonadherence among those aged 55 to 64 years vs those aged 65 to 74 years. Within 10 years of follow-up, HRs for model 1 were 1.86 (95% CI, 1.65-2.10) for those aged 55 to 64 years and 1.63 (95% CI, 1.45-1.83) for those aged 65 to 74 years; model 2 HRs were 1.52 (95% CI, 1.35-1.72) for those aged 55 to 64 years and 1.40 (95% CI, 1.25-1.57) for those aged 65 to 74 years.

Comparing the HR for nonadherence to that of other risk factors through 10 years, presence of 2 or more comorbidities (HR, 4.22; 95% CI, 3.89-4.60) and 1 comorbidity (HR, 2.23; 95% CI, 2.12-2.41) vs no comorbidities, as well as current smoking (HR, 2.72; 95% CI, 2.56-3.03) vs never smoking had HRs greater than the HR for nonadherence (1.73; 95% CI, 1.60-1.89). Compared with a BMI of 18.5 to 29.9, a BMI of 35.0 or more had a similar HR (1.73; 95% CI, 1.57-1.93), and a BMI of 30.0 to 34.9 (HR, 1.30; 95% CI, 1.21-1.40) and former smoking (HR, 1.37; 95% CI, 1.28-1.46) had lower HRs.

Table 3 shows model results for specific causes of death. Through 10 years, deaths from respiratory diseases and digestive diseases had the highest HRs for full nonadherents in both model 1 and 2. In addition to respiratory and digestive diseases, the HR for nonadherents was significantly elevated in both models for cancer and cardiovascular diseases and was elevated in model 1 only for endocrine diseases. Results for different time periods showed a similar pattern, with respiratory and digestive diseases generally having the highest HRs (eTable in the Supplement).

Of the 6954 nonadherents, 6889 (99.1%) were eligible for all year 1 screening tests. Of these, 1599 (23.2%) received all screening tests and 5249 (76.2%) received no tests (41 [0.6%] received some, but not all, tests). In contrast, of the 55 065 full adherents, 53 921 (97.9%) were eligible for all year 1 screening tests, and, of these, 50 578 (93.8%) received all tests.

Discussion

In the present study, 9502 of 64 567 participants (14.7%) in the PLCO Cancer Screening trial intervention arm did not fully adhere to the protocol baseline screenings. We observed substantially higher overall mortality (excluding deaths from cancers studied in the trial) among partial adherents and especially among nonadherents compared with full adherents. Participants volunteered for the trial and were offered screening soon thereafter. Therefore, it was unlikely that participants had a preexisting condition that would both increase their mortality risk and preclude adherence to the screening protocol. After adjusting for medical risk factors for mortality such as smoking, BMI, and major comorbidities as well as marital status and educational level, the association remained significant, with an HR of around 1.5 through 10 years for nonadherents. The most cogent explanation for these findings is that nonadherence to protocol screenings was a marker for a general behavioral profile of nonadherence to medical tests and treatments and that this behavioral profile was associated with increased mortality.

Because deaths from cancers studied in the trial were excluded, nonadherence per se with the PLCO Cancer Screening trial screening tests likely had no, or at most very little, direct effect on the outcome being assessed in this study. Therefore, residual confounding with other unmeasured factors that are likely associated with a nonadherence profile must explain the bulk of the remaining excess risk shown in model 2. These factors could include the clustering of various nonadherence behaviors: nonadherence to cancer screening, chronic disease prevention guidelines, and medical tests and treatment. For example, nonadherence to breast and cervical cancer screening correlates with nonadherence to health pre-

Table 2. Cox Proportional Hazards Regression Model Results

Time Period and Adherence Status	Hazard Ratio (95% CI)	
	Model 1[a]	Model 2[a]
1-5 y		
Fully adherent	1 [Reference]	1 [Reference]
Nonadherent	2.00 (1.74-2.29)	1.63 (1.41-1.87)
Partially adherent	1.60 (1.29-1.98)	1.45 (1.17-1.79)
1-10 y		
Fully adherent	1 [Reference]	1 [Reference]
Nonadherent	1.73 (1.60-1.89)	1.46 (1.34-1.59)
Partially adherent	1.36 (1.19-1.54)	1.26 (1.11-1.46)
1-15 y		
Fully adherent	1 [Reference]	1 [Reference]
Nonadherent	1.59 (1.49-1.69)	1.38 (1.30-1.47)
Partially adherent	1.24 (1.13-1.37)	1.18 (1.07-1.29)

[a] Model 1 adjusted for age, sex, and race/ethnicity. Model 2 additionally adjusted for smoking status, marital status, college education, body mass index, and number of comorbidities.

ventive behaviors, such as avoidance of cigarette smoking and cholesterol level and blood pressure checks.[16] Together, a lifestyle marked by nonadherence to health preventive guidelines and medical tests and treatments may significantly increase mortality risk. Given that a nonadherence behavior profile may have led to prior development of comorbidities, controlling for these factors may have resulted in overadjusting in model 2.

Although we believe that such a general nonadherence phenotype explains the preponderance of the increased risk associated with nonadherence observed in this study, it cannot be ruled out that reverse causation bias may explain a portion of the increased risk. Specifically, some participants may have had an underlying condition(s) at baseline, perhaps incompletely captured by our comorbidity variables, that both made it harder to comply with screening and predisposed the participants to earlier mortality.

Although the literature examining the determinants of adherence to cancer screening may be limited, the literature investigating the determinants of medication adherence is substantial. Determinants of medication adherence include patient-level demographic, sociocultural, and behavioral factors as well as external-level factors, such as complexity of the medication regimen and adverse effects and health system–level factors.[17] Adherence to cancer screening may involve some of the same patient-level factors as well as system-level factors. Adherence to screening in the PLCO Cancer Screening trial varied by smoking status, BMI, and educational level, but the differences were not large. Participants in the PLCO Cancer Screening trial who were nonadherent with baseline screening tended to be nonadherent with postbaseline screenings as well.

In a study of Medicare claims data from 1999 to 2012, nonreceipt of cancer screening was associated with mortality after controlling for age and comorbidities.[18] Women not receiving mammography screening in the past 2 years had a 52% increase in the multivariate hazard for overall mortality, and men not receiving prostate-specific antigen screening in the past year had a 23% increase in the multivariate hazard for overall mortality.[18] Because only a small fraction of deaths were from breast or prostate cancer, the authors concluded that this increase was not due to the direct effect of the screenings.

Table 3. Cox Proportional Hazards Regression Models for Causes of Death

Cause of Death Category[a]	Nonadherent vs Fully Adherent Participants at 10-y Follow-up, Hazard Ratio (95% CI)	
	Model 1[b]	Model 2[b]
Cardiovascular (390-459)	1.61 (1.45-1.80)	1.40 (1.26-1.56)
Respiratory (460-519)	2.67 (2.14-3.34)	1.97 (1.58-2.47)
Cancer (140-239)[c]	1.41 (1.19-1.68)	1.28 (1.08-1.52)
Digestive (520-579)	2.75 (1.86-4.05)	2.26 (1.53-3.35)
Infectious (001-139)	1.47 (0.81-2.67)	1.19 (0.65-2.16)
Endocrine (240-279)	1.67 (1.08-2.59)	1.37 (0.89-2.11)
Neurologic (320-389)	1.19 (0.72-1.96)	1.13 (0.68-1.87)
Accidents (E800-E989)	1.09 (0.72-1.65)	0.96 (0.63-1.44)

[a] *International Classification of Diseases, Ninth Revision* code range given as the underlying cause of death on death certificate or the National Death Index.

[b] Model 1 adjusted for age, sex, and race/ethnicity. Model 2 additionally adjusted for smoking status, marital status, college education, body mass index, and number of comorbidities.

[c] Excluding prostate, lung, colorectal, and ovarian cancers.

Two European trials of one-time-only colorectal cancer sigmoidoscopy screening presented data on rates of mortality from other causes (noncolorectal cancer) among intervention arm adherents and nonadherents.[19,20] However, neither trial computed a risk ratio (RR) of nonadherents to adherents nor discussed the observed rates. To facilitate comparisons, unadjusted RRs for mortality from other causes for nonadherents compared with adherents were computed for these trials. In the United Kingdom Flexible Sigmoidoscopy Screening Trial, 29% of intervention arm participants were nonadherent and the RR of mortality from noncolorectal cancer for nonadherent participants after a median 11 years of follow-up was 1.64 (95% CI, 1.57-1.72).[19] In the SCORE (Screening for Colon Rectum) Italian trial, 42% of participants were nonadherent and, after a median of 11.4 years of follow-up, the RR was 1.55 (95% CI, 1.38-1.73).[20] In comparison, in the PLCO Cancer Screening trial at 10 years, the unadjusted RR for noncompliers was 1.67 (95% CI, 1.56-1.81). In both trials, participants had previously indicated (shortly before randomization) a willingness to

undergo screening if asked[19,20]; therefore, as in the PLCO Cancer Screening trial, participants were presumably healthy enough to undertake the screening, and thus the nonadherence was not likely caused by the presence of an underlying condition that also predisposed participants to increased mortality.

The influence of adherence on mortality has been demonstrated in treatment trials that reported lower mortality by adherence status, even for placebo arm participants.[21-24] For example, in the Coronary Drug Project, a randomized clinical trial investigating the effectiveness of cholesterol-lowering drugs on mortality among men after myocardial infarction, 5-year mortality in the placebo arm was 15% among adherents and 28% among nonadherents, with the differences persisting after statistical adjustment for important covariates.[22] Such findings suggest that good adherence to medical treatment is independently associated with lower mortality.

These findings have implications for the interpretation of screening and other prevention trials with mortality end points. Because a nonadherence phenotype is associated with higher mortality for causes that are not related to the trial, that phenotype may also convey higher risk for the cause of interest, irrespective of the effect of the intervention being studied. This finding implies that per-protocol analyses, which examine trial results by the intervention that participants actually receive, must be conducted according to methods that eliminate any adherence bias.[25] Furthermore, these results imply that observational studies comparing those who undergo screening with those who do not undergo screening have a high likelihood of bias and that controlling for important demographic, behavioral, and medical history factors may not eliminate this bias.

Limitations and Strengths

This study had several limitations. First, nonadherents had higher rates of missing data—approximately 20% to 25% for demographic, behavioral, and comorbidity variables—than did full and partial adherents (<2%). Although this difference could have affected the multivariate modeling results, we controlled for missing data using indicator variables, thereby limiting the effect of the differential percentage of unknowns. In addition, a complete case analysis, in which participants with any missing data were excluded, showed very similar model results to those obtained with indicator variables. Another limitation was that smoking status, comorbidities, and height and weight were self-reported and therefore subject to inaccuracy. Finally, these results are not applicable to younger adults (<55 years of age).

Although the present study had several limitations, to our knowledge, it is among the first to investigate the association between adherence to cancer screening and mortality from unrelated causes. Other major strengths include its prospective design, large size, and long follow-up. In addition, participants' demographics, behaviors, and chronic disease status were collected at baseline, allowing adjustment of these factors in multivariate analyses.

Conclusions

We found statistically significant and clinically important differences in all-cause mortality, excluding mortality from cancers studied in the PLCO Cancer Screening trial, by cancer screening adherence status; those differences remained significant after adjusting for demographic, medical, and behavioral characteristics. Future studies should investigate this association in clinical care settings outside of a research trial context.

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REFERENCES

1. Centers for Disease Control and Prevention. Chronic disease data. https://www.cdc.gov/chronicdisease/data/index.htm. Updated July 23, 2018. Accessed November 16, 2018.

2. Centers for Disease Control and Prevention. Nutrition, physical activity, and obesity: data, trends and maps. https://www.cdc.gov/nccdphp/dnpao/data-trends-maps/index.html. Accessed March 1, 2018.

3. McCullough ML, Patel AV, Kushi LH, et al. Following cancer prevention guidelines reduces risk of cancer, cardiovascular disease, and all-cause mortality. *Cancer Epidemiol Biomarkers Prev*. 2011;20(6):1089-1097. doi:10.1158/1055-9965.EPI-10-1173

4. Nechuta SJ, Shu XO, Li HL, et al. Combined impact of lifestyle-related factors on total and cause-specific mortality among Chinese women: prospective cohort study. *PLoS Med*. 2010;7(9):e1000339. doi:10.1371/journal.pmed.1000339

5. van Dam RM, Li T, Spiegelman D, Franco OH, Hu FB. Combined impact of lifestyle factors on mortality: prospective cohort study in US women. *BMJ*. 2008;337:a1440. doi:10.1136/bmj.a1440

6. Ryerson AB, Eheman CR, Altekruse SF, et al. Annual report to the nation on the status of cancer, 1975-2012, featuring the increasing incidence of liver cancer. *Cancer*. 2016;122(9):1312-1337. doi:10.1002/cncr.29936

7. Office of Disease Prevention and Health Promotion. Healthy People 2020. https://www.healthypeople.gov. Accessed March 13, 2018.

8. Leach CR, Schoenberg NE. The vicious cycle of inadequate early detection: a complementary study on barriers to cervical cancer screening among middle-aged and older women. *Prev Chronic Dis*. 2007;4(4):A95.

9. Khaliq W, Aamar A, Wright SM. Predictors of non-adherence to breast cancer screening among hospitalized women. *PLoS One*. 2015;10(12):e0145492. doi:10.1371/journal.pone.0145492

10. Constantinou P, Dray-Spira R, Menvielle G. Cervical and breast cancer screening participation for women with chronic conditions in France: results from a national health survey. *BMC Cancer*. 2016;16(1):255. doi:10.1186/s12885-016-2295-0

11. Sabatino SA, White MC, Thompson TD, Klabunde CN; Centers for Disease Control and Prevention (CDC). Cancer screening test use - United States, 2013. *MMWR Morb Mortal Wkly Rep*. 2015;64(17):464-468.

12. Gonzalez P, Castaneda SF, Mills PJ, Talavera GA, Elder JP, Gallo LC. Determinants of breast, cervical and colorectal cancer screening adherence in Mexican-American women. *J Community Health*. 2012;37(2):421-433. doi:10.1007/s10900-011-9459-2

13. Prorok PC, Andriole GL, Bresalier RS, et al; Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial Project Team. Design of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening trial. *Control Clin Trials*. 2000;21(6)(suppl):273S-309S. doi:10.1016/S0197-2456(00)00098-2

14. Andriole GL, Crawford ED, Grubb RL III, et al; PLCO Project Team. Prostate cancer screening in the randomized Prostate, Lung, Colorectal and Ovarian Cancer Screening trial: mortality results after 13 years of follow-up. *J Natl Cancer Inst*. 2012; 104(2):125-132. doi:10.1093/jnci/djr500

15. Pinsky PF, Prorok PC, Yu K, et al. Extended mortality results for prostate cancer screening in the PLCO trial with median follow-up of 15 years. *Cancer*. 2017;123(4):592-599. doi:10.1002/cncr.30474

16. Coughlin SS, Uhler RJ, Hall HI, Briss PA. Nonadherence to breast and cervical cancer screening: what are the linkages to chronic disease risk? *Prev Chronic Dis*. 2004;1(1):A04.

17. Iuga AO, McGuire MJ. Adherence and health care costs. *Risk Manag Healthc Policy*. 2014;7:35-44. doi:10.2147/RMHP.S19801

18. Goodwin JS, Sheffield K, Li S, Tan A. Receipt of cancer screening is a predictor of life expectancy. *J Gen Intern Med*. 2016;31(11):1308-1314. doi:10.1007/s11606-016-3787-y

19. Atkin WS, Edwards R, Kralj-Hans I, et al; UK Flexible Sigmoidoscopy Trial Investigators. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. *Lancet*. 2010;375 (9726):1624-1633. doi:10.1016/S0140-6736(10)60551-X

20. Segnan N, Armaroli P, Bonelli L, et al; SCORE Working Group. Once-only sigmoidoscopy in colorectal cancer screening: follow-up findings of the Italian Randomized Controlled Trial—SCORE [published correction appears in *J Natl Cancer Inst*. 2011;103(24):1903]. *J Natl Cancer Inst*. 2011;103(17): 1310-1322. doi:10.1093/jnci/djr284

21. Horwitz RI, Viscoli CM, Berkman L, et al. Treatment adherence and risk of death after a myocardial infarction. *Lancet*. 1990;336(8714):542-545. doi:10.1016/0140-6736(90)92095-Y

22. Coronary Drug Project Research Group. Influence of adherence to treatment and response of cholesterol on mortality in the Coronary Drug Project. *N Engl J Med*. 1980;303(18):1038-1041. doi:10.1056/NEJM198010303031804

23. Gallagher EJ, Viscoli CM, Horwitz RI. The relationship of treatment adherence to the risk of death after myocardial infarction in women. *JAMA*. 1993;270(6):742-744. doi:10.1001/jama.1993.03510060088038

24. Petitti DB. Coronary heart disease and estrogen replacement therapy: can compliance bias explain the results of observational studies? *Ann Epidemiol*. 1994;4(2):115-118. doi:10.1016/1047-2797(94)90056-6

25. Cuzick J, Edwards R, Segnan N. Adjusting for non-compliance and contamination in randomized clinical trials. *Stat Med*. 1997;16(9):1017-1029. doi: 10.1002/(SICI)1097-0258(19970515)16:9<1017::AID-SIM508>3.0.CO;2-V