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Abdominal radiation and diabetes: one more piece in the puzzle

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In 1995, Cécile Teinturier and colleagues¹ noted that a young adult who had been treated with abdominal radiation during early childhood developed diabetes 20 years later. This observation prompted them to review records of 121 nephroblastoma (Wilms' tumour) survivors who had been similarly treated. They reported, in a letter to *The Lancet*,¹ that 6.6% of the survivors had developed diabetes, all diagnosed in young adulthood, and although clinical and laboratory findings were not suggestive of type 1 diabetes mellitus, the patients did have inadequate insulin responses.

Concurrently, Alessandro Cicognani and colleagues² pondered whether the pancreas, being within the field of radiation in the treatment of Wilms' tumour, would consequently *manifest* β -cell dysfunction. They compared the insulin response to an intravenous glucose tolerance test in 22 non-diabetic Wilms' tumour survivors who been treated with abdominal radiation to 22 survivors without this exposure; on average, the 44 survivors were 8 years from completion of their cancer therapy.² The authors found an inadequate first-phase of the insulin response in 31.8% (seven of 22) of the irradiated survivors compared with 4.5% in the non-irradiated group, with a preponderance of abnormalities occurring in men, and seemingly unrelated to bodyweight. These observations led us to investigate this issue using the Childhood Cancer Survivor Study (CCSS).³ We compared 8599 young adult survivors of childhood cancer with 2936 similarly aged siblings, and noted that patients who received abdominal radiation treatment for neuroblastoma were seven times more likely than their siblings to develop diabetes. Patients who received abdominal radiation treatment for either Wilms' tumour or Hodgkin's lymphoma were twice as likely to develop diabetes as their siblings.³ No increased risk of diabetes was seen in survivors of these cancers who were not treated with abdominal irradiation. We found this relation between diabetes and abdominal irradiation to be independent of body-mass index (BMI) and thus surmised that the increased risk was secondary to β -cell dysfunction and not obesity.

In *The Lancet Oncology*, Florent de Vathaire and colleagues,⁴ report on a French–UK cohort of young adult survivors of a childhood solid tumour or lymphoma (excluding leukaemia), and substantially extend our understanding of this late effect of cancer therapy by showing a dose–response relation between radiation to the pancreas and risk of diabetes.⁴ Moreover, they noted that the risk correlated only with radiation to the tail of the pancreas, where the β -cells are concentrated, but not with radiation to the head or the body of the pancreas.

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Although laboratory testing was not included in the study, the relative risk of both insulin dependent and non-insulin dependent diabetes or type 2 diabetes was increased and similar after pancreatic radiation. As in the CCSS, this link between abdominal irradiation and diabetes was apparent irrespective of BMI, though it seemed marginally—but not significantly—stronger for those with increased BMI.

This study has several strengths, including the large population of long-term survivors, confirmation of diabetes by the survivors' physicians, and radiation dose estimates for different regions of the pancreas. The primary weaknesses of the study, similar to our experience in the CCSS, were a lack of prospective laboratory testing to more precisely characterise β -cell function and insulin resistance and the absence of correlative data of visceral and subcutaneous adiposity. The authors suggest, and we agree, that radiation can induce β -cell loss and impairment. Indeed, animal studies show that pancreatic radiation results in degranulation, vacuolisation, mitochondrial destruction, and impaired insulin secretion.^{5, 6} However, additional functional damage is probably necessary for diabetes to develop. Otherwise, we would expect diabetes to occur in childhood, rather than young adulthood, that the risk would not plateau at 20–29 Gy, and that there would be a preponderance of type 1 diabetes.

Importantly, abdominal radiation damages more than just the pancreas. In particular, subcutaneous, but not visceral, adipose tissue is sensitive to radiation exposure.⁷ We hypothesise that with the loss of the normal abdominal subcutaneous depot, fat accumulation occurring with aging is preferentially stored in the deep viscera. Because visceral adiposity is strongly linked to insulin resistance, we speculate that this preferential increase in visceral adiposity might contribute to relative β -cell insufficiency with insulin resistance developing in adulthood. This hypothesis warrants further prospective study.

The clinical implications of this study are important, since radiation remains an integral part of therapy for many children with Wilms' tumour or neuroblastoma. Diabetes is a major risk factor for all-cause and cardiovascular mortality. Additionally, visceral adiposity and insulin resistance are important in tumorigenesis.^{8,9} Further study is therefore needed to clarify the mechanisms underlying diabetes after abdominal radiation. Understanding these mechanisms will, hopefully, result in the development of targeted interventions that will lead to a reduction in risk in this population.

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