Supplementary Table 3. Characteristics of some commonly studied biomarkers of inflammation or oxidative stress

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Biomarker** | **Measure of** | **Smokers vs. never smokers** | **Change with cessation** | **Biological gradient** | **Acute effects from smoking** | **Predictive validity** |
| white blood cells | inflammation | X 1 | X 2 | X 2 |  | CVD 3,4 |
| C-Reactive Protein (CRP) | inflammation | X 5,6 | X 6,7 | X 8,9 | X 5 | CVD 10, lung cancer 11 |
| Interleukin-6 (IL6) | inflammation | X 5,12,13 | X 7,12 | X 8 | X 5 | CVD 14, lung cancer 15 |
| Interleukin-8 (IL8) | inflammation | X 13,16 |  |  |  | CVD17, lung cancer 15,18 |
| soluble intercellular adhesion molecule-1 (sICAM1) | inflammation | X 5 | X 5 | X 19,20 | X 5 |  |
| fibrinogen | inflammation | X 21 | X 22 | X 8,21 | X 5 | CVD 23 |
| Prostaglandin E2 Metabolite (PGE-M) | inflammation | X 9,24,25 |  | X 9 |  | colorectal cancer 26 and gastric cancer 27 |
| monocyte chemoattractant protein-1 (MCP-1) | inflammation | X 5,16,28 |  |  | X 5 | CVD 29 |
| urinary F2 isoprostane | oxidative stress | X 1,30 | X 2,31 | X 2 | X 5,30 |  |
| oxidized low-density lipoprotein (LDL) | oxidative stress | X 30 |  |  | X 30 | CVD 32, lung cancer 33 |
| 8-hydroxy-2’-deoxyguanosine (8OHdG) | oxidative stress | X 30,34 | X 35 | X 36 |  |  |
| serum levels of vitamin C | oxidative stress | X 37,38 |  | X 38 |  | CVD 39 |

References

1. Frost-Pineda K, Liang Q, Liu J, et al. Biomarkers of potential harm among adult smokers and nonsmokers in the total exposure study. *Nicotine Tob Res.* 2011;13(3):182-193.

2. King CC, Piper ME, Gepner AD, Fiore MC, Baker TB, Stein JH. Longitudinal impact of smoking and smoking cessation on inflammatory markers of cardiovascular disease risk. *Arterioscler Thromb Vasc Biol.* 2016.

3. Kannel WB, Anderson K, Wilson PW. White blood cell count and cardiovascular disease. Insights from the Framingham Study. *JAMA.* 1992;267(9):1253-1256.

4. Lee CD, Folsom AR, Nieto FJ, Chambless LE, Shahar E, Wolfe DA. White blood cell count and incidence of coronary heart disease and ischemic stroke and mortality from cardiovascular disease in African-American and White men and women: atherosclerosis risk in communities study. *Am J Epidemiol.* 2001;154(8):758-764.

5. Levitzky YS, Guo CY, Rong J, et al. Relation of smoking status to a panel of inflammatory markers: the framingham offspring. *Atherosclerosis.* 2008;201(1):217-224.

6. Shiels MS, Katki HA, Freedman ND, et al. Cigarette smoking and variations in systemic immune and inflammation markers. *J Natl Cancer Inst.* 2014;106(11).

7. McEvoy JW, Nasir K, DeFilippis AP, et al. Relationship of cigarette smoking with inflammation and subclinical vascular disease: the Multi-Ethnic Study of Atherosclerosis. *Arterioscler Thromb Vasc Biol.* 2015;35(4):1002-1010.

8. Al Rifai M, DeFillippis AP, McEvoy JW, et al. The relationship between smoking intensity and subclinical cardiovascular injury: the Multi-Ethnic Study of Atherosclerosis (MESA). *Atherosclerosis.* 2017;258:119-130.

9. Navarro SL, Kantor ED, Song X, et al. Factors associated with multiple biomarkers of systemic inflammation. *Cancer Epidemiol Biomarkers Prev.* 2016;25(3):521-531.

10. Collaboration ERF. Biomarkers in medicine, drug discovery, and environmental health. In: Vaidya VS, Bonventre JV, eds. Hoboken, N.J. :: Wiley; 2010.

11. Chaturvedi AK, Caporaso NE, Katki HA, et al. C-reactive protein and risk of lung cancer. *J Clin Oncol.* 2010;28(16):2719-2726.

12. Bermudez EA, Rifai N, Buring JE, Manson JE, Ridker PM. Relation between markers of systemic vascular inflammation and smoking in women. *Am J Cardiol.* 2002;89(9):1117-1119.

13. Song XY, Zhou SJ, Xiao N, et al. Research on the relationship between serum levels of inflammatory cytokines and non-small cell lung cancer. *Asian Pac J Cancer Prev.* 2013;14(8):4765-4768.

14. Danesh J, Kaptoge S, Mann AG, et al. Long-term interleukin-6 levels and subsequent risk of coronary heart disease: two new prospective studies and a systematic review. *PLoS Med.* 2008;5(4):e78.

15. Brenner DR, Fanidi A, Grankvist K, et al. Inflammatory cytokines and lung cancer risk in 3 prospective studies. *Am J Epidemiol.* 2016.

16. Berrahmoune H, Lamont JV, Herbeth B, FitzGerald PS, Visvikis-Siest S. Biological determinants of and reference values for plasma interleukin-8, monocyte chemoattractant protein-1, epidermal growth factor, and vascular endothelial growth factor: results from the STANISLAS cohort. *Clin Chem.* 2006;52(3):504-510.

17. Boekholdt SM, Peters RJ, Hack CE, et al. IL-8 plasma concentrations and the risk of future coronary artery disease in apparently healthy men and women: the EPIC-Norfolk prospective population study. *Arterioscler Thromb Vasc Biol.* 2004;24(8):1503-1508.

18. Pine SR, Mechanic LE, Enewold L, et al. Increased levels of circulating interleukin 6, interleukin 8, C-reactive protein, and risk of lung cancer. *J Natl Cancer Inst.* 2011;103(14):1112-1122.

19. Scott DA, Stapleton JA, Wilson RF, et al. Dramatic decline in circulating intercellular adhesion molecule-1 concentration on quitting tobacco smoking. *Blood Cells Mol Dis.* 2000;26(3):255-258.

20. Tsai JS, Guo FR, Chen SC, et al. Changes of serum adiponectin and soluble intercellular adhesion molecule-1 concentrations after smoking cessation. *Clin Chem Lab Med.* 2012;50(6):1063-1069.

21. Bazzano LA, He J, Muntner P, Vupputuri S, Whelton PK. Relationship between cigarette smoking and novel risk factors for cardiovascular disease in the United States. *Ann Intern Med.* 2003;138(11):891-897.

22. Okwuosa TM, Klein O, Chan C, et al. 13-year long-term associations between changes in traditional cardiovascular risk factors and changes in fibrinogen levels: the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Atherosclerosis.* 2013;226(1):214-219.

23. Fibrinogen Studies Collaboration. Plasma fibrinogen level and the risk of major cardiovascular diseases and nonvascular mortality: an individual participant meta-analysis. *JAMA.* 2005;294(14):1799-1809.

24. Duffield-Lillico AJ, Boyle JO, Zhou XK, et al. Levels of prostaglandin E metabolite and leukotriene E(4) are increased in the urine of smokers: evidence that celecoxib shunts arachidonic acid into the 5-lipoxygenase pathway. *Cancer Prev Res (Phila).* 2009;2(4):322-329.

25. Gross ND, Boyle JO, Morrow JD, et al. Levels of prostaglandin E metabolite, the major urinary metabolite of prostaglandin E2, are increased in smokers. *Clin Cancer Res.* 2005;11(16):6087-6093.

26. Cai Q, Gao YT, Chow WH, et al. Prospective study of urinary prostaglandin E2 metabolite and colorectal cancer risk. *J Clin Oncol.* 2006;24(31):5010-5016.

27. Dong LM, Shu XO, Gao YT, et al. Urinary prostaglandin E2 metabolite and gastric cancer risk in the Shanghai women's health study. *Cancer Epidemiol Biomarkers Prev.* 2009;18(11):3075-3078.

28. Deo R, Khera A, McGuire DK, et al. Association among plasma levels of monocyte chemoattractant protein-1, traditional cardiovascular risk factors, and subclinical atherosclerosis. *J Am Coll Cardiol.* 2004;44(9):1812-1818.

29. Piemonti L, Calori G, Lattuada G, et al. Association between plasma monocyte chemoattractant protein-1 concentration and cardiovascular disease mortality in middle-aged diabetic and nondiabetic individuals. *Diabetes Care.* 2009;32(11):2105-2110.

30. Seet RC, Lee CY, Loke WM, et al. Biomarkers of oxidative damage in cigarette smokers: which biomarkers might reflect acute versus chronic oxidative stress? *Free Radic Biol Med.* 2011;50(12):1787-1793.

31. Morrow JD, Frei B, Longmire AW, et al. Increase in circulating products of lipid peroxidation (F2-isoprostanes) in smokers. Smoking as a cause of oxidative damage. *N Engl J Med.* 1995;332(18):1198-1203.

32. Holvoet P, Jenny NS, Schreiner PJ, Tracy RP, Jacobs DR, Multi-Ethnic Study of A. The relationship between oxidized LDL and other cardiovascular risk factors and subclinical CVD in different ethnic groups: the Multi-Ethnic Study of Atherosclerosis (MESA). *Atherosclerosis.* 2007;194(1):245-252.

33. Linseisen J, Wolfram G, Miller AB. Plasma 7beta-hydroxycholesterol as a possible predictor of lung cancer risk. *Cancer Epidemiol Biomarkers Prev.* 2002;11(12):1630-1637.

34. Campos C, Guzman R, Lopez-Fernandez E, Casado A. Urinary biomarkers of oxidative/nitrosative stress in healthy smokers. *Inhal Toxicol.* 2011;23(3):148-156.

35. Prieme H, Loft S, Klarlund M, Gronbaek K, Tonnesen P, Poulsen HE. Effect of smoking cessation on oxidative DNA modification estimated by 8-oxo-7,8-dihydro-2'-deoxyguanosine excretion. *Carcinogenesis.* 1998;19(2):347-351.

36. Irie M, Tamae K, Iwamoto-Tanaka N, Kasai H. Occupational and lifestyle factors and urinary 8-hydroxydeoxyguanosine. *Cancer Sci.* 2005;96(9):600-606.

37. Lykkesfeldt J, Christen S, Wallock LM, Chang HH, Jacob RA, Ames BN. Ascorbate is depleted by smoking and repleted by moderate supplementation: a study in male smokers and nonsmokers with matched dietary antioxidant intakes. *Am J Clin Nutr.* 2000;71(2):530-536.

38. Wei W, Kim Y, Boudreau N. Association of smoking with serum and dietary levels of antioxidants in adults: NHANES III, 1988-1994. *Am J Public Health.* 2001;91(2):258-264.

39. Khaw KT, Bingham S, Welch A, et al. Relation between plasma ascorbic acid and mortality in men and women in EPIC-Norfolk prospective study: a prospective population study. European Prospective Investigation into Cancer and Nutrition. *Lancet.* 2001;357(9257):657-663.