

blood of patients with NSCLC [adenocarcinoma, 40; squamous cell carcinoma, 6; and nonclassified NSCLC, 6] in comparison to 17 healthy control subjects. In addition, 40 patients who received cisplatin-based chemotherapy in a randomized prospective trial were evaluated for the predictive role of MDSC. The authors demonstrated that there was a higher proportion of CD11b⁺CD14⁺ than CD11b⁺CD14⁻ MDSC in the peripheral blood mononuclear cells of patients with NSCLC, and the frequencies of both subsets were higher in patients with NSCLC in comparison to healthy control subjects. Both subsets of MDSC had similar suppressive activity on CD8 T-cell proliferation and IFN- γ production. In contrast, CD11b⁺CD14⁺ cells from healthy donors showed no suppressive ability on CD8⁺ T-cell proliferation or IFN- γ production. Through inhibitor and antibody-mediated blocking experiments, the authors showed that the CD11b⁺CD14⁺ MDSC-mediated suppression of CD8 T cells *in vitro* was via arginase, inducible nitric oxide synthase, the IL-13/IL-4R α axis, and IL-10. The levels of S100A9⁺ expression by CD11b⁺CD14⁺ correlated with their suppressive ability. Furthermore, high levels of CD11b⁺CD14⁺S100A9⁺ MDSC were associated with poor response to cisplatin-based chemotherapy and predicted shorter progression-free survival. Although the CD11b⁺CD14⁻ subpopulation of MDSC had an inhibitory ability that was comparable to the CD11b⁺CD14⁺ cells, there was no association of these cells with performance status or treatment response of patients with NSCLC to chemotherapy. The findings of this study are significant as they show that S100A9 can serve as an important marker for the further characterization of the CD11b⁺CD14⁺ MDSC in patients with advanced NSCLC. The results of this study corroborate the findings from a previous study that demonstrated an increase in the population of CD14⁺S100A9⁺ MDSC in the peripheral blood from patients with colon cancer in comparison with healthy control subjects (5). Since solid tumors contain a significant population of tumor-infiltrating myeloid cells that promote tumor growth, the lack of evaluation of the characteristics of MDSC from the NSCLC samples is a limitation of this study. It is not known if the CD11b⁺CD14⁺S100A9⁺ MDSC are present in the lung tumor microenvironment of the patients with advanced NSCLC. Nevertheless, the results of this study demonstrate that levels of CD11b⁺CD14⁺S100A9⁺ MDSC in peripheral blood can serve as a predictor of response to chemotherapy in patients with advanced lung cancer. Further investigations are required to determine whether modulating the levels and activities of CD11b⁺CD14⁺S100A9⁺ MDSC would improve patient outcome

in advanced lung cancer. MDSC play a central role in immune suppressive pathways and tumor progression, and modulating the activities of this population could prove beneficial as an innovative therapeutic strategy against lung cancer.

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References

1. Fujita M, Kohanbash G, Fellows-Mayle W, Hamilton RL, Komohara Y, Decker SA, Ohlfest JR, Okada H. COX-2 blockade suppresses gliomagenesis by inhibiting myeloid-derived suppressor cells. *Cancer Res* 2011;71:2664–2674.
2. Mundy-Bosse BL, Lesinski GB, Jaime-Ramirez AC, Benninger K, Khan M, Kuppusamy P, Guentherberg K, Kondadasula SV, Chaudhury AR, La Perle KM, *et al*. Myeloid-derived suppressor cell inhibition of the IFN response in tumor-bearing mice. *Cancer Res* 2011;71:5101–5110.
3. Srivastava MK, Zhu L, Harris-White M, *et al*. Myeloid suppressor cell depletion augments antitumor activity in lung cancer. *PLoS* 2012 7:e40677.
4. Feng P-H, Lee K-Y, Chang Y-L, Chan Y-F, Kuo L-W, Lin T-Y, Chung F-T, Kuo C-S, Yu C-T, Lin S-M, *et al*. CD14⁺S100A9⁺ monocytic myeloid-derived suppressor cells and their clinical relevance in non-small cell lung cancer. *Am J Respir Crit Care Med* 2012;186:1025–1036.
5. Zhao F, Hoechst B, Duffy A, Gamrekelashvili J, Fioravanti S, Manns MP, Greten TF, Korangy F. S100A9 a new marker for monocytic human myeloid-derived suppressor cells. *Immunology* 2012;136:176–183.

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Maternal Smoking during Pregnancy and Its Effect on Childhood Asthma

Understanding the Puzzle

Maternal smoking during pregnancy is a well-established and modifiable environmental risk factor for infant respiratory viral infection and childhood asthma (1, 2). *In utero* exposure to maternal smoking influences the development of the fetal respiratory system by impairing an infant's immune system and lung development (3–5). However, as most women who smoke during pregnancy continue to smoke after delivery (6), previous findings of the effect of maternal smoking during pregnancy on childhood asthma often represent a combined effect of maternal smoking during pregnancy and secondhand smoke (SHS) exposure after

pregnancy. The independent effect of *in utero* exposure to maternal smoking has not been well differentiated from the SHS exposure after birth. This is an interesting question, as the relative contribution and mechanisms through which SHS contribute to asthma development are likely to be different with *in utero* exposure to maternal smoking compared with SHS inhalational exposure after birth.

Neuman and colleagues, in this issue of the *Journal* (pp. 1037–1043), conducted a pooled analysis of eight European birth cohorts to assess the independent effect of *in utero* exposure to maternal

smoking during pregnancy on preschool wheeze and asthma (7). Information about maternal smoking during pregnancy, as well as SHS exposure during the first year of life and at age 4 to 6 years, was obtained from parental questionnaires. Compared with children who were exposed neither to maternal smoking during pregnancy nor to SHS during the first year of life, children whose mothers smoked during pregnancy, but who experienced no SHS exposure during the first year of life, were found to have an increased risk of wheeze and asthma at age 4 to 6 years. Further, the harmful association of maternal smoking during pregnancy on childhood wheeze and asthma was observed already for the first-trimester exposure to maternal smoking. Every five-cigarette increase in first-trimester daily exposure to maternal smoking increased the odds of having childhood wheeze by 1.18 (95% confidence interval, 1.02–1.38) and the odds of developing childhood asthma by 1.23 (95% confidence interval, 1.03–1.47). On the other hand, maternal smoking during the third trimester or the first year of life appeared not to be associated with an increased risk of wheeze and asthma.

The finding that first-trimester exposure to maternal smoking plays an important role in the development of childhood wheezing is novel, but contradictory to the results of a recent publication from the Generation R Study (8). Duijts and colleagues reported that maternal smoking during the first trimester only was not associated with wheezing at ages 1, 2, 3, and 4 years. Instead, they found that continued maternal smoking during pregnancy was associated with an increased risk of wheezing. Several differences in study design and outcomes may explain the different conclusion reached by the two studies. Neuman and colleagues in this issue of the *Journal* studied and defined current wheeze as well as asthma at age 5 years (with the exception of one study cohort with outcomes defined at age 4 and one at age 6 years), whereas Duijts and colleagues focused only on childhood wheezing and defined wheezing every year until age 4 years. Second, Neuman and colleagues conducted a pooled analysis of eight cohorts. Compared with the single cohort of the Generation R Study, an analysis of eight cohorts has the advantage of a larger sample size, but it also has the limitation of inconsistent definition of variables from each participating cohort. *In utero* exposure to maternal smoking reduces blood flow and decreases oxygen and nutrient delivery to the fetus, thus leading to abnormal growth and maturation of the airway and lungs (9). Therefore, it is possible that first-trimester-only exposure to maternal smoking affects the risk of wheezing in preschool children by only altering risk of infection, rather than resulting in permanent airway changes. Whether the mechanisms through which fetal exposure contribute to asthma development are the same throughout pregnancy and during early infancy remains unclear. These data suggest that the mechanisms of the detrimental impact of tobacco exposure during fetal life, even during different stages of pregnancy, and early infant exposures may differ, which makes sense given the rapid developmental trajectory during this period.

Neuman and colleagues also reported that postpregnancy SHS exposure did not appear to be associated with an increased risk of wheeze and asthma. As the authors suggest, the lack of association “may be an effect of the parents avoiding direct smoke exposure of their children during early childhood” (7). Similarly, no association between postpregnancy SHS exposure and childhood wheezing or asthma was reported in the Southern California Children’s Health Study (10). Postpregnancy SHS exposure, even if it is not in the causal pathway for development of wheeze and asthma, can trigger wheezing attacks in children with asthma (10), which might in turn explain the significant association between postnatal SHS exposure and childhood wheezing observed in the Generation R study (8).

Asthma is one of the most common chronic diseases of childhood in the United States, and the prevalence of asthma has been increasing over the past three decades. So far, efforts to find effective and targeted primary and secondary asthma prevention measures have not been successful. Maternal smoking during pregnancy has been repeatedly reported to be associated with premature birth, low birth weight, and sudden infant death syndrome, among other adverse outcomes. The evidence of an association between SHS exposure from parental smoking and the onset of childhood asthma was reported to be insufficient in the 2006 U.S. Surgeon General’s report (11). The results of this study in the *Journal*, along with other studies, add to the overwhelming evidence that maternal smoking during pregnancy contributes to childhood asthma. It provides additional evidence for the next Surgeon General’s Report and highlights the importance of effective smoking cessation programs for parents. Women at child-bearing age who quit smoking will not only reduce their children’s risk of the myriad recognized adverse maternal and infant outcomes associated with smoking, but may also decrease their children’s risk of developing childhood asthma, and for those children with asthma, subsequent asthma exacerbations.

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References

1. Carroll KN, Gebretsadik T, Griffin MR, Dupont WD, Mitchel EF, Wu P, Enriquez R, Hartert TV. Maternal asthma and maternal smoking are associated with increased risk of bronchiolitis during infancy. *Pediatrics* 2007;119:1104–1112.
2. Haberg SE, Stigum H, Nystad W, Nafstad P. Effects of pre- and postnatal exposure to parental smoking on early childhood respiratory health. *Am J Epidemiol* 2007;166:679–686.
3. Prescott SL. Effects of early cigarette smoke exposure on early immune development and respiratory disease. *Paediatr Respir Rev* 2008;9:3–9.
4. Stocks J, Devereux C. The effect of parental smoking on lung function and development during infancy. *Respirology* 2003;8:266–285.
5. Gilliland FD, Berhane K, Li YF, Rappaport EB, Peters JM. Effects of early onset asthma and in utero exposure to maternal smoking on childhood lung function. *Am J Respir Crit Care Med* 2003;167:917–924.
6. Murin S, Rafii R, Bilello K. Smoking and smoking cessation in pregnancy. *Clin Chest Med* 2011;32:75–91, viii.
7. Neuman A, Hohmann C, Orsini N, Pershagen G, Eller E, Kjaer HF, Gehring U, Granell R, Henderson J, Heinrich J, et al. Maternal smoking in pregnancy and asthma in preschool children: a pooled analysis of eight birth cohorts. *Am J Respir Crit Care Med* 2012;186:1037–1043.
8. Duijts L, Jaddoe VW, van der Valk RJ, Henderson JA, Hofman A, Raat H, Steegers EA, Moll HA, de Jongste JC. Fetal exposure to maternal and paternal smoking and the risks of wheezing in preschool children: the Generation R Study. *Chest* 2012;141:876–885.
9. Manning FA, Feyerabend C. Cigarette smoking and fetal breathing movements. *Br J Obstet Gynaecol* 1976;83:262–270.
10. Gilliland FD, Li YF, Peters JM. Effects of maternal smoking during pregnancy and environmental tobacco smoke on asthma and wheezing in children. *Am J Respir Crit Care Med* 2001;163:429–436.
11. U.S. Department of Health and Human Services. The health consequences of involuntary exposure to tobacco smoke: a report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Coordinating Center for Health Promotion, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. 2006.