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Article

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Lung Cancer Risk and Demographic Characteristics of Current 20–29 Pack-Year Smokers: Implications for Screening

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Abstract

Background: Based on current recommendations, 30+ pack-years of smoking are required for eligibility for low-dose CT (LDCT) lung cancer screening; former smokers must have quit within 15 years. We investigated whether current smokers with 20 to 29 pack-years have similar lung cancer risks as eligible former smokers and also whether they have a different demographic profile.

Methods: The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) was a randomly assigned screening trial of subjects age 55 to 74 years with chest radiographs (CXR) used for lung cancer. Subjects completed a baseline questionnaire containing smoking history questions. Cox proportional hazards models, adjusted for age and sex, were utilized to estimate hazard ratios (HRs) for various smoking history groups. Next, we utilized the National Health Interview Survey (NHIS), which inquired about smoking history and race/ethnicity, to analyze the demographic profiles of various high-risk smoking history categories. All statistical tests were two-sided.

Results: The PLCO cohort included 18 114 former and 12 243 current LDCT-eligible smokers, plus 2283 20- to 29-pack-year current smokers. The hazard ratio for 20- to 29-pack-year current smokers compared with eligible (30+ pack-year) former smokers was 1.07 (95% confidence interval [CI] = 0.75 to 1.5). Based on the NHIS, 10 million persons in the United States are currently LDCT eligible; an additional 1.6 million (16%, 95% CI = 13.6% to 19.0%) are 20- to 29-pack-year current smokers. The percentage increase in eligibles if 20- to 29-pack-year current smokers were included was substantially greater for women than men (22.2%, 95% CI = 17.9% to 26.7%; vs 12.2%, 95% CI = 9.3% to 15.3%, $P < .001$) and for minorities than non-Hispanic whites (30.0%, 95% CI = 24.2% to 36.0%; vs 14.1%, 95% CI = 11.1% to 17.0%, $P < .001$).

Conclusion: The potential benefits and harms of recommending LDCT screening for 20 to 29-pack-year current smokers should be assessed.

The United States Preventive Services Task Force (USPSTF) recently recommended low-dose CT (LDCT) screening for current and former smokers age 55 to 80 years with at least 30 pack-years of cigarette smoking; former smokers must have quit smoking within 15 years (1). These smoking history criteria matched those of the National Lung Screening Trial (NLST), the study providing the only mature randomly assigned trial evidence for the task force decision (2). Other LDCT screening guidelines, as well as the recently released Medicare coverage guidelines, also use the 30+ pack-year minimum (3,4). In contrast, the National Comprehensive Cancer Network (NCCN) guidelines recommend for LDCT screening those with the NLST smoking history criteria or a 20+ pack-year smoking history and one additional lung cancer risk factor, which could include occupational exposure or pulmonary disease history (5). The rationale for including the latter (20+ pack-year) group was in part to avoid arbitrary exclusion of persons considered at high lung cancer risk but

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who had not yet been characterized in a randomly assigned trial (5).

Many studies have demonstrated a substantial dropoff in lung cancer risk with quitting smoking. Even within 10 to 15 years since quitting, risks can decrease by 50% to 75% (6–9). Therefore, current smokers with 20 to 29 pack-years but no additional risk factors may have greater risk than former smokers with those same pack-years and an additional risk factor. They could even have similar risk to many former smokers meeting the existing USPSTF guidelines of 30+ pack-years and at most 15 years since quit. Few, if any, studies have directly compared the lung cancer risk of these various smoking history categories.

Another important dimension to the issue of screening eligibility involves the demographics of smokers. Studies have shown that among ever-smokers blacks and Hispanics have lower median pack-years than non-Hispanic whites and that, similarly, women have lower median pack-years than men (10). In addition, among men, blacks have a higher proportion of current smokers than non-Hispanic whites. Therefore, if the risk for 20- to 29-pack-year current smokers is roughly equivalent to that of many USPSTF-eligible former smokers (30+ pack-years and at most 15 year since quit), the 30 pack-year limit may artificially exclude proportionally more racial and ethnic minorities than non-Hispanic whites and proportionally more women than men.

The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial was a large, multicenter, randomly assigned trial of screening, evaluating chest radiograph (CXR) for lung cancer screening (11). There was no smoking history eligibility requirement for PLCO (unlike NLST), so the risk for subjects with fewer than 30 pack-years can be analyzed. In this study, we examine lung cancer risk in PLCO, comparing the risk of 20- to 29-pack-year current smokers to that of 30+ pack-year current smokers and USPSTF-eligible former smokers.

In addition, we utilize the National Health Interview Survey (NHIS) to estimate, in the US population stratified by sex and race/ethnicity, the numbers of persons eligible for LDCT screening under the current USPSTF guidelines as well as under potentially expanded guidelines that would include 20- to 29-pack-year current smokers. This is an exploratory analysis because the efficacy of LDCT has not been directly assessed in that population.

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Methods

PLCO Trial – Design

The design of the PLCO trial has been described previously (11). Men and women age 55 to 74 years were randomly assigned from 1993 to 2001 at 10 screening centers across the United States to an intervention or usual care arm. Exclusion criteria included history of a PLCO cancer and current cancer treatment. Intervention arm participants were offered annual posterior-anterior chest radiograph (CXR) for four years. CXR screens were considered positive if a nodule, mass, or other abnormality suspicious for lung cancer was noted. Diagnostic evaluation was decided by subjects and their physicians, not by trial protocol. Written informed consent was obtained for all participants, and each center's institutional review board approved the PLCO trial.

All diagnosed cancers were ascertained, primarily by means of a mailed annual study update (ASU) questionnaire, which asked about any cancers diagnosed in the prior year. Trained abstractors confirmed reported cancers through medical records. Deaths were ascertained through the ASUs, with supplementation by National Death Index searches. Participants were followed for up to 13 years, death, or December 31, 2009, whichever came first.

Participants completed a baseline questionnaire that inquired about demographics, medical history, smoking history, and past screenings. The smoking-related questions asked if subjects had ever smoked cigarettes regularly for six months or longer, if they smoke regularly now, the start and (last) stopping ages of regular smoking, and the number of cigarettes usually smoked per day during periods when the subject smoked, with categories of 1–10, 11–20, 21–30, 31–40, 41–60, 61–80, and 81 or more. A supplemental questionnaire (SQX) was mailed to PLCO participants at six to 12 (median 9.3) years from enrollment; it included similar smoking history questions as the baseline questionnaire.

PLCO Trial—Quantitative Methods and Statistical Analyses

Years since quit (YSQ) at baseline for former smokers was calculated by subtracting age last stopped smoking regularly from current age. Pack-years were computed as the product of smoking duration and cigarettes per day (CPD) divided by 20, with duration calculated as either current age (for current smokers) or age last stopped smoking (for former smokers) minus age started smoking and CPD calculated using the maximum of each CPD category range (100 CPD for the 81+ category).

We utilized Cox proportional hazards model to analyze the relationship of smoking history to lung cancer risk, examining the following smoking history categories: 30+ pack-year current smokers, 20- 29-pack-year current smokers (includes up to 29.9 pack-years), and former smokers with 30+ pack-years and 15 or fewer YSQ. For current smokers at baseline, analysis of the subsequent SQX demonstrated that about 40% were former smokers at the time of the SQX. Also, this analysis showed that 30+ pack-year smokers with YSQ of five or fewer had a substantial relapse rate to current smoking at the time of the SQX (13%), while those with five to 15 YSQ had a very low relapse rate (~3%). Therefore, to minimize misclassification of smoking status, follow-up was limited to three years from baseline for current smokers and former smokers with YSQ of five or fewer. Note the three-year limit for current smokers also assures that few (~3%) with 20 to 29 pack-years at baseline would reach the 30-pack-year mark during the analysis period, assuming continuation with their current CPD rate. Former smokers with YSQ of more than five were censored at study time 15-YSQ, indicating the time their YSQ would exceed 15, assuming no relapse. Never smokers were assumed to continue their status through all study years. The model was adjusted for age and sex. The proportionality assumption of the Cox model was tested using the time-dependent covariate method, and the null hypothesis of proportionality was not rejected ($P = .10$) (12).

To compare with findings from other cohorts, we also ran a Cox model, restricted to the current smokers, to estimate hazard ratios associated with CPD categories (≤10, 11–20, 21–40, and >40); this model also was adjusted for age and sex.

All statistical tests were two-sided, and a P value of less than .05 was considered statistically significant.

National Health Interview Study

To examine the size and characteristics of the US population eligible for LDCT screening, both under current USPSTF guidelines

and under an expanded definition including 20- to 29-pack-year current smokers, we utilized the NHIS, which provides a nationally representative US sample (13). Specifically, the 2010 NHIS included a special Cancer Control Supplement (CCS) questionnaire, in addition to the standard Adult questionnaire. The Adult questionnaire contains smoking-related questions about current smoking status (current, former, never), age started and stopped smoking, and CPD for current smokers It does not ask about CPD for former smokers, though, so one cannot determine pack-years for former smokers from it. The CCS questionnaire, however, did inquire about CPD for former smokers, so combining it with the Adult questionnaire allows for determination of pack-years in all ever-smokers. Because 2010 is the most recent year of the CCS, our NHIS analysis utilizes the 2010 survey results. For CPD, respondents recorded the actual number of cigarettes instead of categories as in PLCO; otherwise, pack-years and YSQ were determined similarly as in PLCO.

The NHIS Adult questionnaire also contained questions about race and Hispanic ethnicity. The category of non-Hispanic white (NHW) was defined as subjects who reported "no" for Hispanic ethnicity and reported "white" alone for race.

Frequencies and their standard deviations were computed incorporating the cluster-based sampling used in the NHIS; specifically, PROC SURVEYFREQ (SAS, Version 9.2) was used with appropriate strata, cluster, and weight variables (14). Survey weights were calibrated to project to overall US population counts.

As noted above, in PLCO pack-years were calculated using the maximum CPD value in each reported category (eg, 10 for 1–10, 20 for 11–20, etc.). Therefore, this method could overestimate pack-years. Because the NHIS did capture actual CPD values, to assess this possibility we calculated from the NHIS data the mean CPD value for each PLCO CPD category among all ever-smokers (stratified by current vs former) and computed an "adjusted" pack-years using this mean value.

Results

Of 154 899 subjects randomly assigned, 148 051 (95.6%) fully completed the smoking section of the baseline questionnaire. The cohort for this analysis consisted of 69 182 never smokers, 12 243 30+ pack-year current smokers, 2283 20- to 29-pack-year current smokers, and 18 114 former smokers with 30+ pack-years and at most 15 YSQ. Table 1 gives baseline demographics and smoking history characteristics of the cohort. Current smokers with 20 to 29 pack-years were less likely to be male and non-Hispanic white than 30+ pack-year current or former smokers. Compared with 30+ pack-year current smokers, those with 20 to 29.9 pack-years had lower median CPD (10 vs 20), similar median duration of smoking, and higher median age (63 vs 60 years).

Table 2 displays lung cancer counts and rates and the results of the Cox proportional hazards models. For the multivariate model controlling for age and sex, the hazard ratio (relative to never smokers) was 29.9 (95% CI = 23.8 to 37.7) for current smokers with 30+ pack-years, 17.8 (95% CI = 12.2 to 26.0) for current smokers with 20 to 29 pack-years, and 16.6 (95% CI = 13.6 to 20.3) for USPSTF-eligible former smokers. Relative to (USPSTF-eligible) former smokers and 30+ pack-year current smokers, 20- to 29-pack-year current smokers had hazard ratios of 1.07 (95% CI = 0.75 to 1.5) and 0.59 (95% CI = 0.42 to 0.85), respectively. Relative to all USPSTF eligibles (former smokers and current smokers combined), the hazard ratio for the 20- to 29-pack-year current smokers was 0.83 (95% CI = 0.59 to 1.16).

For the model examining CPD, hazard ratios for current compared with never smokers were 17.7 (95% CI = 13.9 to 22.5), 19.9 (95% CI = 14.8 to 26.7), 27.8 (95% CI = 20.6 to 37.5), and 27.8 (95% CI = 15.9 to 48.7) for CPD of 1 to 10, 11 to 20, 21 to 40, and more than 40, respectively.

The analysis of adjusted pack-years showed that there was little potential overestimation of pack-years for the 30+ pack-year current or former smokers because mean pack-years decreased by only about 3% (2 pack-years) in these groups in the adjusted analysis. However, for 20- to 29-pack-year current smokers, mean pack-years was substantially reduced, from 23.1 to 16.1. These findings resulted from the fact that the mean CPD, as derived from the NHIS data, was very close to the category maximum used to compute PLCO pack-years, except for the 1–10 category where it was 33% lower and that, further, the 20- to 29-pack-year group typically had reported CPD in this lowest category, in contrast to the 30+ pack-year smokers.

Table 3 displays the NHIS results. A total of 8281 persons age 55 to 80 years completed the survey. An estimated 10.0 million persons age 55 to 80 years meet the existing USPSTF age and smoking history eligibility guidelines for LDCT screening (30+ pack-years and either current smokers or quit within the past 15 years). An additional 1.6 million (aged 55–80 years) are 20- to 29-pack-year current smokers; including this group for screening would increase the eligible pool by 16.3% (95% CI = 13.6% to 19.0%). This percentage increase in the pool of LDCT screening eligibles, if 20- to 29-pack-year current smokers were included, varied substantially by sex and race. It was greater for women (22.2%, 95% CI = 17.9 to 26.7) than men (12.2%, 95% CI = 9.3 to 15.3) and greater for racial/ethnic minorities (30.0%, 95% CI = 24.2 to 36.0) than non-Hispanic

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Table 1. Baseline demographics and smoking history of the analysis cohort

Baseline smoking history category	N	Median (25/75th) pack-years	Median (25/75th) CPD*	Median age, y (25/75th)	Median duration of smoking, y (25/75th)	% male	% Non-Hispanic white
Never smoker	69 182	N/A	N/A	62 (58/67)	N/A	38.8	88.5
Current smoker, 30+ pack-years	12 243	53 (43/72)	20 (20/30)	60 (57/65)	43 (39/47)	58.3	88.5
Current smoker, 20–29.9 pack-years	2283	22.5 (21/25)	10(10/10)	63 (60/67)	44 (41/48)	40.4	74.2
Former smoker, 30+ pack-years & quit within 15 years	18 114	51 (39/71)	30 (20/40)	62 (58/66)	37 (32/42)	62.1	91.0

* Cigarettes per day (CPD) was assessed in categories of 1–10, 11–20, 21–30, 31–40, 41–60, 61–80, >80. High value of range was used to compute CPD and pack-years.

Table 2. Cox proportional hazards model*

Smoking history category	Person-years at risk	Lung cancers	Rate per 10 000 person-years	HR (95% CI) controlling for age, sex
Never smoker	779 504	253	3.2	Referent
Current smoker 30+ pack-years	36 312	271	74.6	29.9 (23.8 to 37.7)
Current smoker, 20–29 pack-years	6633	36	54.3	17.8 (12.2 to 26.0)
Former smoker 30+ pack-years, quit within 15 years	71 833	333	46.4	16.6 (13.6 to 20.3)

* Only the first three study years were included for current smokers. Former smokers were censored when their years since quit exceeded 15, or at three years for those with years since quit of five or less (see text for more details). CI = confidence interval; HR = hazard ratio.

Table 3. US population age 55–80 years in various smoking history categories (in millions)*

Category	All	Men	Women	Non-Hispanic white	Racial/ethnic minorities†
Meets USPSTF smoking eligibility criteria	10.0	5.9	4.1	8.5	1.4
Current smoker 20–29 pack-years	1.6	0.72	0.91	1.2	0.4
Meets USPSTF smoking eligibility criteria or current smoker 20–29 pack-years	11.6	6.6	5.0	9.7	1.8
% increase (95% CI) ‡	16.3 (13.6 to 19.0)	12.2 (9.3 to 15.3)	22.2 (17.9 to 26.7)	14.1 (11.1 to 17.0)	30.0 (24.2 to 36.0)

* Data derived from National Health Interview Survey. CI = confidence interval; NHIS = National Health Interview Survey; USPSTF = United States Preventive Services Task Force.
† Other than non-Hispanic white.
‡ Percent increase of USPSTF criteria plus current smokers with 20–29 pack-years compared with USPSTF criteria alone. The 95% CI was derived from the 95% CI of the reciprocal frequency.

whites (14.1%, 95% CI = 11.1 to 17.0). *P* values were .001 for both comparisons.

Discussion

In this analysis of the PLCO cohort, the lung cancer risk for 20- to 29-pack-year current smokers was similar to that of former smokers meeting the current USPSTF guidelines. With the latter as the referent group, the hazard ratio was 1.07 and the lower 95% confidence interval of 0.75 still indicated only modestly lower risk in the 20- to 29-pack-year group. Although direct estimates from the same cohort of the comparative lung cancer risk in these two groups are lacking, results from other cohorts are generally consistent with those from PLCO.

Thun et al. analyzed smoking and lung cancer mortality data from five large contemporary cohorts (15). For current smokers, the estimated relative risks (averaged between men and women) of 16.3, 23.9, 30.0, and 50.3 for CPD of fewer than 10, 10 to 19, 20 to 39, and 40+, respectively, were similar to those observed in PLCO. A prior PLCO analysis showed that the decrease in lung cancer risk with YSQ was generally consistent with the findings from several large cohorts (16).

The analysis of potential overestimation of pack-years in PLCO showed that, while this was unlikely for the 30+ pack-year ever smokers, there was the possibility for substantial overestimation in the 20- to 29-pack-year current smokers. However, pack-years being overestimated in this group implies that the group was diluted with under-20-pack-year smokers, who would presumably be at lower risk, so, accordingly, the observed hazard ratio would be an underestimate of the true risk for 20- to 29-pack-year current smokers. Therefore, the conclusion that this category has at least as high a risk as the USPSTF-eligible former smokers (in aggregate) would still hold. It is also possible, because smoking is not a socially desirable behavior, that there could be systematic under-reporting of smoking intensity, whereby those reporting 20 to 29 pack-years actually had greater exposure; this would bias the results towards overestimating the risk in this category.

According to the findings from the NHIS, the addition of 20- to 29-pack-year current smokers would increase the overall pool of LDCT screening eligibles by 16.3% but result in substantially larger percentage increases for women and racial/ethnic minorities. Although the overall percentage increase was lower in PLCO (7.5%) than in NHIS, similar trends were seen in terms of greater proportional increases for women and minorities (6.2% increase for non-Hispanic whites vs 19.4% for minorities, 5.0% increase for men vs 11.1% for women). This is also consistent with other studies showing lower pack-years for minorities and women among ever smokers (10). Assuming the lung cancer risk is sufficiently high in 20- to 29-pack-year current smokers to warrant LDCT screening, the 30+ pack-year limit would exclude a substantially greater proportion of racial/ethnic minorities (23.1%) than non-Hispanic whites (12.3%) and a greater proportion of women (18.2%) than men (10.9%) (percent excluded equals I/(100+I), where I is percentage increase).

Compared with non-Hispanic whites, black men have elevated US lung cancer rates, black women similar rates, and Hispanics and Asians lower rates (17). An analysis of incidence rates and population smoking history data showed that, among black men, increased lung cancer rates were not because of increased smoking rates, duration or intensity; rather, black men had higher rates at each level of smoking-related risk (10).

Further, although black women had similar lung cancer rates as whites, based on their smoking history profiles their risk should be lower. This highlights the possibility, at least in blacks, that lung cancer risks for a given smoking history category (eg, current smokers with 20–29 pack-years) could be greater than those predicted from predominantly white cohorts.

There are also reasons to proceed cautiously in extending screening recommendations to 20- to 29-pack-year current smokers. This group was not included in the NLST, so there is the untested assumption that the trial's mortality benefit can be extrapolated to them. However, the Dutch-Belgian NELSON LDCT screening trial, which is expected to report its results this year, has a minimum pack-year limit of 15 or 18.75 depending on smoking pattern (over half a pack for 30+ years or over ¾ of a pack for 25+ years), so 20- to 29-pack-year current smokers are included in that trial (18).

In addition, to date there is little evidence of how LDCT performance metrics in the clinical care arena (including sensitivity, specificity, rates of invasive diagnostic procedures, compliance with screening and screenee risk profile) compare with those observed in randomly assigned trials or other research venues. Until LDCT screening performance in population settings is better understood, expansion of screening to additional populations may incur unanticipated harms. For example, some nonwhite minorities have more underlying comorbidities on average, so that lung cancer therapy may carry more harm. It is also important to stress that smoking cessation has benefits that greatly exceed those of LDCT screening alone, so recommending screening for current but not former 20- to 29-pack-year smokers should not create perverse incentives against quitting.

A limitation of this analysis is that smoking status was collected essentially at one time (although a subset had smoking status updated a median of 9 years postbaseline). Therefore, the smoking status of PLCO current smokers going forward in study time was unknown, which is why follow-up was limited to three years postbaseline. As a sensitivity analysis, we also ran the models with five years of follow-up for current smokers. The resulting hazard ratios, compared with never smokers, were 16.9 (95% CI = 13.9 to 20.7) for former smokers, 16.0 (95% CI = 11.4 to 22.4) for current smokers with 20 to 29 pack-years, and 33.0 (95% CI = 27.1 to 40.4) for 30+ pack-year current smokers; the hazard ratio for 20- to 29-pack-year current smokers compared with the former smokers was 0.95 (95% CI = 0.70 to 1.28). Thus, the risks in this analysis were also similar between 20- to 29-pack-year current smokers and eligible former smokers. A limitation of the NHIS data was that participation in NHIS was voluntary, although the response rate was high, about 90% (13). Additionally, as with the PLCO data, the NHIS smoking history data were self-reported.

In conclusion, current smokers with 20 to 29 pack-years had similar lung cancer risk in this study to LDCT-eligible former smokers. Additionally, this group was over-represented by women and racial/ethnic minorities. The potential benefits and harms of recommending LDCT screening for this group should be assessed.

Notes

No authors report any conflicts of interest. Dr. Pinsky had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The authors are employees of the National Cancer Institute (NCI); other than that, there were no other sources of financial support for this project.

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