Re: Differences in Lung Cancer Risk Between Men and Women: Examination of the Evidence

The large, hospital-based, case-control study by Zang and Wynder (1) provides evidence for greater susceptibility to tobacco carcinogens among women. In contrast, as the authors noted, the early cohort studies of lung cancer (2, 3) were not consistent with the hypothesis of greater susceptibility to tobacco carcinogens among women.

We are writing to provide further evidence from a small cohort study supporting the hypothesis that cigarette smoking is a stronger predictor of lung cancer among women than among men. Our findings are based on a 23-year follow-up of the Alameda County Study, a prospective, population-based study conducted in Alameda County, California, 1965-1988 (4). Our findings were originally presented in 1987 to the Society for Epidemiologic Research (5).

In our earlier work (5), cited in subsequent publications (6, 7), we reported that pack-years was a stronger predictor of lung cancer mortality in women than in men in the Alameda County Study. The study population consisted of whites, blacks, and Asians, who were 30 years or older in 1965 and were current or never smokers. These 1815 men and 2478 women were followed for mortality during the period from 1965 through 1988. During that period, 64 deaths from lung cancer were identified in the cohort through in-state and out-of-state tracing and linkage to vital statistics records.

The sex ratio for lung cancer mortality depended on age at entry, reflecting the rapidly rising rates of lung cancer mortality among women during the 1980s. The sex ratio showed a statistically significant inverted U-shape with age. There was no sex difference in lung cancer mortality for birth cohorts under 50 years of age at entry in 1965, but there was a large male excess for birth cohorts aged 60-69 years. Multiple logistic regression was used to model this age-by-sex interaction and to estimate the association between pack-years and lung cancer mortality. We found a significant pack-years-by-sex interaction (P = .01) despite the small number of cases available. The odds ratio for 40 pack-years (versus non-smokers) among women was 6.9 (95% confidence interval = 3.3-14.4). It was 2.1 (95% confidence interval = 1.2-3.5) among men. This finding persisted when the Cox proportional hazards model was used for analysis and occurred despite evidence that inhalation and packs per day were lower among women.

The discrepancy between these findings and those in earlier cohort studies may be due to the inclusion of women with higher smoking exposures in our cohort. We agree with Zang and Wynder (1) that lower exposures among female smokers probably masked larger relative risks for women in the early cohort studies of lung cancer. Larger smoking associations among women were reported for case-control studies with cases collected in the 1980s and beyond [e.g., Zang and Wynder (7), Brownson et al. (7), Risch et al. (6)]. This later period reflects rising lung cancer incidence and mortality in birth cohorts with higher female smoking exposures. The history of this evidence reminds us that epidemiologic associations depend on the timing of observation. Uncovering a larger relative risk for women has important public policy implications and may advance our understanding of the cause of lung cancer.

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References


Notes

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Response

The results of the cohort study by Cohn et al. (1) provide further evidence that both amount and duration of exposure are crucial variables in estimating cancer risk (2). In accordance with our findings (2, 3) and results of several other investigations (4-6), Cohn et al., using pack-years of smoking as the exposure measure, observed a higher relative risk for lung cancer in females. In other studies (7-9), however, this sex difference may have been masked as a result of a failure to adjust for differences in either duration of smoking or tar yield.
Letters to the Editor


Lynch et al. Respond

Doug Carroll and George Davey Smith have raised several concerns, and we thank them for their interest in our study. We agree that our measure of systolic blood pressure reactivity is unconventional, but that does not necessarily disqualify it as a valid way to assess the underlying phenomenon of cardiovascular response to stress. We have already shown that this measure predicts incident hypertension in middle-aged men.

The period preceding exercise is characterized by emotional, behavioral, and physiological arousal similar to that evoked by challenging mental tasks and the cold pressor test. The bike test portends a serious and potentially stressful physical challenge for the participant, and reactivity scores derived by this method may not be as sensitive to the problems of “task engagement” that can arise with computer-based mental challenges. In addition to the measure of reactivity derived from the bicycle test, the Kuopio Ischemic Heart Disease Risk Factor Study also collected, as part of the 4-year examination, a set of reactivity measures derived from a battery of computer-based mental challenges. The reactivity measures based on mental challenges also show cross-sectional relationships with carotid atherosclerosis.

We were aware of the potential for the bicycle-based reactivity measure to be affected by prior exercise and/or fitness levels, but preliminary analyses revealed the same results stratified by fitness level or excluding those who reported bicycling as their main form of conditioning physical exercise. Reactivity was only modestly correlated with maximal oxygen uptake ($r = -0.14$) and not related to exercise considered to be aerobically conditioning ($r = 0.02$).

Analyses conducted with continuous versions of the variables produced essentially the same conclusions. The variables were dichotomized for consistency with previous publications that have used these measures of cardiovascular reactivity and socioeconomic position.

The overall F statistic test investigates any differences among the categories, but because we had hypothesized a priori that the particular combination of low socioeconomic status and high reactivity would be related to the greatest progression of carotid atherosclerosis, we felt that this pairwise comparison was appropriate. We are sympathetic to the general point raised by Carroll and Davey Smith in regard to the inconsistent significance of F statistics under the conventional criteria. However, we are also aware of the power problems related to assessing interactions. Greenland has suggested that the precision of the interaction estimate may be only one quarter of that of the main effect estimate.

Levels of statistical significance reflect both magnitude of effects and sample size and thus represent inherently confounded information. There is nothing magical about the 5% confidence level. Its overly rigid application for delimiting the importance of findings, particularly for interactions, should be approached with caution.

Finally, Carroll and Davey Smith remind us that claims of interaction should be given credence only when there is evidence of main effects. In analyses yet to be published, we have shown that, in models adjusted for age and the technical factors described in the article, the measure of systolic blood pressure reactivity based on anticipation of the bicycle test is a statistically significant and important predictor of carotid atherosclerosis.

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References


On Contraception and Abortion in Armenia

I am disturbed by the research study on abortion in Armenia recently published in the Journal. The authors of the study make a case for improved contraceptive services, which I applaud. Having worked in the field of family planning since 1981, I appreciate the importance of preventive family planning services for women. However, to argue their case, the authors make some false statements about abortion that I feel need clarification.

The impetus for this study seems to be the decline in fertility, the increase in maternal mortality, and the increase in infertility rates between 1980 and 1995 in Armenia. It appears that the covert, or not overt, research question being addressed is the following: Is abortion the cause of these public health changes in Armenia? As the article continues, though, it becomes clear that the researchers are unable to answer this question and, instead, confuse correlation with causation.

Yes, fertility has declined, maternal mortality has increased, and infertility has increased. However, the researchers fail to prove that these public health changes can be attributed to the high rates of abortion in Armenia.

Lacking modern or effective birth control methods, women in the USSR and Eastern Europe have historically used abortion as their method of birth control. Given the lack of alternatives and the typical rate of fertility, it makes perfect sense that a 40-year-old woman would have had an average of 8 abortions.

It is not abortion, or what the authors call “induced abortion,” that leads to high rates of maternal morbidity; rather, it is illegal and/or poorly performed abortions that can result in infection, infertility, or even death. However, continuing a pregnancy and giving birth is also very dangerous to women's health in the developing world;