



Editorial

Obesity in oncology: How do you tackle an ever expanding real-world concern?



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Cancer is a heterogeneous disease that, to this day, still presents phenomenal challenges, but one which also, every so often, presents opportunities that enable better understanding and real progress. Nothing illustrates this better than the current resurgence in interest in specific cancer hallmarks, such as immune evasion or cellular energetics/metabolism¹; indeed, immunotherapy (checkpoint inhibition) has been fostering much enthusiasm since treatment paradigm shifts were achieved, not only in melanoma and urological malignancies, but also, more recently, in lung cancer.

This contrasts with the tentative efforts surrounding cancer-associated metabolism – even though it was first postulated, in the 1920s, by Otto Warburg.² As such, its clinical translation remains seemingly lagging behind with only, but a few notable exceptions like, the use of asparaginase (leukaemia armamentarium) and in a broader sense, the antimetabolites therapeutic family (e.g. thymidylate synthase (TS) inhibitors), peppered along the way with a few ongoing clinical trials primarily in enzymatic approaches or drug repurposing (e.g. metformin).³ Meanwhile, and while awaiting for the coming-of-age of metabolism based precision strategies, i.e. tumour specific traits profiled and better exploited, there is one area in particular, where there is established evidence, and that is the association between an increased body weight and cancer-related outcomes. In 2002, the International Association for Research on Cancer (IARC) reported that a high body mass index (BMI) was linked to an increased risk of breast and uterine tumours, clear cell renal carcinoma and also, oesophagus or colon adenocarcinoma.⁴ At that time, there was a recognition of the data made available from large, prospective, epidemiological studies. One such study was the American Cancer Society Cohort, where 900,000 participants were followed-up for 16 years, thereby becoming apparent that obese individuals with a BMI of 40 kg/m² or above, had higher cancer mortality risk (men: relative risk [RR], 1.52; 95%CI, 1.13–2.05 and women: [RR], 1.62; 95%CI, 1.40–1.87).⁵ Recently, the IARC listing expanded to other gastrointestinal tract cancers (namely, gastric cardia, hepatobiliary and pancreas), gynaecological tumours (ovary), as well as thyroid cancer, meningioma, and even, multiple myeloma.⁶

Furthermore, a joint effort by Cancer Research UK and the UK Health Forum⁸ has also forecasted the potential increase in high BMI-related cancer cases. Alarming, this was projected to be as high as 670,000 new cases over the next 20 years, and highlighted that if the high BMI risk could be reduced from the predicted trend, by as little as 1%, that would equate to roughly an overall avoidance of 64,000 new cases.⁷

Obesity, broadly identified as a BMI over the cut-off of 30, and the implications of its high prevalence, especially as a contributor to poorer health-related outcomes and overall mortality, are well-known in numerous chronic conditions.^{8,9} Additionally, in most settings, it is also clear that there are many overriding benefits to be had, if a 6-month weight loss of 8–10% (of initial weight) is attained, preferably through therapeutic interventions emphasizing both dietary intake and physical activity, even if long-term sustainability remains a challenge.¹⁰ Likewise, regarding cancer-related outcomes, intuitively, it may be assumed that striving for weight loss or weight *normalization* might also be pertinent. Yet, in oncology, the beneficial impact of weight loss, in obese individuals, has not been consistently observed. Hence, current evidence stating only that there is a “cancer preventive effect of the absence of excess body fatness” (IARC, 2016). Besides, and as the focus widens beyond the traditional relationships between obesity and cancer incidence, all the way to the therapeutic management once the cancer has been diagnosed, the aforementioned weight loss benefits can only come to fruition, if and when the relationship between an excessive body weight and cancer is understood to be both causal and reversible.

Many reasons might be pointed out for this current lack of understanding. Firstly, the majority of body composition-related studies in oncology, are still geared up to investigate undernutrition. Even though, classically, gastrointestinal cancers – including: oesophageal, gastric, hepatocellular, pancreatic, and colorectal – present with varied, often severe, degrees of weight loss, there is now mounting evidence, also linking excess body weight to poorer outcomes. Secondly, during study design, tumour molecular complexity is often not taken into account. For example, an obese breast cancer patient might have a 35–40% increased risk of recurrence and death, but this type of percentage seems to better relate to hormone receptor-positive breast cancer, than for other types of breast cancers, e.g. triple-negative or human epidermal growth

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factor receptor 2-positive.¹¹ Another reason, concerns the underrepresentation of obese participants in clinical trials, this situation might be explained by a selection bias, as more aggressive treatment regimens require the inclusion of those that are metabolically healthier (e.g. cardiac toxicity concerns).¹² Lastly, and beyond clinical trial accrual, these individuals can also be at risk, either because of a lack of overweight/obesity recognition (e.g. the overuse of BMI as a proxy/surrogate for body adiposity), of diagnostic delay (for example: biomarker hemodilution), of worse adverse events (e.g. surgical complications) or even, of treatment planning inaccuracies caused by an increased body surface.

To add to the complexity, it is possible to observe paradoxical effects, i.e. a higher BMI category allows for inconsistent/different direction of mortality according to different causes. This so called obesity paradox, has been recognized in stroke and in renal cancer, where although observational studies associate obesity with higher cancer risk, retrospectively it has been shown that a higher BMI seems to improve outcomes, like overall survival. Concomitantly, there is even the possibility of “paradox within the paradox”, as further non-linear relationships are described.¹³

At this point, it is important, as well, to reflect on the relevance of the degenerative loss of skeletal muscle mass (sarcopenia), very much prevalent in obese populations, which has been shown to be a clinically useful predictive biomarker of adverse effects of systemic chemotherapy/targeted agents, perioperative complications and, thought to directly impact on prognosis. As it has been recently reported in urothelial carcinomas, the identification of specific subsets of sarcopenic obese patients, might prove a useful decision-making prognostic biomarker for all stages of cancer management.¹⁴

For all these reasons, it is urgent to become much better at teasing out the metabolic factors that may be causally relating obesity and cancer outcomes. It is known, that a normal weight while maintaining physical fitness prevents metabolic imbalances, such as insulin resistance and high circulating levels of hormones. And although, the mechanistic relationship between obesity and progressive carcinogenesis is still far from clear, these two metabolic players seem to be recurrent. But, there are many intertwining and overlapping pathways that relate, not only, to hormones or insulin signalling, but also, to growth factors and inflammation. Visceral fat will secrete more hormones and a plethora of molecules that interfere with overall metabolism, and of particular concern, it also seems to be more prone to inflammation. In obese women, inflamed breast white adipose tissue is a common occurrence and there is now indication, of this, contributing to tissue remodelling, through changes in the extracellular matrix which enhance stiffness, an already known booster of cancer risk or aggressiveness.¹⁵ Therefore, the persistent use of reductionist approaches will fail to understand the full potential of modulating metabolic-health for effects of cancer progression risk management. In addition, and of high relevance to the oncology practice, obesity metabolic interplay can easily be exacerbated when certain cancer therapeutic agents are used (e.g. glucocorticoids, androgen-deprivation or phosphatidylinositol 3-kinase/Akt/MTOR inhibitors).

Thus so far, excessive body weight with its associated metabolic drivers seem to provide a framework supportive of a causal association with cancer, whilst fuelling a persistent activation of metabolic signalling cascades and enhancing oncogenic transformation, which, in turn drive a phenotype capable of sustaining proliferation, resistance to apoptosis and invasion.^{16,17} Plus, with emergence of obesity as an independent risk factor, its insidious effects must be investigated for reversibility and in doing so, eliciting the extent in benefit from weight management interventions within this context.¹⁸ Again, the literature is littered with confounders, inconsistencies and heterogeneous study designs. Amidst, there are some encouraging reports of a reduction in

cancer incidence or recurrence following bariatric surgery.¹⁹ Interestingly, these same research outcomes shine a light onto the fact that conservative weight loss interventions – i.e. the standardized metabolic goal of a reduction of 8–10% in body weight, typically leads to a relative modest weight loss and even rarer events of weight *normalization* or “absence of excess of body fatness” (IARC, 2016), and as such, might not suffice to modulate obesity-associated systemic factors and modify risk and/or outcomes. So, it still remains to be demonstrated which weight loss percentage, and beyond that, which lifestyle associations, i.e. dietary choices/patterns and physical activity, will provide metabolic advantages that can be sustained and meaningful from a molecular oncobiology perspective. On a positive note, there is now some early confirmation, that in individuals with a high polygenic susceptibility for heart disease, healthy lifestyle choices do seem to be capable of eliciting an independent deterministic contribution to disease outcome.²⁰ Will these findings also be reproducible in oncology? It is reasonable to anticipate an increased degree of complexity arising from the tumour–host relationship modulated, not only, by the highly heterogeneous inter and intra-tumour genetic expression, but also, by selective pressures (clonal evolution) and shifts in epigenetic marks.²¹

Certainly, we do seem to be able to describe obesity-cancer associations but we also need to become better at unravelling relationships of causality between healthy choices, genetics, metabolism and their influence in cancer-related outcomes. Only then, the field will be able to move beyond lifestyle broad-spectrum prescriptions and realize true tailoring, accomplishing the highlighted needs of stratified/personalized nutritional approaches.²²

To conclude and at a time, where there has been an increasingly widespread call for steps to be taken towards a more pragmatic, real-world oncology; where access to evidence and generalisability of research impact can be mainstay and above all, consistent with the real-world needs of both patients and healthcare settings, it becomes a priority, for the improvement of overall outcomes, to establish which and when overweight/obese patients with cancer will benefit from weight loss – after all, the concerns around current stubborn and ever expanding worldwide obesity rates are as real, as “real-world” can be.

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