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ORIGINAL REPORT

Lung Cancer Incidence in Never Smokers

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ABSTRACT

Purpose
Lung cancer is a leading cause of cancer death worldwide. Although smoking remains the predominant cause of lung cancer, lung cancer in never smokers is an increasingly prominent public health issue. However, data on this topic, particularly lung cancer incidence rates in never smokers, are limited.

Methods
We reviewed the existing literature on lung cancer incidence and mortality rates among never smokers and present new data regarding rates in never smokers from the following large, prospective cohorts: Nurses' Health Study; Health Professionals Follow-Up Study; California Teachers Study; Multiethnic Cohort Study; Swedish Lung Cancer Register in the Uppsala/Örebro region; and First National Health and Nutrition Examination Survey Epidemiologic Follow-Up Study.

Results
Truncated age-adjusted incidence rates of lung cancer among never smokers age 40 to 79 years in these six cohorts ranged from 14.4 to 20.8 per 100,000 person-years in women and 4.8 to 13.7 per 100,000 person-years in men, supporting earlier observations that women are more likely than men to have non–smoking-associated lung cancer. The distinct biology of lung cancer in never smokers is apparent in differential responses to epidermal growth factor receptor inhibitors and an increased prevalence of adenocarcinoma histology in never smokers.

Conclusion
Lung cancer in never smokers is an important public health issue, and further exploration of its incidence patterns, etiology, and biology is needed.

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INTRODUCTION

In the United States, lung cancer incidence and mortality rates have been steadily declining over the past decade, following the well-documented decline in the prevalence of tobacco smoking.[1-3] However, in the United States, lung cancer remains the leading cause of cancer death, killing more patients than breast, colon, and prostate cancers combined.[4] Although tobacco smoke is the predominant risk factor for development of lung cancer, there is a distinct group of patients who develop the disease without a history of tobacco smoking. Clinical observations suggest that the percentage of never smokers among lung cancer patients may be increasing; however, it is unclear whether this apparent trend represents an increase in lung cancer incidence among never smokers or the increasing prevalence of never smokers in the general population. The growing number of never smokers in the United States and other countries underscores the importance of understanding the epidemiology and biology underlying lung cancer in this population.

Are lung cancer rates among never smokers increasing? Although we can take only the first step towards answering this question, in this article, we review the current knowledge regarding the incidence patterns and biology of non–smoking-associated lung cancer and suggest future research directions to improve understanding of this disease in the growing at-risk population. To this end, we summarize the existing literature on lung cancer incidence rates among never smokers and present new data on rates from selected large, prospective cohorts. Finally, we present evidence suggesting biologic and genetic differences between smoking-related and non–smoking-related lung cancers and posit important new research questions.

In the United States, the most widely used resource for documenting cancer trends in population groups is the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) cancer registries.[5] However, SEER and most other

cancer registries do not collect information on patient smoking history, which precludes the examination of cancer incidence patterns by smoking status. Furthermore, information on the prevalence of current and former smokers within subgroups of age, sex, and race/ethnicity in the general population (data necessary for detailed incidence calculations) is difficult to obtain for many populations. SEER data have been linked with population-based tobacco use information,[6] but this approach allows only for ecologic correlations between the population-level prevalence of smoking and incidence of lung cancer in broad demographic subgroups; individual patient-level data on smoking status are still needed for more specific inference on patterns of smoking-related cancer.[7]

Previous studies reporting incidence rates of lung cancer in never smokers cannot easily be compared because of dissimilar population standards for age adjustment of incidence rates. We present updated and previously unpublished incidence data, age adjusted to a common population, for lung cancer in never smokers from six cohorts. We also provide distributions of lung cancer histology and age at diagnosis to illustrate differences in the characteristics of lung cancer according to smoking status. It is important to emphasize that, although these data add to the sparse body of knowledge on incidence rates of lung cancer in never smokers, they cannot contribute to an understanding of whether rates have changed over time, primarily because cohort recruitment in all of these studies took place over a circumscribed period of time.

METHODS

Using data from six large cohort populations (Table 1), truncated (ie, limited to age 40 to 79 years, rather than all ages),[8] age-adjusted incidence rates were calculated based on the 2000 United States standard population, with the proportions of 5-year age groups between 40 and 79 years recalculated to summate to 1.0. The age-adjusted incidence rates, with exact Poisson 95% CIs,[18] were limited to adults age 40 to 79 years to facilitate comparison among the cohorts. We also examined the percentage, with exact binomial 95% CI,[18] of lung cancer patients age 40 to 79 years at diagnosis with adenocarcinoma histology and the median age at diagnosis of current, former, and never smokers in each cohort (Table 2). Histology was ascertained through medical records or linkage to cancer registries for all cohorts for which such information was available, as detailed in Table 1.

Details about the methodology of the Nurses' Health Study (NHS),[9,10] Health Professionals Follow-Up Study (HPFS),[9,11] California Teachers Study (CTS),[12] Multiethnic Cohort (MEC) Study,[13,14] Swedish Uppsala/Örebro Lung Cancer Register (U/OLCR),[15] and First National Health and Nutrition Examination Survey Epidemiologic Follow-Up Study (NHEFS)[16] have been previously reported and are listed in Table 1. These six cohorts were selected because they were prospective, provided prediagnosis data on smoking status, observed cohort members for validated diagnoses of incident cases of lung cancer, enrolled adults age 40 to 79 years, and provided diversity both geographically and demographically.

RESULTS

Table 2 presents the age-adjusted incidence rates of lung cancer in never, former, and current smokers in all six cohorts. These rates per 100,000 person-years for never smokers age 40 to 79 years were 15.2 (female) in the NHS, 11.2 (male) in the HPFS, 20.8 (female) in the CTS, 13.7 (male) and 20.7 (female) in the MEC, 4.8 (male) and 14.4 (female) in the U/OLCR, and 12.7 (male) and 19.3 (female) in the NHEFS. By comparison, age-adjusted rates in current smokers are roughly 12 to 30 times higher. Overall rates were comparable between the US population-based cohorts, including MEC and NHEFS, and

Table 1. Characteristics of the NHS, HPFS, CTS, MEC, U/OLCR, and NHEFS Cohort Members Included in This Analysis

Characteristic	NHS[9,10]	HPFS[9,11]	CTS[12]	MEC[13,14]	U/OLCR[15]	NHEFS[16]
Dates of follow-up	1976 to 2002	1986 to 2002	1995-1996 to 2002	1993-1996 to 2001	2003	1971-1975 to 1992
Age at baseline, years	30-55	40-75	33-79*	45-75	40-79	25-74
Population at risk, No.						
Male	—	51,529	—	82,460	438,966†	5,075
Female	121,700	—	108,329	101,359	447,603†	7,637
Incident lung cancer patients, 40-79 years at diagnosis, No.						
Male	—	528	—	1,078‡	273	160
Female	1,817	—	393	805‡	250	75
Region	United States	United States	California	California/Hawaii	Uppsala/Örebro, Sweden	United States
Ethnicity	Mostly white	Mostly white	Mostly white	Multiple	Mostly white	Multiple
Follow-up for lung cancer	Biennial questionnaires and medical records, if possible	Biennial questionnaires and medical records, if possible	Linkage to cancer registry	Linkage to cancer registry	Linkage to cancer registry	Questionnaires approximately every 5 years and inpatient records or death certificates§
Smoking data	Biennial questionnaires	Biennial questionnaires	Baseline questionnaire	Baseline questionnaire	Questionnaire for at-risk population; medical records or clinical assessment for patients	Baseline and follow-up questionnaire

Abbreviations: NHS, Nurses' Health Study; HPFS, Health Professionals Follow-Up Study; CTS, California Teachers Study; MEC, Multiethnic Cohort Study; U/OLCR, Swedish Uppsala/Örebro Lung Cancer Register; NHEFS, First National Health and Nutrition Examination Survey Epidemiologic Follow-Up Study.
*Age range of eligible cohort members was restricted to those potentially age 40 to 79 years during follow-up.
†Population at risk based on 2003 census count of males and females age 40 to 79 years in Uppsala/Örebro (Statistics Sweden: www.scb.se)[17]; smoking status in population at risk based on a survey of 68,000 randomly selected Uppsala/Örebro residents (64% of whom completed the survey) at the beginning of 2004.
‡Age range of incident lung cancer patients was 45 to 79 years at diagnosis.
§The NHEFS lacked information on tumor histology.

Table 2. No. of Lung Cancer Patients and Lung Cancer AAIR Per 100,000 Person-Years Among Adults Age 40 to 79 Years, Percentage of Patients With Adenocarcinoma Histology, and Median Age at Diagnosis by Smoking Status in the Cohorts

Cohort	Smoking Status		
	Never	Former	Current
NHS, female			
Incident lung cancer patients, No.	168	711	938
Age-truncated AAIR	15.2	76.9	293.3
95% CI	9.1 to 24.5	63.7 to 93.2	266.7 to 322.9
Adenocarcinoma, %	70	50	42
95% CI	62 to 78	46 to 54	39 to 46
Median age at diagnosis, years	64	68	64
HPFS, male			
Incident lung cancer patients, No.	43	312	173
Age-truncated AAIR	11.2	67.6	304.5
95% CI	6.5 to 19.0	56.4 to 82.5	277.4 to 334.7
Adenocarcinoma, %	54	51	30
95% CI	37 to 71	45 to 57	23 to 39
Median age at diagnosis, years	67	71	68
CTS, female			
Incident lung cancer patients, No.	91	179	123
Age-truncated AAIR	20.8	65.6	264.4
95% CI	13.5 to 31.2	54.8 to 79.4	240.0 to 291.7
Adenocarcinoma, %	64	54	34
95% CI	53 to 74	46 to 61	26 to 43
Median age at diagnosis, years	67	70	67
MEC, male*			
Incident lung cancer patients, No.	47	520	511
Age-truncated AAIR	13.7	80.0	314.6
95% CI	9.0 to 21.5	67.1 to 96.1	284.6 to 347.7
Adenocarcinoma, %	53	42	31
95% CI	38 to 68	37 to 46	27 to 36
Median age at diagnosis, years	72	72	69
MEC, female*			
Incident lung cancer patients, No.	142	270	393
Age-truncated AAIR	20.7	65.2	233.7
95% CI	13.5 to 31.1	53.5 to 80.2	208.5 to 261.8
Adenocarcinoma, %	58	46	32
95% CI	49 to 66	40 to 52	28 to 37
Median age at diagnosis, years	72	70	67
U/OLCR, male			
Incident lung cancer patients, No.	10	124	139
Age-truncated AAIR	4.8	59.8	173.7
95% CI	2.2 to 10.6	48.1 to 74.5	153.4 to 197.0
Adenocarcinoma, %	67	36	34
95% CI	30 to 93	28 to 45	26 to 42
Median age at diagnosis, years	64	71	64
U/OLCR, female			
Incident lung cancer patients, No.	37	68	145
Age-truncated AAIR	14.4	51.4	149.4
95% CI	8.2 to 23.6	39.9 to 66.0	129.4 to 172.4
Adenocarcinoma, %	64	46	38
95% CI	46 to 79	33 to 58	30 to 46
Median age at diagnosis, years	67	66	63
NHEFS, male†			
Incident lung cancer patients, No.	4	45	111
Age-truncated AAIR	12.7	141.4	362.7
95% CI	10.2 to 18.2	124.9 to 161.0	334.8 to 393.6
Median age at diagnosis, years	78	72	69

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Table 2. No. of Lung Cancer Patients and Lung Cancer AAIR Per 100,000 Person-Years Among Adults Age 40 to 79 Years, Percentage of Patients With Adenocarcinoma Histology, and Median Age at Diagnosis by Smoking Status in the Cohorts (continued)

Cohort	Smoking Status		
	Never	Former	Current
NHEFS, female†			
Incident lung cancer patients, No.	15	10	50
Age-truncated AAIR	19.3	69.1	168.8
95% CI	14.2 to 27.5	57.2 to 84.1	146.1 to 194.5
Median age at diagnosis, years	71	67	62

Abbreviations: AAIR, age-adjusted incidence rate for invasive lung cancer (per 100,000 person-years) standardized to US 2000 standard million population between age 40 and 79 years; NHS, Nurses' Health Study; HPFS, Health Professionals Follow-Up Study; CTS, California Teachers Study; MEC, Multiethnic Cohort Study; U/OLCR, Swedish Uppsala/Örebro Lung Cancer Register; NHEFS, First National Health and Nutrition Examination Survey Epidemiologic Follow-Up Study.
*MEC participants and lung cancer patients were restricted to age 45 to 79 years; the incidence rate of lung cancer in those 40 to 44 years old was assumed to be half that among those 45 to 49 years old for calculation of AAIRs.
†The NHEFS lacked information on tumor histology.

the cohorts of highly selected populations, including NHS, HPFS, and CTS, although rates in the U/OLCR were consistently lower than in the US cohorts. In 2002, the age-adjusted (standardized to the 2000 US standard population) incidence rates of lung cancer in all males and females in Sweden overall were 29.9 and 20.0 per 100,000 person-years, respectively,[19] whereas the rates among white males and females in the entire United States were 72.5 and 49.9 per 100,000 person-years, respectively.[20]

As expected, lung cancer age-adjusted incidence rates in all six cohorts were significantly lower in never smokers than former or current smokers. Adenocarcinoma was more common in never smokers than in former or current smokers in all cohorts for which information about histology was available, although the small number of patients who never smoked resulted in wide CIs (Table 2). Although never smokers were slightly older at lung cancer diagnosis than current smokers in two population-based cohorts (MEC and NHEFS), this difference was not observed in the majority of cohorts evaluated (NHS, HPFS, CTS, and U/OLCR; Table 2).

Among female never smokers, the incidence rates in CTS and MEC were slightly, albeit nonsignificantly, higher than the rate in NHS, which was established nearly two decades earlier than the other two cohorts. Likewise, the incidence rate of non–smoking-associated lung cancer was slightly but nonsignificantly higher among males in MEC than males in the earlier established HPFS, although the discrepancy could be a result of racial/ethnic differences in risk of lung cancer in never smokers. Although a higher relative risk of lung cancer associated with smoking has been demonstrated in racial/ethnic groups that are more prevalent in MEC than in HPFS,[14] data on rates of non–smoking-associated lung cancer by racial/ethnic group are limited.

Evaluating comparable groups of males and females, rates of non–smoking-associated lung cancer were consistently higher among females in the NHS, MEC, U/OLCR, and NHEFS cohorts compared with males in the HPFS, MEC, U/OLCR, and NHEFS cohorts. The higher rate among females suggests sex-based differences in either susceptibility or exposure to risk factors (such as secondhand smoke) for non–smoking-associated lung cancer.

DISCUSSION

Our analysis of recent cohort data finds truncated age-adjusted incidence rates of lung cancer in never smokers ranging from 4.8 to 20.8 per 100,000 person-years in men and women 40 to 79 years old. Because the effects of time cannot be separated from those of aging in these cohorts, we cannot assess secular trends in the incidence rate of non–smoking-associated lung cancer in these cohorts, and we also cannot compare these rates to historical data to evaluate incidence changes over time. However, establishing the current incidence rates, as we have done, is an important step in better understanding this distinct disease subset. To put the problem of lung cancer in never smokers in perspective, the rates we report are similar to age-adjusted rates for myeloma (13.2 per 100,000) in men or cervical (15.4 per 100,000) or thyroid cancer (17.3 per 100,000) in women age 40 to 79 years old diagnosed in the United States between 1998 and 2002.[20]

Better understanding of the incidence rate and etiology of lung cancer in never smokers is important because of the implications for therapeutic trials and epidemiologic studies of lung cancer. Differences in lung cancer biology between never smokers and smokers are illustrated by findings from several studies. One of the most striking distinctions is the observed differential response to drugs that target the epidermal growth factor receptor (EGFR). Compared with current or former smokers diagnosed with lung cancer, never smoker patients treated with these agents have higher response rates to treatment and better survival.[21,22] In a randomized phase III trial with the EGFR kinase inhibitor gefitinib in refractory, advanced lung cancer patients, never smokers treated with gefitinib compared with placebo had a reduced risk of death from lung cancer (relative risk for survival analysis, hazard ratio [HR] = 0.67, $P = .012$), whereas the HR of lung cancer death in former/current smokers did not differ between the gefitinib and placebo arms (HR = 0.92, $P = .242$).[21] In the registration trial (BR.21) for the EGFR kinase inhibitor erlotinib, the overall response rate to erlotinib was 24.7% for never smokers and 3.9% ($P < .001$) for former/current smokers.[22] Of all the variables tested, only a history of never smoking was a significant independent predictor of improved survival with erlotinib therapy.[22]

The biology underlying the differential response to treatment with EGFR inhibitors is an area of active investigation and helps to illustrate why lung cancer in never smokers may behave differently. Mutations in the *EGFR* are seen more often in tumors from never smokers.[23-26] Differences in EGFR protein expression may also contribute to differences in treatment response,[23] with a distinct EGFR pathway immunohistochemical profile seen in never versus current smokers.[27] Other analyses have also demonstrated distinct

mutational or expression patterns in *KRAS* TP53, p53, and nitrotyrosine (a marker of nitric oxide protein damage) in tumors of never smokers compared with smokers.[26,28]

Most reports show a modest survival benefit for non–small-cell lung cancer (NSCLC) patients who are never smokers compared with smokers, regardless of therapy. This was seen for never smokers in the BR.21 trial with erlotinib (HR = 0.8, $P = .048$ compared with current/former smokers regardless of therapy)[22] and in a review of 12,000 Southern California NSCLC patients (comparing current/former with never smokers, HR = 1.09, $P = .045$).[29] Additionally, a single-institution review of 650 patients with NSCLC found the 5-year overall survival rate to be 16% for current smokers versus 23% for never smokers ($P = .004$).[30] Another review of 311 patients with early-stage lung cancer found that the relative risk of death was 0.45 ($P = .042$) comparing never smokers with current smokers.[31] Finally, among 61 patients with screen-detected lung cancer in Japan, the mean tumor volume doubling time was twice as long in 31 never smokers (607 ± 392 days) as it was in 30 current smokers (292 ± 297 days, $P = .001$).[32] The implications of these results for epidemiologic studies are clear; improvements in lung cancer survival over time might be a result of an increasing proportion of never smokers among lung cancer patients rather than improved therapies.

Other evidence for a biologic difference in lung cancer between smokers and never smokers comes from differences in histology. Adenocarcinomas seem to be more common in never smokers, light smokers, and former smokers, whereas squamous cell or other histologic types are more common in heavy smokers and current smokers.[27,33,34] Furthermore, the prevalence of adenocarcinoma among lung cancer patients increases with years since quitting smoking.[35] Likewise, our data show a higher proportion of adenocarcinoma among never smokers than among former or current smokers (Table 2).

As our data show, lung cancer rates in never smokers are comparable to the incidence rates of cervical cancer or myeloma in the United States, yet the etiology of this disease is not well understood. Identifying risk factors for lung cancer among never smokers has been an area of active inquiry. Secondhand smoke has been established as a major risk factor among never smokers.[36-38] Occupational exposures, such as asbestos, chromium, arsenic, and others, also play a role, although more so in smokers.[39-41] Domestic radon exposure may also contribute to the risk of lung cancer in never smokers,[42,43] although some controversy remains,[44] and arsenic in drinking water has also been implicated.[45,46] Other factors including indoor pollutants (cooking oil vapors and coal burning),[47] previous lung disease,[48-50] dietary factors,[51,52] family history,[37,53,54] and genetic factors may also affect lung cancer development.[55-60]

Overall, lung cancer incidence rates in the U/OLCR cohort were consistently lower than in the US cohorts. Although the lower prevalence of smoking in Sweden compared with the United States likely contributes to the lower overall incidence rate of lung cancer in Sweden,[19,20] perhaps in part as a result of lower exposure to secondhand smoke among never smokers, it does not entirely explain our finding of lower rates of lung cancer among never smokers only or among smokers only. Instead, the discrepancies between the countries even within strata of smoking status suggest differences in smoking patterns among smokers and in the prevalence of environmental or genetic cofactors for lung cancer among both smokers and never smokers. The cumulative risk of lung cancer among Swedish male smokers is also considerably lower than that among men from other European countries.[61]

The biologic differences in lung cancer in never smokers versus current/former smokers are apparent primarily in differential response to specific therapies (most notably EGFR inhibitors) and in distribution of histology (increased adenocarcinoma in never smokers), as supported by our data. Our data also support the observation that women are more likely than men to have non–smoking-associated lung cancer, which is in contrast to the finding that men had a higher mortality rate from non–smoking-associated lung cancer than women in the American Cancer Society Cancer Prevention Study cohorts.[62] This discrepancy could be, in part, a result of better survival among women than men with non–smoking-associated lung cancer, although data on this subject are lacking. The literature does support a survival benefit for women versus men with lung cancer overall.[63] Clearly, more research is needed regarding the intriguing etiology, prognosis, treatment, and outcomes of non–smoking-associated lung cancer.

Despite the emergence of clinical and epidemiologic studies focused on identifying biologic and genetic differences between smoking- and non–smoking-associated lung cancers and risk factors for non–smoking-associated lung cancer, it remains uncertain whether the incidence of lung cancer in never smokers is increasing. Evaluation of secular trends is possible in longitudinal studies with open enrollment over a long span of time, such that incidence changes caused by aging are distinguishable from secular changes. To our knowledge, there have been only two published examples of data of this type. The first is a linkage of the nationwide Swedish construction workers' health care program to the national cancer registry, which documented an increase in the age-adjusted (standardized to the 2000 World Standard Population) incidence rate of non–smoking-related lung cancer between 1976 to 1980 (1.5 per 100,000) and 1991 to 1995 (5.4 per 100,000).[64] The second is a comparison of two American Cancer Society Cancer Prevention Study cohorts, in which the age-adjusted (standardized to the combined age distribution of the two cohorts and, therefore, not directly comparable to the Swedish construction workers' study) mortality rate of non–smoking-associated lung cancer in women increased slightly, but statistically significantly, from 12.3 per 100,000 in 1959 to 1972 to 14.7 per 100,000 in 1982 to 2000, with most of the increase occurring among women age 70 to 84 years.[62] The mortality rate among men, however, did not change over time.

In a comparison of two large, hospital- and community-based case-control studies conducted in the United Kingdom in 1950 and 1990, the percentage of never smokers among the male lung cancer patients was 0.5% in both studies, whereas the percentage of never smokers among male controls increased from 4.5% to 19.0%.[65] Among women, the percentage of lung cancer patients who never smoked was 37.0% in 1950 and 7.6% in 1990, whereas the percentage of never-smokers among female controls decreased less dramatically from 54.6% to 50.3%. These results suggest that the proportion of lung cancer patients who never smoked does not necessarily reflect population-level changes in smoking prevalence.

In the United States, a study of 100 NSCLC patients seen at a single institution in the late 1980s determined smoking status through questionnaires and medical record review and found that 11% of patients were never smokers.[33] In a large case series of 11,969 NSCLC patients from three Southern California counties (1995 to 2003), investigators estimated that 9.7% of patients were never smokers.[29] In this study, a nonsignificant increase in the prevalence of never smokers with NSCLC was noted in 1999 to 2003 versus 1995 to 1999.

To examine trends in the incidence of lung cancer among never smokers, cancer registry data would need to add information on patients' smoking status obtained from medical records or patient interviews. Smoker misclassification rates have generally been small when the validity of self-reported smoking status has been investigated,[66-69] although one study found a false reporting rate of 8% for those claiming to be never smokers.[70] Smoking is the critical variable in this proposed research, and investigators will need to carefully verify smoking status. In addition to smoking data, the numbers of never smokers in age-, sex-, and race/ethnicity-specific population groups, needed for denominators to calculate rates, would have to be estimated from large population surveys because the proportion of never smokers and rate of lung cancer vary by these characteristics.[71]

If an increase in non–smoking-associated lung cancer incidence is indeed taking place, the next step will be determination of the underlying cause. The role of secondhand smoke has received considerable exploration,[66] as have other environmental toxins and some genetic polymorphisms. A viral etiology has even been proposed, with some literature supporting a potential role of human papillomavirus in lung cancer development,[72,73] as well as pathologic similarities between bronchioloalveolar carcinoma and the retrovirus-induced ovine pulmonary adenocarcinoma.[74] With lung cancer persisting as the leading cause of cancer mortality in the United States, research into the epidemiology of lung cancer in never smokers should be an important public health priority.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The authors indicated no potential conflicts of interest.

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