July, 2007

COPD and lung cancer have come a long way...baby

David M. Mannino

JOHN R. BALMES, M.D.
*UCSF Lung Biology Center
 San Francisco, California*
 MICHELLE V. FANUCCHI, PH.D.
*School of Veterinary Medicine
 University of California, Davis
 Davis, California*
 WILLIAM N. ROM, M.D., M.P.H.
*New York University School of Medicine
 New York, New York*

References

- Kim JJ. Ambient air pollution: health hazards to children. *Pediatrics* 2004;114:1699–1707.
- Spier CE, Little DE, Trim SC, Johnson TR, Linn WS, Hackney JD. Activity patterns in elementary and high school students exposed to oxidant pollution. *J Expo Anal Environ Epidemiol* 1992;2:277–293.
- Burri PH. Postnatal development and growth. In: Crystal RG, Editor. *The lung: scientific foundations*. Philadelphia: Lippencott-Raven; 1997. pp. 1013–1026.
- Avol EL, Gauderman WJ, Tan SM, London SJ, Peters JM. Respiratory effects of relocating to areas of differing air pollution levels. *Am J Respir Crit Care Med* 2001;164:2067–2072.
- Gauderman WJ, McConnell R, Gilliland F, London S, Thomas D, Avol E, Vora H, Berhane K, Rappaport EB, Lurmann F, et al. Association between air pollution and lung function growth in Southern California children. *Am J Respir Crit Care Med* 2000;162:1383–1390.
- Schwartz JD, Katz SA, Fegley RW, Tockman MS. Analysis of spirometric data from a national sample of healthy 6- to 24-year-olds (NHANES II). *Am Rev Respir Dis* 1988;138:1405–1414.
- Burnett RT, Smith-Doiron M, Stieb D, Raizenne ME, Brook JR, Dales RE, Leech JA, Cakmak S, Krewski D. Association between ozone and hospitalization for acute respiratory diseases in children less than 2 years of age. *Am J Epidemiol* 2001;153:444–452.
- Lewis TC, Robins TG, Dvonch JT, Keeler GJ, Yip FY, Mentz GB, Lin X, Parker EA, Israel BA, Gonzalez L, et al. Air-pollution associated changes in lung function among asthmatic children in Detroit. *Environ Health Perspect* 2005;113:1068–1075.
- Peel JL, Tolbert PE, Klein M, Metzger KB, Flanders WD, Knox T, Mulholland JA, Ryan PB, Frumkin H. Ambient air pollution and respiratory emergency department visits. *Epidemiology* 2005;16:164–174.
- Dales RE, Cakmak S, Doiron MS. Gaseous air pollutants and hospitalization for respiratory disease in the neonatal period. *Environ Health Perspect* 2006;114:1751–1754.
- Triche EW, Gent JF, Holford TR, Belanger K, Bracken MB, Beckett WS, Naeher L, McSharry JE, Leaderer BP. Low-level ozone exposure and respiratory symptoms in infants. *Environ Health Perspect* 2006;114:911–916.
- Gent JF, Triche EW, Holford TR, Belanger K, Bracken MB, Beckett WS, Leaderer BP. Association of low-level ozone and fine particles with respiratory symptoms in children with asthma. *JAMA* 2003;290:1859–1867.
- McConnell R, Berhane K, Gilliland F, London SJ, Islam T, Gauderman WJ, Avol E, Margolis HG, Peters JM. Asthma in exercising children exposed to ozone: a cohort study. *Lancet* 2002;359:386–391.
- Kunzli N, Lurmann F, Segal M, Ngo L, Balmes J, Tager IB. Association between lifetime ambient ozone exposure and pulmonary function in college freshmen: results of a pilot study. *Environ Res* 1997;72:8–23.
- Tager IB, Balmes J, Lurmann F, Ngo L, Alcorn S, Kunzli N. Chronic exposure to ambient ozone and lung function in young adults. *Epidemiology* 2005;16:751–759.
- Bell ML, Dominici F, Samet JM. A meta-analysis of time-series of ozone and mortality with comparison to the national morbidity, mortality, and air pollution study. *Epidemiology* 2005;16:436–445.
- Devlin RB, McDonnell WF, Mann R, Becker S, House DE, Schreinemachers D, Koren HS. Exposure of humans to ambient levels of ozone for 6.6 hours causes cellular and biochemical changes in the lung. *Am J Respir Cell Mol Biol* 1991;4:72–81.
- Horstman DH, Folinsbee LJ, Ives PJ, Abdul-Salaam S, McDonnell WF. Ozone concentration and pulmonary response relationships for 6.6-hour exposures with five hours of moderate exercise to 0.08, 0.10, and 0.12 ppm. *Am Rev Respir Dis* 1990;142:1158–1163.
- Kinney PL, Nilsen DM, Lippmann M, Brescia M, Gordon T, McGovern T, Fawal HE, Devlin RB, Rom WN. Biomarkers of lung inflammation in recreational joggers exposed to ozone. *Am J Respir Crit Care Med* 1996;154:1430–1435.
- American Thoracic Society. Protective NAAQS standard for ozone. Resolution 708 at I-06 AMA House of Delegates. Las Vegas, NV: December 2006.

DOI: 10.1164/rccm.200704-607ED

COPD and Lung Cancer Have Come a Long Way . . . Baby

A famous tobacco advertisement from the 1970s made the claim that women were biologically superior to men:

We make Virginia Slims especially for women because they are biologically superior to men . . . Women have two “X” chromosomes in their sex cells while men have only one “X” chromosome and a “Y” chromosome, which some experts consider to be the inferior chromosome . . . In view of these and other facts, the makers of Virginia Slims feel it highly inappropriate that women continue to use the fat stubby cigarettes designed for mere men. Virginia Slims. Slimmer than the fat cigarettes men smoke . . . You’ve come a long way, baby. (1)

Duplication of the X chromosome has obvious genetic advantages, but does this translate into resistance to the respiratory health effects of tobacco use, such as chronic obstructive pulmonary disease (COPD) and lung cancer? This duplication results in a variety of hormonal and enzymatic outcomes that, ultimately, make women and men different but also, potentially, confers sex-related differences in susceptibility to disease.

In recent years, COPD has become an “equal opportunity” disease with more women developing COPD and suffering COPD-related morbidity and mortality in high-income countries around the world (2–5). The increasing prevalence of COPD

among women in high-income countries is due, in large part, to the historic increase in smoking among women in these populations. In low- and moderate-income countries, COPD prevalence remains lower in women compared with men and the risk factors for disease may also vary, with exposure to indoor air pollutants, poor diet, and poverty being more important than they are in high-income countries (6, 7).

In a similar way, lung cancer has also become a disease affecting an increasing number of women (8). Since the mid 1980s in the United States, more women have died annually of lung cancer than from breast cancer (9). By 1999, 4.6% of deaths among women and 5.1% of deaths among men were from COPD and 5.0% of deaths among women and 7.6% of deaths among men were from lung cancer (8). The link between COPD and lung cancer has been well established in several different cohorts, although the reasons for this association remain unclear (10–12). The question remains whether, all exposures being equal, women are more or less likely to develop COPD and lung cancer when compared with men.

The article by Ben-Zaken Cohen and colleagues in this issue of the *Journal* (pp. 113–120) (13) explores sex-related differences in the development of COPD and lung cancer and in the metabolism of tobacco smoke constituents. The authors acknowledge

that this is an area of research with a great deal of uncertainty. Women have a lower risk of cardiovascular mortality during early adulthood (14), compared with men, so one explanation for increased susceptibility might be a cohort effect—that is, the pool of people at risk for developing cardiovascular and respiratory disease changes over time because a larger proportion of men die of cardiovascular disease at a young age. This lower risk of cardiovascular mortality in women is most likely related to hormonal and sex differences that, ironically, may be the exact same factors that the authors point to as increasing the risk of developing COPD and asthma.

Ben Zaken-Cohen and coworkers (13) show that certain cytochrome p450 (CYP) enzymes, CYP1A1, CYP1A2, and CYP3A4 (Table 1) have increased expression in women and suggest that these differences may lead to sex-related differences in susceptibility to tobacco smoke (and presumably other smoke) toxins. Table 1 in their article also shows, however, that we do not know whether the other enzymes in the cytochrome P450 family are up- or down-regulated in women. Does up-regulation (or down-regulation) of these enzymes lead to the development of lung cancer? This is unknown but certainly an area where a great deal more research is needed and welcome.

Does impaired lung function in women lead to a differentially higher risk of lung cancer than that seen in men? Figure 1 in Ben Zaken-Cohen and colleagues' article (13) demonstrates that when one compares women with men, the loss of lung function is more important as a risk factor for lung cancer in women. Interestingly, though, in the studies from which these data were derived (10, 15), men were significantly more likely to develop lung cancer than women. Thus, an alternative explanation for the pattern seen in Figure 1, is that, among men and women with the best lung function (quintile 5), women are actually less likely to develop lung cancer than men and that this benefit is extinguished when lung function is lost.

While COPD and lung cancer in women have come a long way in the past 35 years, we still have a long way to go to understand how men and women differ in their risk for exposures to tobacco smoke and other factors in the development of these diseases. Ben Zaken-Cohen and colleagues provide some provocative and investigable reasons for sex differences in the development of COPD and lung cancer and the relationship between these two important and lethal diseases (13). Whether women are more or less likely to develop these diseases remains an open question, but developing a better understanding of how sex and hormonal differences influence disease development and progression can hopefully lead to improved interventions and outcomes for our patients.

Conflict of Interest Statement: D.M.M. serves on advisory boards for Boehringer Ingelheim, Pfizer, GlaxoSmithKline (GSK), and Ortho Biotech; is on the speaker's

bureau for Boehringer Ingelheim, Pfizer, GSK, and Dey; and has received research grants from GSK, Novartis, and Pfizer.

DAVID M. MANNINO, M.D.

University of Kentucky College of Public Health
Lexington, Kentucky

References

1. Phillip Morris Advertising Archive. We make Virginia slims especially for women because they are biologically superior to men. You've come a long way, baby [ad from 1971]. Available from: http://tobaccodocuments.org/ads_pm/2058502098.html?ocr_position=hide_ocr (accessed April 16, 2007).
2. Mannino DM, Homa DM, Akinbami LJ, Ford ES, Redd SC. Chronic obstructive pulmonary disease surveillance: United States, 1971–2000. *MMWR Surveill Summ* 2002;51:1–16.
3. Lacasse Y, Brooks D, Goldstein RS. Trends in the epidemiology of COPD in Canada, 1980 to 1995. COPD and Rehabilitation Committee of the Canadian Thoracic Society. *Chest* 1999;116:306–313.
4. Soriano JB, Maier WC, Egger P, Visick G, Thakrar B, Sykes J, Pride NB. Recent trends in physician diagnosed COPD in women and men in the UK. *Thorax* 2000;55:789–794.
5. Keistinen T, Vilkinen S, Tuuponen T, Kivela SL. Hospital admissions for chronic obstructive pulmonary disease in the population aged 55 years or over in Finland during 1972–1992. *Public Health* 1996;110:257–259.
6. Menezes AM, Perez-Padilla R, Jardim JR, Muino A, Lopez MV, Valdivia G, de Montes OM, Talamo C, Hallal PC, Victora CG. Chronic obstructive pulmonary disease in five Latin American cities (the PLATINO study): a prevalence study. *Lancet* 2005;366:1875–1881.
7. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJL. Global burden of disease and risk factors. Washington, DC: The World Bank; 2006.
8. Kazerouni N, Alverson CJ, Redd SC, Mott JA, Mannino DM. Sex differences in COPD and lung cancer mortality trends: United States, 1968–1999. *J Womens Health (Larchmt)* 2004;13:17–23.
9. Greenlee RT, Murray T, Bolden S, Wingo PA. Cancer statistics, 2000. *CA Cancer J Clin* 2000;50:7–33.
10. Mannino DM, Aguayo SM, Petty TL, Redd SC. Low lung function and incident lung cancer in the United States: data from the First National Health and Nutrition Examination Survey follow-up. *Arch Intern Med* 2003;163:1475–1480.
11. Tockman MS, Anthonisen NR, Wright EC, Donithan MG. Airways obstruction and the risk for lung cancer. *Ann Intern Med* 1987;106:512–518.
12. Purdue MP, Gold L, Jarvholm B, Alavanja MC, Ward MH, Vermeulen R. Impaired lung function and lung cancer incidence in a cohort of Swedish construction workers. *Thorax* 2007;62:51–56.
13. Ben-Zaken Cohen S, Paré PD, Man SFP, Sin DD. The growing burden of chronic obstructive pulmonary disease and lung cancer in women: examining sex differences in cigarette smoke metabolism. *Am J Respir Crit Care Med* 2007;176:113–120.
14. Bello N, Mosca L. Epidemiology of coronary heart disease in women. *Prog Cardiovasc Dis* 2004;46:287–295.
15. Hart CL, Hole DJ, Gillis CR, Smith GD, Watt GC, Hawthorne VM. Social class differences in lung cancer mortality: risk factor explanations using two Scottish cohort studies. *Int J Epidemiol* 2001;30:268–274.

DOI: 10.1164/rccm.200704-590ED

Can a Deep Breath Blow Away the Fog Surrounding Airway Hyperresponsiveness?

The most consistent diagnostic feature of asthma is the presence of airway hyperresponsiveness (AHR). Therefore, understanding the mechanisms underlying AHR seems essential for the development of interventions to control or cure asthma. Despite enormous research effort, we still do not fully understand why the asthmatic airways respond to much lower concentrations of provoking agents than do normal airways. We do know, however, that the lung volume at which we breathe and the presence of

deep inspirations (DIs) have the capacity to markedly modulate these airway responses and exhibit different effects on individuals with and without asthma. Therefore, it seems reasonable to propose that an understanding of mechanisms underpinning the DI responses may shed light on the nature of AHR itself.

During bronchial challenge, DI causes bronchodilation in individuals without asthma (1), whereas this effect is less marked or absent in patients with asthma (2). In spontaneous asthma