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Response to the commentary letter entitled “‘Diagnostic radiography and thyroid cancer’ - causation or simply an association?” to our article entitled “Diagnostic radiography exposure increases the risk for thyroid microcarcinoma: a population-based case-control study” that was published in the European Journal of Cancer Prevention 2015; 24(5):439–46

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We thank Dr. Wiltshire and Dr. Balasubramanian for their commentary on our article (Zhang et al., 2015). Let us respond with the following points:

1. Our study population included incident thyroid cancer patients who were diagnosed with papillary (84.8%), follicular (12.1%), medullary (2.6%), anaplastic (0.2%), or other thyroid cancers (0.2%). Well-differentiated thyroid cancer included both papillary and follicular thyroid cancer cases; it accounted for 96.9% of all cases. We had limited statistical power to analyze the data for medullary and anaplastic thyroid cancer subtypes. We agree with Drs. Wiltshire and Balasubramanian’s comment that our study results can only speak for well-differentiated thyroid cancer. Future studies with sufficient statistical power are needed to investigate whether diagnostic radiography is associated with other thyroid cancers (namely, medullary and anaplastic cancers).
2. Recall bias could have a significant impact on the results generated from case-control study if there were no precautions strategies being exercised during the implementation of the study. In our study, the interviewers were blinded to the study hypothesis and the questionnaire also included questions on other exposures such as lifestyle, medical history, occupation and diet. We value and appreciate Drs. Wiltshire and Balasubramanian’s suggestion that including “random/unrelated” questions in the

questionnaire, such as questions about ultrasound and MRI scans, would be helpful to estimate the extent of recall bias for the sake of future studies. Although the recall bias cannot be quantified *per se* due to the lack of knowledge about the “true” association between exposure and outcome, the direction of bias can often be discerned. In our study, the positive findings were only limited to thyroid microcarcinoma, supporting the notion that differential recall bias was less likely to play a major role in our study. Therefore, the potential recall bias was likely to be non-differential, which biased the results towards null.

3. We agree that a sensitivity analysis excluding participants who had diagnostic radiography exposure within a five-year period prior to thyroid cancer diagnosis could be useful to confirm the observed association. In our study, the information on time of exposure was only asked for the first procedure but not for each subsequent procedure. Therefore, the suggested sensitivity analysis cannot be conducted based on the existing data.
4. We appreciate Drs. Wiltshire and Balasubramanian’s counter arguments that the observed dose-response relationship may also simply reflect an increased probability of detection of “incidental” cancer and that the stronger associations shown with diagnostic radiography focusing closer to the thyroid anatomically could also be the result of an increased detection of incidental cancer. We have discussed the possibility that individuals who have had diagnostic x-ray exposure are more likely to undergo medical screening and, therefore, their thyroid cancers are more likely to be diagnosed before a microcarcinoma progresses (Zhang et al., 2015). Future studies should collect detailed information on the chronology of each procedure, and the reason for performing it, in order to fully-characterize the link between diagnostic radiography and risk of well-differentiated thyroid microcarcinomas.
5. Moysich and colleagues found that Chernobyl-related ionizing radiation exposure increased the risk of thyroid cancer in children; these tumors were almost exclusively papillary carcinomas (Moysich et al., 2002). However, Chernobyl-related ionizing radiation had an extremely high dose as compared to diagnosis-related radiation. Additionally, Moysich also reported that Chernobyl-related thyroid carcinomas were more aggressive, had an unusually short latency period, and showed a lower female-to-male ratio as compared to sporadic thyroid cancers in children. It is possible that etiologic role of diagnostic radiography in thyroid cancer is different from that of the extremely high-dose radiation that occurred following the atomic bomb detonations in Japan and nuclear accidents such as the Chernobyl event.
6. Higher prevalence of *RET/PTC* rearrangements in radiation-induced thyroid cancer were mainly identified from post-Chernobyl tumors, which resulted from extremely high-dose radiation exposure (Nikiforova et al.,

2004). Chernobyl-related radiation-induced *RET/PTC* rearrangements were also associated with more aggressive tumor behavior (Rabes et al., 2000). However, no clear evidence has shown that low-dose radiation exposure through medical practice induces *RET/PTC* rearrangements. Although Seaberg and colleagues found that ionizing radiation exposure resulting from various sources was associated with more aggressive tumor pathology (Seaberg et al., 2009), this relationship is still inconclusive (Seaberg et al., 2009; Furlan and Rosen, 2004). Our study did not find that diagnostic radiography was associated with multifocal disease and lymph node involvement.

7. While over-diagnosis of thyroid cancer has been considered to play a major role in the current unprecedented increasing incidence of thyroid cancer, other unknown environmental or lifestyle factors are also important and need to be identified (Morris et al., 2013; Udelsman and Zhang, 2014). Although we did not directly collect information on access to healthcare, we had information on education, family income, race, and occupation, all of which have been correlated with healthcare access (Morris et al., 2013). We adjusted education in the final models. Additional adjustment for family income, race, and occupation did not result in material changes in the observed associations and thus were not included in the final models. Female gender is an established risk factor for thyroid cancer. Besides adjustment for gender in the final models, we also conducted a stratified analysis between men and women. The associations between diagnostic radiography and thyroid cancer were similar between men and women ($P_{\text{interaction}}=0.87$), suggesting that gender was less likely to bias the observed associations.

We appreciate the insightful comments provided by Drs. Wiltshire and Balasubramanian. We believe that these extra explanations strengthen our conclusion that diagnostic radiography is strongly associated with an increased risk of well-differentiated thyroid microcarcinoma. In addition, more studies that include detailed information on each diagnostic procedure (including reason for procedure, radiation dose, and age of patient at time of procedure) are warranted to fully understand the association between diagnostic radiography and risk of thyroid cancer. It is also important to characterize the molecular signatures of thyroid microcarcinoma and fully understand the biology of these entities.

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