Differential Molecular Changes in the Lung after Low and High Carcinogen Doses and Implications for Designing Molecular Epidemiology and other Studies of Radiation-Induced Lung Cancer

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Lung Cancer Mortality Worldwide by Gender: Lung cancer was the most commonly diagnosed cancer worldwide as well as the leading cause of cancer death in males in 2008 **(**Jemal *et al.* 2011**)**. For females, it was the fourth most commonly diagnosed cancer and the second leading cause of cancer death. Lung cancer accounted for 13% of the total cases and 18% of the cancer deaths. For males, the highest lung cancer incidence rates are in Central and Eastern Europe, Southern Europe, and Northern America. For females, the highest lung cancer incidence rates are in Northern America, Northern Europe, and Eastern Asia. Rates are lowest in Eastern, Western, and Middle Africa for both males and females. A major cause of lung cancers globally is smoking-related chemicals (Belinsky *et al.* 2004; Belinsky 2005; Tellez *et al.* 2011).

Low-Dose, Low-LET Radiation and Lung Cancer: High-dose-carcinogens (including ionizing radiation) induce lung cancer via causing cancer facilitating mutations and epigenetic silencing (episilencing) of tumor suppressor genes (Belinsky *et al.* 2004; Tellez *et al.* 2011; Chen *et al.* 2011) and immunosuppression (Gonzales *et al.* 2011; Gott *et al.* 20011). The episilencing in part involves suppressing protective microRNAs (e.g., miR-200b, miR-200c, miR-205), which facilitates epithelial-to-mesenchymal transition (EMT) and the emergence of stem-like cells, which can lead to neoplastic transformation (Damiani *et al.* 2008) and subsequent lung tumors (Tellez *et al.* 2011). Low-LET radiation doses < 100 mGy delivered at a high rate or doses < 1000 mGy deliver at a low rate have not measurably elevated lung cancer risk. Additionally, genes which are up- and down-regulated by low radiation doses differ from those which are up- and down-regulated by high radiation doses, including microRNA genes (differential molecular changes; Cha *et al.* 2009; Scott 2011a).

Lung cancer risk from low-dose radiation has been evaluated by regulatory agencies based on the linear-no-threshold (LNT) hypothesis whereby any radiation hit (energy deposition event) to the lung of each member of a very large population will cause at least one lung cancer case. Doubling the number of hits (with the same hit-size distribution for a single hit) will then double the number of cancer cases. It is clear that the LNT hypothesis cannot be valid when one considers that by age 20 (years), natural radiation hits to everyone exceeds 630 trillion (Scott 2011b) and have not been found to be associated with an increase risk of any type of cancer. The only association is found for a reduced risk of cancer (Scott *et al.* 2009).

Evidence for Radiation Adaptive Responses/Hormesis: There is strong evidence for radiation adaptive responses (radiation hormesis) related to irradiation of the lung. Repeated small x-ray doses up to a total dose of about 750 mGy (human TB patients; Howe 1995) prevented sporadic lung cancers (radiation adaptive response/hormesis). Chronic, low-rate, gamma-ray exposure was deduced to have prevented plutonium-239 alpha-radiation-induced lung cancers in rats (Scott *et al.* 2008) and in Mayak facility workers (Scott *et al.* 2009). Residential radon concentrations near the Environmental Protection Agency action level of 4 picocuries/liter were found to be associated with a significantly reduced (*PROFAC* > 0.6) lung cancer risk (Scott *et al.* 2009; Thompson *et al.* 2008). The *PROFAC* (protection factor) is a parameter of our hormetic relative risk (HRR) model and represents the on average dose-independent proportion of lung cancer cases that are prevented as a result of radiation activated natural protection (ANP). The *PROFAC*

is a measure of the radiation effect in a population after low doses and dose rates as is also the excess relative risk (αD; slope α, dose D) under the LNT hypothesis. Interestingly, the effect ratio $PROFAC/\alpha D$ exceeds 1000 when $PROFAC > 0.2$ and $\alpha D \leq 0.0001$, supporting the view that relatively small sample sizes can be sufficient for designing epidemiological studies of radiation adaptive responses in the lung for populations exposed to low doses of low- or low- plus high-LET radiation (e.g., residential-radon-exposed persons; radon-exposed miners; Mayak Pu facility workers; Taiwanese exposed chronically over years to cobalt-60 gamma rays in their apartments; and down-winders of the ongoing Fukushima radiological emergency).

Components of radiation ANP include activated DNA damage repair, antioxidant production, selective elimination of precancerous cells via epigenetically regulated apoptosis (epiapoptosis), and activation of anticancer immunity (presumably via epigenetic pathways).

Epidemiology Study Designs are biased in Favor of the LNT Hypothesis: Epidemiology studies have used flawed descriptive-model-related designs that eliminate evidence for an adaptive response and for a large threshold. The design flaws include the following: (1) dose lagging (throwing away radiation dose); (2) including significant numbers of persons exposed to ANP-invoking doses in the control group; (3) averaging over wide dose-intervals removing nonlinearities; (4) adjusting for phantom risk factors; (5) including high-dose data and forcing the LNT model (e.g., via application of a DDREF) for low-dose-risk assessment, regardless of the absence of evidence for radiogenic cancers at low doses or evidence for a significant risk reduction. DDREF is the low dose and dose rate effectiveness factor used to supposedly account for the effect of low doses and dose rates. Interestingly, application of the DDREF guarantees concluding that any amount of radiation could cause cancer no matter how small the dose.

Designing Molecular Epidemiology Studies of Radiation-Associated Lung Cancer: Low-dose, low-LET radiation increases expression of lung-cancer-suppressive, adaptive-response genes, some of which likely affect apoptosis of genomically unstable cells and anticancer immunity. High-dose radiation (low- or high-LET) epigenetically silences adaptive-response genes possibly including microRNA genes that suppress epithelial-to-mesenchymal transition, neoplastic transformation and lung cancer occurrence. The indicated possible differential low- and high-dose molecular changes require special consideration when designing molecular-epidemiology and other studies of radiation-induced lung cancer; otherwise researchers may have insufficient power to reject an invalid LNT hypothesis when it is appropriate to do so as appears to have been the case in numerous previous epidemiological studies involving low doses and dose rates of low-LET or low- plus high-LET radiation.

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