Occupational Exposures and Lung Cancer

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Despite decreases in the incidence of certain cancers and associated mortality, cancer remains highly lethal and very common. About 41% of Americans will develop some form of cancer (including non-melanoma skin cancer) in their lifetimes. One fifth of Americans will die from cancer. Notwithstanding important progress made in reduction of lung cancer in the USA with anti-smoking campaigns, it still tops the list for the most common cause of cancer death in the USA, as well as the world. Lung cancer is a global public health problem. There were an estimated 2.1 million lung cancer cases and 1.8 million deaths in 2018 worldwide. Incidence and mortality rates vary 20-fold between regions, mainly because of variation in carcinogen exposure such as tobacco smoking. However, if tobacco smoking were removed altogether, lung cancer would still be in the top 10 cancers worldwide (Samet et. al. 1.). There are a number of well-known lung carcinogens where exposure occurs mainly in the workplace. But, studies of lung cancer in occupational populations are often hampered by small sample size and inability to control for, or assess interactions with, tobacco smoking. It is critical to understand the risks posed by exposures to occupational lung carcinogens in order to develop effective control programs for this deadly disease.

Here, two papers address major issues related to occupational lung cancer (2. Ge, 2020a; 3. Ge, 2020b). One critical feature in this published work is the large sample sizes garnered by pooling multiple case-control studies in their respective assessments of occupational diesel exhaust and crystalline silica exposure while adjusting for and examining interactions with tobacco smoking. Both papers leverage a large pooled sample of 14 case-control studies in Europe and Canada, numbering a total of 37,866 cases (16,901 lung cancer and 20, 965 controls).

The first paper showed diesel exhaust exposure caused increased lung cancer risk even in the lowest category of cumulative exposure using a job-exposure matrix. Moreover, lung cancer risk was increased in non-smoking workers and there were super additive joint effects of

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diesel and smoking in males for all four lung cancer subtypes. Finally, there was evidence for cell subtype differential risk with the highest frequency of squamous cell and small cell, and lowest of adenocarcinoma. Although diesel was classified by the International Agency for Research on Cancer (IARC) as a class 1 human carcinogen based on prior studies, including a large cohort study performed by the US National Cancer Institute and National Institute for Occupational Safety and Health (4. Silverman et. al.), the added power of the current study aids our understanding of exposure-response at relatively low levels of cumulative exposure, smoking interactions, and cell type distribution. The public health consequences of the results are significant, as there are an estimated 1 million US workers, 3.6 million European workers, and millions more in Asia are exposed to diesel exhaust.

The second paper examined the risk of occupational exposure to crystalline silica and lung cancer using the same large pooled data. Although silica is also classified as a class 1 human carcinogen by IARC, the results addressed key knowledge gaps. There was an increased risk of lung cancer with cumulative occupational exposure in both workers with and without silicosis, and in current, former and never smokers. Moreover, there was increased risk for all major histologic subtypes of lung cancer. Finally, there was a super-multiplicative risk with smoking and silica exposure for overall lung cancer risk. This paper has great significance at the current time because in addition to the nearly 2 million silica exposed workers in the USA, 11.5 million in India, millions in China, Turkey, Australia, and elsewhere, there has been an uptick in the number of workers exposed to crystalline silica while manufacturing and installing stone countertop materials for household use and sandblasting of denim for fashionwear (5. Lancet Respiratory Medicine, 2019).

For decades, research has been focused on mechanisms of carcinogenesis, the genetics of cancer initiation and progression, and the epidemiology of cancer as a complex chronic disease. Researchers have aimed to identify avoidable causes of cancer, increase early

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detection, and develop treatments to improve outcomes in patients with cancer. The relative contributions of genetic and non-genetic (i.e., “environmental,” broadly speaking) factors to the development of common cancers have been studied and debated for decades. Relative contributions are expressed in terms of the “population attributable fraction” — the proportion of disease incidence that would be eliminated if a given risk factor, such as smoking or asbestos exposure was removed. Toxic exposures in the environment, including workplace exposures, are responsible for a substantial percentage of all cancers (6. Christiani 2011). Precise apportionment is not possible because of gaps in the exposure data, interactions between environmental and lifestyle carcinogens, and differences from country to country in exposure patterns (7. Landrigan et. al.) However, credible estimates from the World Health Organization and the International Agency for Research on Cancer (8. 9. Espina et al; 10 Straif 2008) suggest that the fraction of global cancer currently attributable to toxic environmental exposures is between 7% and 19%.

Efforts at reducing mortality from lung cancer have included early detection and precision therapies. While more effective therapies and better early detection and screening methods are indispensable, the most valuable approaches to reducing cancer morbidity and mortality lie in primary prevention — avoiding introducing carcinogenic agents into the environment and eliminating existing exposures to carcinogenic agents. The first approach would be most effective if carcinogenic substances were identified before they could be introduced, although it is impossible to quantify the success of this approach. The value of the second approach has been demonstrated by the disappearance or reduced incidence of particular types of cancers following the elimination of specific occupational exposures. For example, occupational-related small-cell lung cancer was eliminated after exposure to Bis-chloromethyl ether (used in producing bulletproof glass) was reduced; and mesothelioma incidence was decreased after restrictions or bans were placed on asbestos use. Furthermore,

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risk has been reduced through greater regulatory control over compounds that remain in use — for instance, the US Occupational Safety and Health Administration restrictions on exposure to asbestos fibers, coke oven emissions, crystalline silica and other carcinogens.

A sobering realization about occupational lung cancer is that despite significant advances in reducing occupational carcinogen exposures in North America and Western Europe, the number of workers exposed globally to agents such as crystalline silica and diesel continues to rise. It's time for all stakeholders work together to reduce the burden of occupational lung cancer by developing effective prevention measures to identify, control and eliminate exposures to carcinogenic agents.

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References

1: Samet JM, Avila-Tang E, Boffetta P, Hannan LM, Olivo-Marston S, Thun MJ, Rudin CM. Lung cancer in never smokers: clinical epidemiology and environmental risk factors. Clin Cancer Res. 2009 Sep 15;15(18):5626-45. doi: 10.1158/1078-0432.CCR-09-0376. PMID: 19755391; PMCID: PMC3170525.

2. Ge C, Peters S, Olsson A, Portengen L, Schüz J, Almansa J, Behrens T, Pesch B, Kendzia B, Ahrens W, Bencko V, Benhamou S, Boffetta P, Bueno-de-Mesquita B, Caporaso N, Consonni D, Demers P, Fabiánová E, Fernández-Tardón G, Field J, Forastiere F, Foretova L, Guénel P, Gustavsson P, Ho V, Janout V, Jöckel KH, Karrasch S, Landi MT, Lissowska J, Luce D, Mates D, McLaughlin J, Merletti F, Mirabelli D, Plato N, Pohlabeln H, Richiardi L, Rudnai P, Siemiatycki J, Świątkowska B, Tardón A, Wichmann HE, Zaridze D, Brüning T, Straif K, Kromhout H, Vermeulen R. Respirable Crystalline Silica Exposure, Smoking, and Lung Cancer Subtype Risks: A Pooled Analysis of Case–control Studies *Am J Respir Crit Care Med* [online ahead of print] 24 April 2020; https://www.atsjournals.org/doi/abs/10.1164/rccm.201910-1926OC.

3. Ge C, Peters S, Olsson A, Portengen L, Schüz J, Almansa J, Ahrens W, Bencko V, Benhamou S, Boffetta P, Bueno-de-Mesquita B, Caporaso N, Consonni D, Demers P, Fabiánová E, Fernández-Tardón G, Field J, Forastiere F, Foretova L, Guénel P, Gustavsson P, Janout V, Jöckel KH, Karrasch S, Landi MT, Lissowska J, Luce D, Mates D, McLaughlin J, Merletti F, Mirabelli D, Pándics T, Parent MÉ, Plato N, Pohlabeln H, Richiardi L, Siemiatycki J, Świątkowska B, Tardón A, Wichmann HE, Zaridze D, Straif K, Kromhout H, Vermeulen R. Diesel Engine Exhaust Exposure, Smoking, and Lung Cancer Subtype Risks: A Pooled Exposure-response Analysis of 14 Case–control Studies *Am J Respir Crit Care Med* [online ahead of print] 24 April 2020; https://www.atsjournals.org/doi/abs/10.1164/rccm.201911-2101OC.

4: Silverman DT, Samanic CM, Lubin JH, Blair AE, Stewart PA, Vermeulen R, Coble

AJRCCM Articles in Press. Published May 12, 2020 as 10.1164/rccm.202004-1404ED

JB, Rothman N, Schleiff PL, Travis WD, Ziegler RG, Wacholder S, Attfield MD. The Diesel Exhaust in Miners study: a nested case-control study of lung cancer and diesel exhaust. J Natl Cancer Inst. 2012 Jun 6;104(11):855-68. doi: 10.1093/jnci/djs034. Epub 2012 Mar 5. PubMed PMID: 22393209; PubMed Central PMCID: PMC3369553.

5: Editorial:The world is failing on silicosis. Lancet Respir Med. 2019 Apr;7(4):283. doi: 10.1016/S2213-2600(19)30078-5. Epub 2019 Mar 11. PMID: 30872128.

6: Christiani DC. Combating environmental causes of cancer. N Engl J Med. 2011 Mar 3;364(9):791-3. doi: 10.1056/NEJMp1006634. PubMed PMID: 21366471.

7: Landrigan PJ, Espina C, Neira M. Global prevention of environmental and occupational cancer. Environ Health Perspect. 2011 Jul;119(7):A280-1. doi: 10.1289/ehp.1103871. PubMed PMID: 21719377; PubMed Central PMCID: PMC3222998.

8: WHO (World Health Organization) Asturias Declaration: A Call to Action. WHO International Conference on Environmental and Occupational Determinants of Cancer: Interventions for Primary Prevention. Asturias, Spain:WHO. 2011a. Available: http://www.who.int/phe/news/events/international_conference/Call_for_action_en.pdf

9: Espina C, Porta M, Schüz J, Aguado IH, Percival RV, Dora C, Slevin T, Guzman JR, Meredith T, Landrigan PJ, Neira M. Environmental and occupational interventions for primary prevention of cancer: a cross-sectorial policy

AJRCCM Articles in Press. Published May 12, 2020 as 10.1164/rccm.202004-1404ED

framework. Environ Health Perspect. 2013 Apr;121(4):420-6. doi:10.1289/ehp.1205897. Epub 2013 Feb 5. Review. PubMed PMID: 23384642; PubMed

Central PMCID: PMC3620754.

10: Straif K. 2008. The burden of occupational cancer. Occup Environ Med 65:787–788.

AJRCCM Articles in Press. Published May 12, 2020 as 10.1164/rccm.202004-1404ED