Original investigation

Smoking Status and Survival Among a National Cohort of Lung and Colorectal Cancer Patients

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Abstract

Introduction: The purpose of this study was to explore the association of smoking status and clinically relevant duration of smoking cessation with long-term survival after lung cancer (LC) or colorectal cancer (CRC) diagnosis. We compared survival of patients with LC and CRC who were never-smokers, long-term, medium-term, and short-term quitters, and current smokers around diagnosis.

Methods: We studied 5575 patients in Cancer Care Outcomes Research and Surveillance (CanCORS), a national, prospective observational cohort study, who provided smoking status information approximately 5 months after LC or CRC diagnosis. Smoking status was categorized as: never-smoker, quit >5 years prior to diagnosis, quit between 1–5 years prior to diagnosis, quit less than 1 year before diagnosis, and current smoker. We examined the relationship between smoking status around diagnosis with mortality using Cox regression models.

Results: Among participants with LC, never-smokers had lower mortality risk compared with current smokers (HR 0.71, 95% CI 0.57 to 0.89). Among participants with CRC, never-smokers had a lower mortality risk as compared to current smokers (HR 0.79, 95% CI 0.64 to 0.99).

Conclusions: Among both LC and CRC patients, current smokers at diagnosis have higher mortality than never-smokers. This effect should be further studied in the context of tumor biology. However, smoking cessation around the time of diagnosis did not affect survival in this sample.

Implications: The results from our analysis of patients in the CanCORS consortium, a large, geographically diverse cohort, show that both LC and CRC patients who were actively smoking at diagnosis have worse survival as compared to never-smokers. While current smoking is detrimental to survival, cessation upon diagnosis may not mitigate this risk.

Introduction

Lung (LC) and colorectal (CRC) cancers are two leading causes of cancer death in the United States, with over 370 000 new cases in 2013.¹ Cigarette smoking is the primary risk factor for LC and is responsible for 87% of incident cancers.² Smoking is also likely associated with an increased risk of CRC incidence and mortality.^{3,4} Nearly 40% of LC patients and 14% of CRC patients were smoking within the year before cancer diagnosis, and 14% of LC patients and 9% of CRC patients smoked approximately 5 months after diagnosis.⁵

Smoking is associated with survival among cancer patients. The 2014 Surgeon General's report summarized evidence on smoking and prognosis among those diagnosed with cancer.⁶ The report concluded that current smoking versus never smoking was associated with shorter survival times, greater all-cause and cancer-specific mortality, and lower probability of disease-free survival among cancer patients. Former smokers tend to have intermediate risk of mortality and intermediate median survival times compared to current and never-smokers, although relatively few studies assessed effects of former smokers separately. According to the report, more information is needed on whether quitting at cancer diagnosis can improve chances of survival. The four existing studies investigating the effect of quitting at diagnosis suggested a benefit of smoking cessation at diagnosis versus continued smoking on overall survival (OS) and a dose response relationship between smoking heaviness and survival.⁶

Smoking cessation decreases smoking-related morbidity and mortality. Five years after smoking cessation, the risks of coronary heart disease and aerodigestive tract cancers are halved; stroke risk falls to that of a nonsmoker.^{7,8} Although, in the general population, decreases in all-cause and cause-specific mortality with increasing duration of smoking cessation have been shown in large cohort studies,⁹ clinically relevant "time since quit" categories have been largely absent from large studies of smoking cessation among cancer patients.

With regard to LC specifically, continued smoking after an LC diagnosis has been associated with an increased risk of recurrence, a second primary LC, and worse survival among patients with non-small cell lung cancer (NSCLC).^{10–15} Several studies of patients with early-stage NSCLC have found that smokers have worse survival compared with non-smokers and former smokers.^{13,16–22} With regard to CRC, continued smoking at diagnosis, and following surgery, has been associated with decreased survival, increased disease-specific mortality, and all-cause mortality.^{23–26} Studies have generally found that former smokers have an intermediate risk of mortality compared to current and never-smokers.^{23–26} Longer durations of abstinence prior to diagnosis were associated with greater survival among women.²⁵ Those with greater tobacco exposure (eg, >40 pack years; tobacco use prior to age 30) had lower disease free survival and higher mortality.^{25,27} Relations between smoking and disease-specific and all-cause mortality were strongest in those with tumors exhibiting high microsatellite instability. In addition to survival outcomes, smoking is associated with greater surgical complications among CRC patients.²³

In this study, we sought to better understand the association of smoking status and duration of smoking cessation with survival after LC or CRC diagnosis (Supplementary Figure 1). Specifically, we compared survival for a large, multiregional prospective cohort of LC and CRC patients of all stages among never-smokers, long-term quitters, medium-term quitters, short-term quitters, and current smokers around the time of diagnosis.

Methods

Study Design

Participants were enrolled in Cancer Care Outcomes Research and Surveillance Consortium (CanCORS),²⁸ a prospective, population-based and health system-based cohort of 9737 patients diagnosed with LC or CRC during 2003 to 2005.²⁸ Details on study design and procedures have been published previously.^{28,29} The study was approved by the human subjects committees at all participating institutions.

Cohort Selection

Patients aged 21 and older diagnosed with incident, first primary LC or CRC were identified within weeks of their diagnosis and surveyed by telephone approximately 4–6 months after diagnosis (the baseline survey). If patients were deceased or too sick to participate, a surrogate was interviewed. Informed consent for participation was provided by all patients or surrogates. Medical records were abstracted (available for 87% of participants) to obtain information about cancer characteristics and comorbid illness; additional details on cancer characteristics were obtained from cancer registries if medical record data were unavailable. This examination included only CanCORS participants who were alive at the time of enrollment, completed a full patient survey and had medical records abstracted at baseline ($N = 5643$). We excluded 68 patients who did not have vital status information. Thus, the final analytical sample included 5575 patients (Figure 1). Included participants differed from the full sample in that they were in earlier stage at the time of the baseline survey, had longer survival, were younger, were more likely to be from a VA or integrated healthcare delivery site, more likely to be of white race, were predominantly drawn from the Midwest and West geographical regions, and completed the survey closer to the time of diagnosis. The study was approved by the human subjects committees at all participating institutions.

Data Collection and Measures

Surveys were conducted using computer assisted telephone interviews in English, Spanish and Chinese. The response rate was 51% and the cooperation rate was 60%³⁰; comparisons of responders and non-responders have been described previously.³¹ Participants in CanCORS have been shown to be demographically similar to patients with these cancers in Surveillance, Epidemiology, and End Results registries.³²

Figure 1. Analytical sample selection.

Smoking Status

Previous research on smoking and quitting and survival in cancer patients has used a variety of current and former smoking categories and timeframes. The majority distinguish between current, former and never-smokers.^{23,24,26,33,34} Some research investigating the optimal length of time quit prior to diagnosis or treatment for longer survival include a category for those who have quit around the time of diagnosis (within 1 or 2 years),^{35,36} many distinguish between short term quitters (1 to 8–10 years prior to diagnosis^{22,25,36}) and medium and long-term quitters (≥8–10 years). In order to be consistent with previous literature, we included never-smokers, short term quitters, medium-term quitters and long-term quitters as described below. Smoking around the time of diagnosis was determined based on three questions from the baseline survey (Supplementary Figure 2).⁵ Participants were considered *current smokers* at diagnosis if they answered “yes” to the question, “Do you smoke cigarettes regularly now?” Participants were considered *short-term quitters* around time of diagnosis if they answered “yes” to the question “Have you ever smoked cigarettes regularly?”, “no” to “Do you smoke cigarettes regularly now?” and answered the question “How old were you the last time you were smoking regularly?” with an age that was between 0 and 1 year older than their age at diagnosis. Participants were considered *medium-term quitters* around time of diagnosis if they answered “yes” to the question “Have you ever smoked cigarettes regularly?”, “no” to “Do you smoke cigarettes regularly now?” and answered the question “How old were you the last time you were smoking regularly?” with an age that was greater than 1 year and less than 5 years older than their age at diagnosis. Participants were considered *long-term quitters* if they answered “yes” to the question “Have you ever smoked cigarettes regularly?”, “no” to “Do you smoke cigarettes regularly now?” and answered the question “How old were you the last time you were smoking regularly?” with an age that was greater than 5 years older than their age at diagnosis. We selected a 5 year cut off for long-term quitters as many health risks of smoking normalize after 5 years post-quit.^{19,20} Participants were considered *never-smokers* if they answered “no” to the question “Have you ever smoked cigarettes regularly?”

Sociodemographics

Sociodemographic variables included age, gender, race/ethnicity, marital status, education, self-reported insurance status, geographic region, and research site.

Cancer

Baseline cancer type, tumor histology, treatment, and stage were included as cancer-specific variables.³⁷

Medical Comorbidities

Comorbidities at diagnosis were abstracted from the medical record and represented as a summary index value (none, mild, moderate, severe) across the 27 co-morbid conditions included in the Adult Comorbidity Evaluation 27 (ACE-27) instrument.³⁸

Health Behaviors

Reported frequency of alcohol use was categorized into heavy drinkers (≥4 days/week), social drinkers (1 day/month to 1–3 days/week) and light/never drinkers (≤1 day/month) at baseline. Body mass index (BMI), categorized as <19, 19–25, and >25, was also included.

Psychosocial

Depression was measured using an 8-item version of the Center for Epidemiological Studies Depression Scale (CES-D) assessing the presence or absence of symptoms over the past week; a cutoff of six positive items or greater was considered consistent with depression.³⁹

Survival

Follow-up was measured in days from the date of diagnosis until the date of death, last contact, or last vital status update, whichever occurred earliest. Follow-up for vital status was ascertained from health plan records (for integrated system and VA health sites), and state and national death records linked to population-based cancer registries (for geography-based sites). Participants were censored at last follow up date. Vital status was last updated in the spring of 2012 for most sites except for participants from the Group Health Cooperative of Puget Sound (June 2010), Northern California (October 2011), UCLA/RAND (October 2011), UNC (May 2010), and the Veterans' Affairs Hospitals (November 2011).

Statistical Analyses

Because the LC and CRC cohorts differed on sociodemographic and clinical characteristics,⁵ we stratified analyses by tumor site. Chi-square tests assessed sociodemographic and clinical characteristics by smoking status. To evaluate survival effects in continued smokers versus those who quit smoking, we used the product-limit life-table method and associated Kaplan-Meier survival curves at the univariate level. A log-rank test was used to compare survival between groups in each cancer cohort. We used Cox proportional hazards regression modeling to identify factors independently associated with survival, adjusting for smoking status, sociodemographic factors, time from diagnosis to completion of the baseline survey, cancer stage, and comorbidities at the baseline survey. We used the Efron approximation method to correct for tied failure times.⁴⁰ The interaction effects of smoking status and (1) stage and (2) comorbidity were evaluated in separate Cox models. We also tested three-way interactions between BMI, alcohol, and smoking status on survival. We tested for violations of the proportional hazards assumption with the proportionality test function of SAS, using a transformation of Martingale residuals.⁴¹ For variables violating the proportional hazards assumption, we created separate models entering time-dependent covariates by including a linear interaction of the covariate with time.

All analyses were conducted using SAS 9.4 (SAS Institute; Cary, NC). Two-sided *p* values of <.05 were considered statistically significant.

Results

Smoking Status

The cohort included 2465 patients with LC and 3110 patients with CRC. Among the LC cohort (Supplementary Table 1), there were 251 (10.2%) never-smokers, 916 (37.2%) long-term quitters, 231 (9.4%) medium-term quitters, 711 (28.8%) short-term quitters, and 356 (14.4%) current smokers at baseline. At most recent follow-up, 157 never-smokers (62.1%), 660 long-term quitters (71.0%), 172 (73.8%) medium-term quitters, 515 short-term quitters (71.9%), and 289 current smokers (81.0%) had died (*p* < .0001). Among the CRC cohort, there were 1398 (45.0%) never-smokers, 1128 (36.3%) long-term quitters, 108 (3.5%) medium-term quitters, 187 (6.0%) short-term quitters, and 289 (9.3%) current smokers at baseline.

(Supplementary Table 1). At most recent follow-up, 463 never-smokers (32.6%), 423 long-term quitters (37.0%), 45 (40.5%) medium-term quitters, 73 short-term quitters (38.4%), and 122 current smokers (42.2%) had died ($p = .008$). Sociodemographic and clinical differences, across smoking groups, appear in Supplementary Table 1.

Survival

The median OS for patients with LC by smoking status was 1354 days (95% CI 1159 to 1832) for never-smokers, 967 days (95% CI 852 to 1085) for long-term quitters, 946 days (95% CI 705 to 1130) for medium-term quitters, 838 days (95% CI 741 to 982) for short-term quitters, and 689 days (95% CI 605 to 756) for current smokers, unadjusted Wilcoxon rank sum test $p < .001$ (Figure 2a). The median OS for participants with CRC by smoking status was not reached as the Kaplan-Meier survival curve did not fall to 0.5 (Figure 2b). The percent of patients with CRC alive at 5 years was 71.7% among never-smokers, 68.4% for long-term quitters, 63.0% for medium term quitters, 62.6% for short-term quitters, and 63.7% for current smokers (unadjusted Wilcoxon rank sum test, $p = .02$).

LC Mortality

After adjusting for sociodemographic covariates, stage at diagnosis, and comorbidities, the hazard ratio (HR) for mortality for never-smokers compared to current smokers was 0.71 (95% CI 0.57 to 0.89), and the HRs for mortality among long-term, medium-term, and short-term quitters did not differ significantly from current smokers (Table 1). The overall association of smoking status with mortality was statistically significant ($p = .02$). In former smokers, duration of smoking abstinence was not associated with mortality (HR = 0.92, 95% CI 0.82 to 1.03). Other factors predicting mortality included being over 70 years old versus younger than 60 (HR 1.17, 95% CI 1.03 to 1.34), male sex (HR 1.23, 95% CI 1.10 to 1.37), care in an integrated healthcare delivery system versus population-based site (HR 0.85, 95% CI 0.72 to 0.99), stage III, IIIB or IV disease versus I/II (HR 2.31, 95% CI 1.93 to 2.68, 2.74,

95% CI 2.35 to 3.18, and 4.58, 95% CI 4.04 to 5.18, respectively), moderate/severe comorbidity versus none (HR 1.24, 95% CI 1.05 to 1.50 and 1.65, 95% CI 1.39 to 1.95, respectively), not being married or partnered (HR 1.14, 95% CI 1.02 to 1.27), having a BMI between 19 and 25, over 25 or unknown versus BMI less than 19 (HR 0.62 95% CI 0.51 to 0.74, HR 0.59 95% CI 0.49 to 0.711, HR 0.46 95% CI 0.28 to 0.75, respectively), and days from diagnosis to completion of the baseline survey (HR 0.998, 95% CI 0.997 to 0.999). In this cohort, there was no interaction between smoking status and (1) stage or (2) co-morbidity and mortality. There was no interaction between smoking status, BMI and alcohol on mortality.

CRC Mortality

After adjusting for sociodemographic covariates (Table 1), stage at diagnosis, advanced stage, time from diagnosis to completion of the baseline survey, and comorbidities, smoking status was not independently associated with mortality (p -value for overall significance = .34). However, never-smokers had a lower risk of death as compared to current smokers (HR 0.79, 95% CI 0.64 to 0.99). Among former smokers, there was no association between duration of smoking abstinence and mortality (HR = 0.88, 95% CI 0.73 to 1.06). In adjusted analyses, other factors associated with mortality included age (HR for age >70 vs. <60: 1.73, 95% CI 1.47 to 2.04; HR for age 60–69 vs. <60: 1.27, 95% CI 1.11–1.47), male sex (HR 1.27 95% CI 1.08 to 1.50), being black versus white (HR 1.31 95% CI 1.10 to 1.5556), having some college or college versus less high school degree (HR .83 95% CI 0.69 to 0.99), not being married or partnered (HR 1.22 95% CI 1.07 to 1.39), stage III or IV disease versus I/II (HR 1.85, 95% CI 1.59 to 2.15 and HR 6.79, 95% CI 5.85 to 7.88, respectively), having a BMI over 25 versus less than 19 (HR 0.60 95% CI 0.45 to 0.81), and moderate/severe comorbidity versus none (HR 1.36, 95% CI 1.11 to 1.65 and HR 1.52, 95% CI 1.22 to 1.91). In this cohort, there was no interaction between smoking status and (1) stage or (2) co-morbidity and mortality. There was no interaction between smoking status, BMI and alcohol on mortality.

Figure 2. Smoking status predicts survival following diagnosis in (a) lung and (b) colorectal (CRC) cancer patients.

Table 1. Cox Proportional Hazards Model for Mortality of LC and CRC Patients

Parameter	HR (LC)		95% HR CI (LC)		HR (CRC)		95% HR CI (CRC)	
Smoking status (current smoker = REF)								
Quit less than 1 year ago	0.99		0.85	1.16	0.87		0.64	1.18
Quit 1–5 years ago	0.91		0.76	1.12	0.83		0.57	1.18
Quit greater than 5 years ago	0.91		0.78	1.07	0.83		0.67	01.04
Never-smoker	0.71		0.57	0.89	0.79		0.64	0.98
Age (<60 = REF)								
≥70	1.17		1.03	1.34	1.73		1.47	2.04
60–69	0.99		0.86	1.13	1.27		1.08	1.50
Gender (female = REF)								
Male	1.23		1.10	1.37	1.27		1.11	1.47
Race/ethnicity (white = REF)								
Other	0.97		0.81	1.16	0.75		0.60	0.94
Hispanic/Latino	1.05		0.82	1.35	0.84		0.66	1.08
Black	0.92		0.78	1.08	1.31		1.10	1.56
Education (<High School = REF)								
Some college/college	0.91		0.79	1.04	0.83		0.69	0.99
High school graduate	0.90		0.78	1.04	0.93		0.77	1.12
Marital status (married/partnered = REF)								
Not married/partnered	1.14		1.02	1.27	1.22		1.07	1.39
Research site (population based = REF)								
VA Administration Hospital	0.98		0.80	1.21	1.03		0.82	1.28
Integrated healthcare delivery system	0.85		0.72	1.00	0.98		0.79	1.22
Geographic region (Midwest = REF)								
West	0.91		0.80	1.21	1.10		0.66	1.85
South	0.90		0.75	1.07	0.85		0.50	1.46
Stage (Stage I/II = REF)								
Stage IV	4.58		4.04	5.18	6.79		5.85	7.88
Stage IIIB (LC only)	2.74		2.35	3.18				
Stage IIIA (LC)/ Stage III (CRC)	2.31		1.98	2.68	1.85		1.59	2.15
Comorbidity (ACE-27) at diagnosis (None = REF)								
Severe	1.65		1.39	1.95	1.52		1.22	21.91
Moderate	1.24		1.05	1.50	1.36		1.11	1.65
Mild	1.10		0.95	1.27	1.03		0.87	1.22
Not reported	1.08		0.90	1.28	1.05		0.86	1.28
Alcohol use (≤1x/month = REF)								
More than 1x/week	0.98		0.88	1.11	0.84		0.71	1.01
1x/month to 1x/week	0.94		0.83	1.06	0.99		0.86	1.15
Depression (<6 = REF)								
≥6 on the CESD-SF	0.96		0.84	1.09	1.16		0.97	1.39
Not reported	1.09		0.87	1.37	1.09		0.83	1.43
Days from diagnosis to baseline survey	1.00		1.00	1.00	1.00		1.00	1.00
BMI (<19 = REF)								
19–25	0.62		0.51	0.74	0.77		0.58	1.03
>25	0.59		0.49	0.71	0.60		0.45	0.81
Not reported	0.46		0.28	0.75	0.79		0.45	1.37

LC = lung cancer; CRC = colorectal cancer; HR = Hazard Ratio; CI = Confidence Interval; VA = Veterans' Affairs; ACE-27 = Adult Comorbidity Evaluation; CESD-SF = Center for Epidemiologic Studies Depression scale short-form; BMI = body mass index.

Discussion

Cigarette smoking is a major driver of mortality in LC, and recent evidence suggests an association between smoking and CRC mortality as well.^{3,4} We examined the association of smoking status on mortality among LC and CRC patients in a large, multi-regional cohort. This study adds to the literature examining mortality in CRC patients based on smoking status around the time of diagnosis. In addition, this study examines relations between clinically meaningful time-since-quit categories and mortality among quitters with never or current smokers. We found that smoking status around the time of diagnosis was independently associated with mortality in LC patients. Specifically, we found that the hazard for death

for never-smokers compared to current smokers with LC was 29% lower and it was 21% lower for never-smokers as compared to current smokers among CRC patients. We did not find an association between duration of abstinence in former smokers and survival, suggesting that it is current smoking, and not having a smoking history, that is associated with greater mortality.

These findings are similar to those in the 2014 Surgeon General's Report which found that smoking is associated with poorer survival across cancer type.⁶ Our findings differ from the Surgeon General's report in that the report found that, in the few studies that assessed the effect of former versus never smoking and quitting smoking after diagnosis, being a former smoker at diagnosis and quitting after diagnosis improved survival.

The findings from our analysis are also consistent with previous studies demonstrating better survival for never versus current smokers at the time of LC diagnosis.^{16,19,21,42} In several studies of patients with NSCLC, OS was worse for current smokers versus never-smokers; however, these findings are limited by the lack of granularity among nonsmokers (ie, never vs. former).^{16,19-21,42} In a study of 4200 never, former, and current smokers in the National Comprehensive Cancer Network NSCLC cohort, the survival benefit of having quit smoking >12 months before diagnosis was limited to young patients with stage IV disease.¹⁷ In a cohort of 5229 patients with LC, Ebbert et al.⁴³ found that longer duration of smoking abstinence was associated with improved survival in women with NSCLC; however this study did not adjust for co-morbid illness at the time of cancer diagnosis. Warren et al.⁴⁴ examined associations between overall and cancer-specific survival among current, never, former, and recent quit categories (where recent quit was defined as having quit within 12 months of cancer diagnosis), and found that in disease sites with large recent quit cohorts (lung and head/neck), current smoking increased overall and cancer-specific mortality risk as compared with recent quit. Our study improves upon this earlier work by examining the impact of more clinically meaningful long-, medium-, and short-term quit status separately from never-smoking status on mortality, and further by including robust information on co-morbid illness in Cox regression modeling. Adjusting for comorbidity may have nullified the effect of smoking on OS. Based on these findings, clinicians should carefully consider comorbidity in the assessment and management of cancer patients, especially if they are smokers.

Similar to LC patients, in CRC patients, never-smokers had improved survival compared to current smokers. In previous work, findings on the influence of smoking on survival in CRC have been mixed.⁴⁵⁻⁴⁷ There are some data suggesting that cigarette use is associated with worse survival in patients with CRC,^{9,24-26} but other studies did not find a difference in OS among current smokers, former smokers, and never-smokers.⁴⁸⁻⁵² While several studies did not account for possible interactions between smoking status and molecular phenotypes, Phipps et al.²⁵ showed that there was a pronounced increase in the risk of death for smokers with CRC whose tumors demonstrated high microsatellite instability.

Our study has several strengths. First, the CanCORS data represents a large, diverse group of cancer patients. Second, the dataset contains detailed information regarding patient and clinical characteristics. Nevertheless, these findings must be considered in the context of a few limitations. Smoking status was self-reported at a single timepoint and analyses did not permit evaluation of the effect of smoking cessation after diagnosis. We only included patients who completed the full baseline survey, so patients with advanced disease who were too ill were omitted from these analyses because surrogates were not asked detailed questions about patients' smoking status. Further, those who did not survive until baseline (a median of 5 months post-diagnosis) were not able to participate. Thus, there is likely an overrepresentation of early-stage disease in this sample. Also, there were relatively small numbers of ever-smokers in the CRC cohort, which likely resulted in limited power for finding differences. Finally, we lacked information on epidermal growth factor receptor (*EGFR*) mutant and anaplastic lymphoma kinase (*ALK*) fusion oncogene positive NSCLCs. *EGFR* mutations and *ALK* rearrangements are more prevalent among never or light smokers and confer improved survival due to higher response rates to tyrosine kinase inhibitors.⁵³⁻⁵⁷ Because we were unable to adjust for *EGFR* mutation or *ALK* rearrangement status,

our analyses likely underestimate the detrimental effect of smoking among patients with LC.

In conclusion, the results from this analysis of 5575 patients suggest that individuals with LC and CRC who were smoking around the time of diagnosis had worse survival compared with never-smokers. Future studies should prospectively examine the effects of quitting smoking around the time of diagnosis as well as the long-term impact of continued smoking after a cancer diagnosis. Other important areas for investigation include the impact of smoking cessation on adverse events during cancer treatment and quality of life after a cancer diagnosis.

Supplementary Material

Supplementary data are available at *Nicotine & Tobacco Research* online.

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Declaration of Interests

JM is employed by and owns stock in Anthem Inc. The other authors have no conflicts of interest to report.

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