Are most cancer deaths in more developed nations now from smoking? Recent smoke load/cancer death association trends

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“New, improved cohort data suggest that the number of deaths, number of body sites and socioeconomic breadth of smoking-attributable cancer mortality have been considerably underestimated.”

Research is linking tobacco use to an increasingly dominant share of cancer deaths globally. Increasing smoking in less developed nations and females [1,101], improving cohort [2], time-series [3] and demographic analyses [4,5], and large drops in breast, uterine and stomach cancer death rates, are linking smoking to large, increasing shares of premature cancer deaths. With several colleagues, I recently used time-series analysis to link over two-thirds of the 2003 Massachusetts male all-age, all-sites age-standardized cancer death rate to smoking [3]. Others linked smoking to previously ill-studied types of non-lung cancer deaths [2]. Methods minimizing selection misclassification and detection biases suggest that smoking is causing non-lung cancer death tolls that may be over twice [2,3,6–12] current ‘conservative’ official US CDC, WHO, Smoking-Attributable Mortality, Morbidity, and Economic Costs (SAMMEC), and other Cancer Prevention Study-II (CPS-II) based estimates [8,13,14,102].

While official estimates of smoking tolls generally report some conservative bias, the potential immensity of those biases seems to be underappreciated. Researchers extrapolating CPS-II smoker risk estimates into national and global smoking-attributable mortality estimates reported that “...death rates among the non-smokers and the smokers in the CPS-II study cannot be generalized even to the USA, let alone to other populations. For example, the probability that a 35-year-old man will die before 70 is 34% at USA 1985 death rates, but only 13 and 32% at the nonsmoker and smoker death rates in years 3–6 of CPS-II” [15]. WHO global tobacco death tolls estimates use a ‘conservative’

adjustment that others term “...obviously not a satisfactory procedure, for it is crude and arbitrary and may seriously underestimate some of the true hazards of tobacco” [15].

Officials underestimating tobacco tolls may have misled increasing majorities of Americans to agree with statements that ‘It seems like everything causes cancer’ [103]. Resulting researcher confusion may have contributed to the January 2009 *Proceedings of the US National Academy of Sciences* mention that: “Although epidemiologic studies have identified cigarette smoking as an important risk factor in mortality for at least a half century, there is no consensus on how great the risk is. The large studies that have garnered the bulk of attention are based on nonrepresentative samples and have typically recorded smoking status at baseline without changing the classification of individuals as their smoking status changes. Measurement error [or misclassification bias] in smoking status has the effect of reducing the estimated risk...”, and thus underestimating cancer and other tolls from smoking [5].

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New, improved cohort data suggest that the number of deaths, number of body sites and socioeconomic breadth of smoking-attributable cancer mortality have been considerably underestimated [2]. CDC and WHO CPS-II-based (official) estimates link smoking to modest fractions of both cancer sites and US female

non-lung cancer and all-cause deaths at ages 35+ years (5.5 and 14%, respectively, of such female US deaths in 2004). However, methods minimizing exposure and outcome misclassification biases attributed approximately 28% of all and 64% of current smoker 1980–2004 US healthy volunteer, married, female nurse (Nurse), all-cause deaths to self-reported ever smoking ‘regularly’. Those Nurse non-lung cancer deaths from smoking include many deaths (10% of all Nurse and 40% of current smoker Nurse deaths) from cancers at sites that the CDC and WHO count as not smoking-related, yet still exclude deaths from second-hand, insensible [16], never regular and misreported smoking [17].

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Possible mechanisms for the large discrepancies between official and methodologically improved estimates [2] of non-lung cancer tolls from smoking have been limitedly reviewed. Thus, I will elaborate on the possible impacts of multiple conservative biases in official estimates of non-lung cancer death tolls from smoking. Those biases include disproportionate: selection of lighter, quit-prone smokers [15,18]; misclassification of lighter smoking as ‘never’ smoking [17]; misclassification of former smoking as ‘current’ smoking [14,19]; and detection of ‘lung cancer’ in smokers [20–22].

Selection biases from omitting high-risk smokers from a cohort can seriously bias extrapolations across dissimilar years or levels of exposure, times, death rates and nations. It appears that selection bias may seriously afflict the CPS-II non-lung cancer death relative risks, which officials have extrapolated across two decades nationally and over eleven decades globally [102,104]. CPS-II studied a select, very low mortality rate 1% of the US 1982–1988 population [18,23], and found female smoker relative mortality risks of 1.9 for all causes and less for death from non-lung cancers. Jousilahti has noted that even with an 84% participation rate in a general Scandinavian population, the concurrent non-participants had over half of all suicides in the general population, and ‘tobacco-related’ disease death rates that were twice those of the participants [24]. Therefore, official extrapolations of CPS-II non-lung cancer death relative risks

are prone to underestimate general population non-lung cancer risks nationally and globally, especially given observed rises in female smoke loads as measured by lung cancer rates. Those rates rose through to approximately 1990 in higher socio-economic status (SES) and 1998 in lower SES counties in the USA [25], and are rising globally [1].

Wide discrepancies exist, especially in higher SES groups, between official US estimates of female non-lung cancer burdens from smoking and a 2008 analysis of Nurses data by Kenfield *et al.*, which included both biennial exposure reassessment with improved definitions of both current and ever smoking that reduced exposure misclassification bias, and juried cause of death assignment to minimize detection/cause of death misclassification biases [2]. Those Nurse smokers were shown to have a non-lung cancer death hazard ratio of approximately 2 at age 34–83 years after adjustment for self-reported cardiac risk factors [2]. This and an ex-smoker hazard ratio of approximately 1.3 suggests smoker and all-person Nurse non-lung cancer death smoking-attributable fractions (SAFs) of approximately 40 and 20%, respectively, despite the presumably high access to healthcare and the increasing rarity (8% prevalence in 2002) of active smoking in the Nurses [2]. The Nurses also had at least cardiovascular disease incidence excesses associated with insensible smoking as reflected by their toenail nicotine levels [16].

SAF estimates are generally ‘very sensitive’ to the misclassification of smokers as unexposed ‘never smokers’ [105]. Consequently, past categorization of CPS-II second-hand, forgetful and intermittent smokers as ‘never’ smokers may have underestimated SAFs. CPS-II ‘lifetime never smokers’ probably nearly all smoked at least second-hand at times, since almost 90% of representative US adults had detectable cotinines, indicating recent active or passive smoking in 1990 [106]. Many CPS-II ‘lifetime never smokers’ probably smoked forgetfully as well [17]. In addition, the CPS-II definition of ‘lifetime never smoker’ included even heavy smokers who denied ever smoking over 364 days in a row, for example by having annually abstained for Christmas. In a predecessor study to CPS-II, Doll and Hill report applying the same biased definition of ‘lifetime never smoker’, since no true ‘nonsmokers’ existed [26].

The actual impact of the biased definition of ‘lifetime never smoker’ used in CPS-II has not been well quantified. At least one comparative study of lung cancer in various ‘lifetime

never smokers' concludes that they nearly all have similar lung cancer rates, except for some Asian females. However, that study does not address the lack of blinded assessment of outcomes in the CPS-II, and consequent detection bias relative to Nurses data, which minimized that bias through juried cause of death assignment [2]. Misclassifying CPS-II lighter smokers as 'never' smokers may have elevated CPS-II, ages 45–54 years 'never' smoker lung cancer rates to 5/100,000, approaching the approximately 7.7/100,000 seen in White females and males in West Los Angeles in 2003–2006, with 15 and 8% current and 53 and 52% ever-active smoking prevalences, respectively, in 2003 to 2005. Those smoking prevalences and observed CPS-II 'never' smoker lung cancer rates [27] and age 45–54 years current and age 35+ ex-smoker lung cancer relative risks of 18 in males and 12 in female current smokers, and 8.7 and 4.5, respectively, in ex-smokers, suggest West Los Angeles unexposed population lung cancer rates per 100,000 of approximately one in males and two in females, approximately 20–40% of the levels cited for CPS-II 'never' smokers.

Official SAF estimates are further prone to underestimation due to their underlying exposure misclassification biases from probable differences in smoking cessation rates between CPS-II participants and nonparticipants [14]. Such biases may be large, since most CPS-II 'smokers' resurveyed 12 years after enrollment denied current smoking [14]. In addition, CPS-II participants were disproportionately educated [18] and studied when educational differences in smoking cessation [28], and probably preimpairment (healthy) quitting of smoking [29], reached historic highs. Misclassifying more years of former smoking as 'smoker' person years appears to be a primary difference between the smoker all-cause mortality hazard ratios of 2.8 versus approximately 2.1 in Nurses [2,30], and 3.4 versus 2.8 in women, and 2.4 versus 2.1 in men, in a high participation rate Finnish population [19] with less (2-year maximum) versus more (6-year maximum) cessation-related 'smoking' status misclassification.

Detection bias from undetected non-lung cancer or lung cancer deaths among CPS-II 'lifetime never smokers', and overdiagnosis of such deaths among 'smokers' may also have biased estimates of non-lung cancer smoking-attributable mortality globally [20,21], especially in women given their modest smoker non-lung cancer relative risks [22]. Over- and under-diagnoses of lung cancer in smokers and nonsmokers tend to cancel each other out in general populations with mixtures of smokers and nonsmokers. Therefore, if non-lung cancer and other deaths were mistakenly attributed to lung cancer in CPS-II smokers, the Peto/WHO methods of indirect extrapolations based on CPS-II smoker lung cancer rates would result in underestimation of non-lung cancer and other deaths rates globally [15].

In conclusion, increasing evidence suggests that tobacco use causes much larger shares of premature cancer deaths and, especially, currently preventable cancer deaths than the already high current official estimates. Specifically, the estimates of the US and global non-lung cancer death tolls from smoking may be substantial underestimates, especially in females. Based on their lung cancer and other mortality rates, those CPS-II-based estimates compared 'lifetime never smokers' who probably smoked at least secondhand or forgetfully to 'smokers', who were disproportionately light and quitting 'smokers' rather than representative 'smokers' [14,19]. Suggestions that official smoking-attributable mortality estimates have selection, misclassification and other biases and underestimation are consistent with multiple cancer death time-series analyses [5,7,9,11,12] and prior cohort [14,19,24] and sensitivity analyses [8].

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