

Lung cancer rates as an index of tobacco smoke exposures: validation against black male ~ non-lung cancer death rates, 1969–2000

Bruce Leistikow, M.D., M.S.*

Department of Epidemiology and Preventive Medicine, University of California, Davis, Davis, CA 95616, USA

Abstract

Background. Researchers use lung cancer death rates (rates) as an index of the cumulative burdens of smoking. That index lacks direct validation and calibration. So this study directly validates and calibrates that index against annual ~ non-lung (all-sites minus lung and stomach) rates from 1969 to 2000 in United States black men, then estimates their cancer death rate smoking-attributable fractions (SAFs).

Methods. This study uses linear regression, age-adjusted rates from <http://www.seer.cancer.gov/canques>, and the formula $SAF = (1 - ((\text{rate in the unexposed}) / (\text{rate in the exposed})))$. Estimated rates in the unexposed range between the 1969 rate and the rate predicted for a population with no smoking-attributable lung cancers. Stomach and lung cancer rate SAFs were based on published cohort studies.

Results. Lung cancer death rates predicted 98% and 97% of the variances in ~ non-lung cancer death rates throughout their 1969–1990 34% rise and subsequent declines, respectively (each $P < 0.0001$). The findings suggest that the SAF of the all-sites cancer death rate in black men peaked at 66% in 1990.

Conclusions. Lung cancer death rates were a good index of smoke exposure for predicting ~ non-lung cancer death rates in black men. Smoking may cause most premature cancer deaths in black men.

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Introduction

The lung cancer death rate is perhaps the best available index of the cumulative hazards of tobacco smoking (smoking) according to the World Health Organization [1], tobacco industry [2,3] cancer society, and government-supported researchers [4–7]. Yet that index or exposure load measure has not been directly validated. Nor has the index been directly calibrated against observed exposure/disease associations in geographically representative populations. Nor have the smoking-attributable fractions (SAFs) of cancer death rates been directly estimated. Instead, estimates of smoking-attributable cancer or all-cause death numbers or percents have most often been indirectly calibrated using results from a nearly 20-year-old cohort study of disproportionately healthy, educated, white, volunteer Americans [4–7]. Such

death SAFs may be misleadingly low due to selection and misclassification biases [8], and ignoring the marked prematurity of many deaths from smoking. Studies of smoking-attributable age-adjusted death rates in representative populations with continuous exposure monitoring are needed.

To best calibrate lung cancer death rates as an index of exposure load, one should compare highly representative populations that are nearly identical with the exception of marked smoke exposure disparities. In particular, those populations should have very little medical-care-related mortality disparity. A time series study in a highly underserved population undergoing a large tobacco/lung cancer epidemic may meet all of the above criteria—comparability of the more and less exposed populations (in this case, a single population over time), marked exposure disparities, and minimization of medical care effects.

Both direct validation and calibration of the smoke exposure index and quantitative assessment of the cause of the 1969–1990 cancer death epidemic in United States (U.S.) black men are greatly needed. So this study performs

* Epidemiology and Preventive Medicine, University of California, Davis, 1 Shields Avenue, Davis, CA 95616. Fax: +1-530-752-3239.

E-mail address: BNLeistikow@ucdavis.edu.

the first such direct index validation, index calibration, and epidemic assessment. Black men were studied due to their relative deficits of medical care and immigration, and their disproportionately large and recent cancer death epidemic [9]. Over 30 years of annual cancer death rates were studied since it is unlikely that annual changes in cumulative hazards from other carcinogens would consistently shadow annual smoke exposure changes throughout so long a period.

Specifically, this study assesses the steep 1969–1990 71% and 34% rises in the black male lung and ~non-lung (all-sites excepting lung and stomach) cancer death rates, respectively. Then, it assesses the steep 1990–2000 19% and 11% drops in the black male lung and ~non-lung cancer death rates, respectively (<http://www.seer.cancer.gov/canques>). Those results are used to help estimate upper- and lower-bound SAFs of all-sites cancer death rates in U.S. black men in 1990 at the peak of the cancer death epidemic, and more recently in 2000.

Methods

To increase the power of the study, just black men are included. Their cancer death rate increases were more recent and steep than whites or women, and less likely to be affected by medical care since black men are particularly underserved [10]. This is supported by past findings that 80–82% of tobacco-related cancers in California's lowest socioeconomic groups are still initially diagnosed at late stages as late as 1996–2000 [11]. Also, men did not benefit from recent likely treatment-related decreases in female uterine, cervix, breast, and possibly colon cancer death rates.

The study assesses ~non-lung cancer death rates since unlike stomach cancers [12], there are no known recent hygiene-related decreases in ~non-lung cancers that would weaken correlations between smoke exposure loads and ~non-lung cancer death rates. Likely smoking-related lung and stomach cancer deaths [13] are included in the estimated SAF of all-sites cancer.

The study used strong, widely approved data sources, smoke exposure measures, and regression methods. Specifically, <http://www.seer.cancer.gov/canques> age-adjusted cancer death rates (rates) using the 2000 U.S. age standard were used. Age-adjusted lung cancer death rates were used as a smoke exposure load biomarker that integrates the effects of current, cumulative, synergistic, secondhand, early onset, in utero, and other smoke exposures [1]. Exposure/disease (lung/non-lung cancer death rate) associations were assessed using linear regression.

The estimated SAF were calculated using the formula $\text{SAF} = (1 - (\text{rate in the unexposed} / \text{rate in the exposed}))$. The study assesses a range of possible rates in the unexposed and corresponding SAF. That allows for uncertainties including whether any observed 1969–1990 or

1990–2000 trends can be extrapolated to exposure loads below 1969's.

The rate in the unexposed was possibly as high as the lowest observed rate in the period, and possibly as low as that extrapolated from the observed data to the lowest possible level expected for a population with no smoking-attributable lung cancer deaths. To ensure that a fuller range of possible SAFs were included in that extrapolation, it used the steeper 95% confidence limit for beta (the observed lung/~non-lung cancer mortality ratio) for the 1990–2000 period. The lung cancer death rate in the unexposed was estimated using observed relative risks (RR) in men, corrected for both (1) those RRs' possibly high (up to 57%) levels of misclassification of current and former smoking status [8] and (2) secondhand smoke exposures in the "never smoker" control group. Lung cancer death RRs adjusted for misclassification of smoking status were estimated by multiplying the observed RR times 1.15, the approximate age-standardized ratio of adjusted/observed RRs of all-cause mortality in that population [8]. The resulting SAF was then further adjusted for the estimated 500 U.S. male non-smoker secondhand smoking lung cancer deaths [14] using the formula $\text{adjusted SAF} = ((\text{misclassification adjusted SAF} \times \text{total lung cancer deaths}) + (\text{secondhand smoke lung cancer deaths})) / (\text{total lung cancer deaths})$. That produces an estimated 90.6% SAF for male lung cancer deaths in 1999. That SAF was used for both the 1990 and 2000 upper-bound SAF estimates. That SAF and the 1999 all-race rate suggest an unexposed population estimated rate of $9.4\% \times 76.91 = 7.2 \text{ deaths } 100,000^{-1} \text{ year}^{-1}$.

The best estimate ~non-lung cancer rate in the unexposed was based on the above extrapolation formulae with two changes. The regression slope or beta value used was the point estimate slope from the observed 1969–1990 data. The SAF used was 89.4% based on the above paragraph's formulae but using a RR misclassification adjustment factor of just 1.075 (versus 1.15 used in the upper-bound SAF estimate above). That SAF and the 1999 rate suggest that the unexposed population's age-adjusted lung cancer rate was 8 per 100,000 per year.

The best-estimate SAF of stomach cancer deaths was based on a published cohort study [15] and the above-mentioned partial correction for misclassification of smoking status. The lower and upper bound all-sites cancer death SAF were based on the cohort study without and with correction for full potential misclassification of those who quit cigarettes during follow-up [8].

To get a better picture of the societal burden from smoking, this study calculated SAFs of age-adjusted death rates, rather than SAFs of death numbers. The smoking-attributable all-sites cancer death rate estimate equals the sum of the smoking-attributable rates of ~non-lung, lung, and stomach cancer deaths. The stomach and lung cancer rate SAFs are estimated to equal, for example, the SAF of stomach cancer deaths times the stomach cancer death rate.

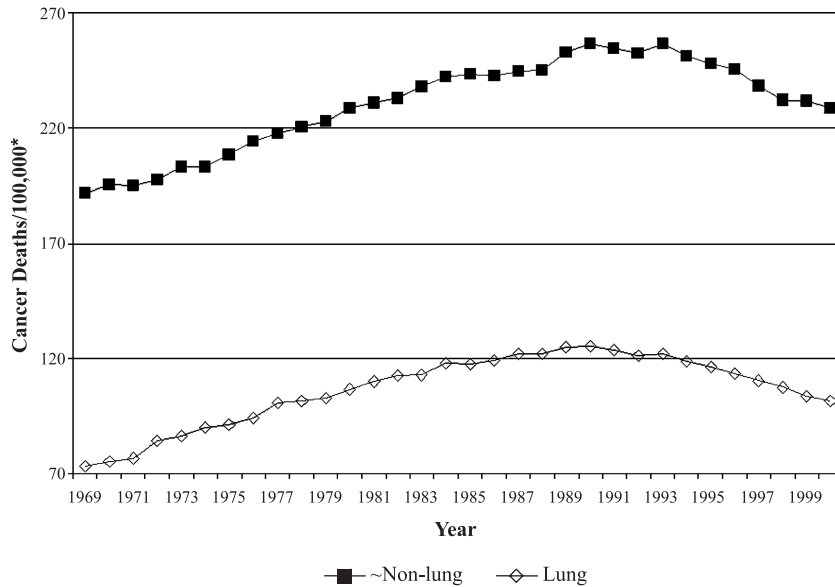


Fig. 1. United States black male lung and ~non-lung cancer death rates, 1969–2000. Adjusted to the 2000 U.S. age standard.

This assumes that smoking causes those deaths at the same age as other causes. This is likely conservative since most smoking-attributable deaths are highly premature [16].

Results

U.S. black males’ ~non-lung cancer annual death rates are graphed versus year in Fig. 1 and versus the annual smoke exposure load (lung cancer rate) in Fig. 2. The ~non-lung cancer rates were nearly perfectly correlated ($R^2 = 0.97+$) with their smoke exposure loads, as measured by their lung cancer death rates (Fig. 2). The

near-perfect correlations held both during smoke exposure loads’ steep increases from 1969 to 1990 [$R^2 = 0.98$; $P < 0.0001$; $y = 1.20x + 101$; 95% confidence interval (CI) for beta = 1.11–.28] and 1990+ decreases [$R^2 = 0.97$; $P < 0.0001$; $y = 1.27x + 100$; 95% confidence interval (CI) for beta = 1.09–1.44].

The above findings suggest best-estimate 1990 and 2000 U.S. black male all-sites cancer death rate SAFs of 66.1% and 62.2%, respectively. Their estimated SAFs are 45.4% in 1990 and 38.2% in 2000 if one assumes that black men had no cancer deaths from smoking or secondhand smoke exposure in 1969 (Table 1). The 1990 and 2000 U.S. black male all-sites cancer death SAFs may approach 72.6% and

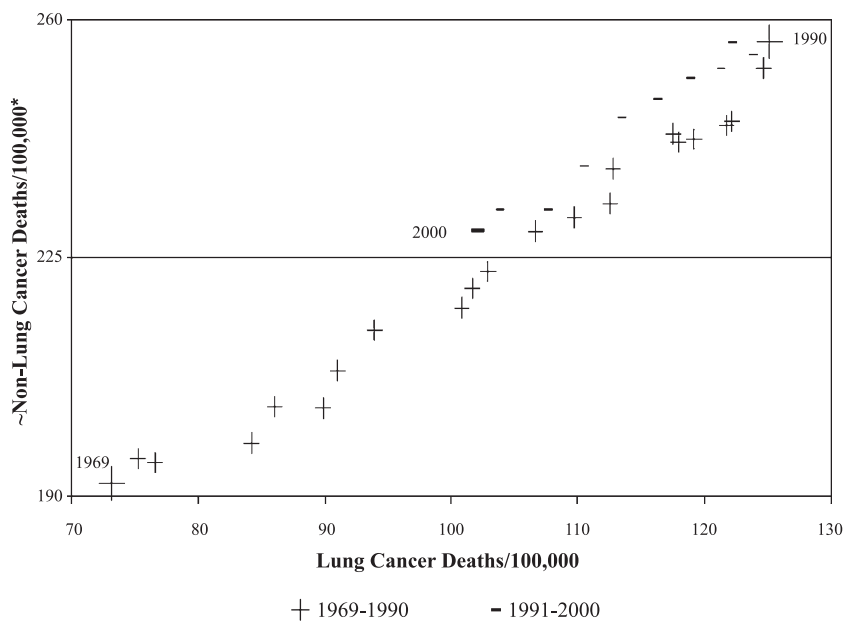


Fig. 2. United States black male lung vs. non-lung cancer annual death rates, 1969–2000. Adjusted to the 2000 U.S. age standard.

Table 1
Estimated, lower-bound, and upper-bound smoking-attributable fractions (SAF) of ~non-lung and all-sites cancer mortality rates^a in black men in the United States in 1990 and 2000

	Estimated SAF [%]	SAF lower-bound estimate (assumes unexposed in 1969) [%]	SAF upper-bound estimate [%]
1990 ~ Non-lung cancer	57	25.3	66.2
2000 ~ Non-lung cancer	51.7	16.2	62.0
1990 All-sites cancer	66.1	45.4	72.6
2000 All-sites cancer	62.2	38.2	72.3

^a Adjusted to the 2000 U.S. age standard.

72.3%, respectively, if previous lung and stomach cancer RRs were underestimated due to unrepresentative samples, secondhand effects, and misclassification effects that exceed half the possible effect on the all-cause mortality RR. Estimated black male SAFs of ~non-lung cancer death rates range from 16.2% in 2000 assuming no exposure in 1969, to possibly as high as 66.2% in 1990 if one extrapolates the 1990–2000 smoke exposure load/~non-lung cancer death rate association (Table 1).

Discussion

During two decades of steep rises, and a subsequent decade of steep falls, U.S. black male smoke exposure loads and ~non-lung cancer death rates have moved in near-perfect lockstep up and starting down. The smoke exposure load/~non-lung cancer death rate associations are strong, dose-response, biologically plausible, and reversible. The associations have been consistent year-by-year for over 30 years, with the modest explicable exception of the years 1988–1992 as the introduction of prostate-specific antigen (PSA) testing increased black male ~non-lung cancer death rates [17]. The associations are consistent with an association that is more likely to be causal. The associations suggest that lung cancer death rates are the best available index of smoke exposure loads in this use, population and period.

The associations suggest much higher SAFs of ~non-lung and all-sites cancer death rates than the about 35% SAFs of male cancer death counts figure from previous national estimates [18]. However, none of the prior national estimates were (1) SAFs of rates or (2) specific to blacks. The discrepancy between the SAFs of age-adjusted rates and SAFs of counts is consistent with the previously observed over 8 years of prematurity of the average death due to smoking [16].

This study has multiple strengths including directness, representativeness, timeliness, dose-response, some conservative bias, and very high (1) statistical significance, (2)

strength of association, and (3) consistency over 31 years. This is the first study of non-lung and all-sites cancer death etiology that uses an exposure biomarker that integrates the effects of current, cumulative, synergistic, secondhand, early onset, in utero, and other smoke exposures. It is biologically plausible that the same smoke effects that contribute to lung cancer death rates would simultaneously contribute to ~non-lung cancer death rates. This study's best estimate and upper-bound SAFs may still be too low. This study assumes both that lung and stomach cancer deaths in the smoke-exposed occur at the same ages as in the unexposed and the lowest possible unexposed male lung cancer death rate is 7.2/100,000, above the rate of 4.3 reported in all U.S. men in 1930 [19].

The primary weakness of this study is the time series/ecological study design. Such designs lack individual-level data, and, especially if cross-sectional, brief, or solely during a rise or a fall, are highly subject to uncontrolled confounding and biased risk estimates. To minimize those risks, over three decades of time-series data including both rising and falling cancer death rates were studied. It seems very unlikely that a confounder would rise in near-perfect lockstep with the smoke exposure load for 21 years, reverse course in the very year that the smoke exposure load reversed course, then fall in near-perfect lockstep with the smoke exposure load for an additional 10 years. The smoking-relatedness of the cancer epidemic in black men is consistent with many other such recent large male cancer death epidemics internationally (unpublished data).

The higher SAFs of all-sites and ~non-lung cancer death in this study could be due to uncontrolled confounding, falsely low previous SAF estimates, or discrepancies between the SAFs of age-adjusted rates, used in this study, versus the SAFs of deaths from previous studies. The consistent results over 31 years strongly argue against confounding. The previous estimates' flaws all suggest that the previous estimates were misleadingly low. Perhaps most misleadingly, by calculating SAFs of deaths, the previous estimates falsely implied that all cancer deaths, from young family breadwinners to dependent centenarians, are equally burdensome to society. That implied that age-adjustment of death rates and the prematurity and societal costs of deaths are irrelevant. Other flaws of the previous estimates include strong selection bias (unrepresentative, white, healthier, and more educated volunteer subjects), unadjusted RRs, and misclassification bias (perhaps 56% of the "current" smokers had quit during follow-up, secondhand smoking was common, and unknown proportions of "never" smokers smoked before or after cohort enrollment) [8]. Those RR adjustments are needed due to known secondhand smoke effects, increased use of possibly more toxic menthol and light cigarettes [20,21], and changes in smoking behavior and RRs over time [22].

This study's results support numerous important inferences, only seven of which will be mentioned here. First, as hypothesized, lung cancer death rates were a valid index of

at least tobacco smoke carcinogen load for the last 31 years in U.S. black men. Second, it appears that cancer prevention efforts for black men with active or secondhand smoke exposure probably should focus nearly exclusively on reducing smoke exposures, at least until there is strong evidence that other interventions substantially affect black male cancer death rates. Third, the virtually fixed lung/non-lung cancer death ratio over 31 years of the smoking–cancer epidemic suggests that black male lung and non-lung cancer deaths from smoking may have similar time courses and mechanisms, perhaps due to smoking’s immunosuppression [23], or nicotine inhibition of apoptosis [24]. Fourth, the fixed lung/~ non-lung cancer death ratio suggests that medical care changes have most likely had little effect on smoking-related cancer death rates in black men; or, far less likely, have had identical time courses and effects in both lung and non-lung cancer. A lack of medical care effects on smoking–cancer death rates is suggested by the known deficits of health care and the dearth of information suggesting increased black male lung cancer survival rates. Fifth, it appears that smoking may cause nearly 2/3 of the black male cancer death rate. Therefore, it appears that just greatly reducing smoke exposure loads in black men would be enough to reverse U.S. black versus white cancer mortality disparities or black male versus black female cancer mortality disparities. Sixth, the results suggest, but do not test, that other male ethnic or national groups with high lung cancer death rates from smoking also will have high ~ non-lung cancer death rates from smoking. Seventh, the results suggest that large discrepancies in the strength of states’ tobacco control programs may induce large cancer mortality disparities.

Further research is needed to better test most of the above inferences and validate the use of lung cancer as an index of current smoke exposure burdens beyond ~ non-lung and all-sites cancer mortality in black men.

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