**Invited Editorial**

Hypertension and cardiovascular risk factors when treating cancer patients: Under-recognised and under-treated

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**Disclosure statement**

Dr Essa has nothing to declare. Professor Lip reports consultancy and speaker fees from Bayer, Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daiichi-Sankyo outside the submitted work. No fees received personally

Professor Pettitt has received research funding from AstraZeneca, Celgene, Chugai, Gilead, GSK/Novartis, Napp and Roche and speaker fees and hospitality from Celgene, Gilead and Roche.

**Word count excluding figure/references** – 984

Cancer and cardiovascular disease (CVD) account for nearly 50% of all mortality in the United States (US)1. It is common practice to view cardiovascular (CV) risk factors and cancer as 2 separate disease processes. However, the vast similarities between both, and multiple interactions, suggest some element of shared underlying biology2. The demographic profile of oncology patients shares many similarities with the profile of patients with CVDs, and as a result, cardiac condition often co-exist and are a frequent complicating factor during complex and aggressive cancer treatments4. Furthermore, CVD is disproportionately represented in survivors of cancer5, likely multifactorial secondary to downstream treatment effects and factors that resulted in the cancer initially. In the US, improvements in detection, early diagnosis, and treatment of cancer have resulted in a marked reduction of overall mortality in the last 20 years6. This pattern is likely to be the same in other countries with developed healthcare systems. This means that the burden of CVD in cancer is likely to increase in line with the increasing survivors of cancer. In oncology, CVD is a leading cause of morbidity and mortality3. In 2009, after increasing recognition of this issue, the international cardio-oncology society was born7. Cardio-oncology is a relatively new clinical field focusing on the diagnosis, prevention, and treatment of the cardiovascular consequences of cancer and its treatment.

The scale of CVD prevalence in oncology cannot be understated. Retrospective data in survivors of childhood cancers demonstrate that these patients have an 800% increased risk of CVDs8. Compared to their cancer free siblings, the relative risk of coronary artery disease and heart failure was over 10x higher8. Similar results are also seen in adult data, in 2019, retrospective data from 108,215 cancer survivors and 523,541 controls was reviewed and CVD risks compared9. The authors concluded that survivors of most site-specific cancer had increased long term risks for CVD compared to the general population, however there was significant variation between cancer sites9. Alarmingly, this pattern is also seen in childhood cancer survivors, for whom CVD was the leading cause of death above the age of 6010.

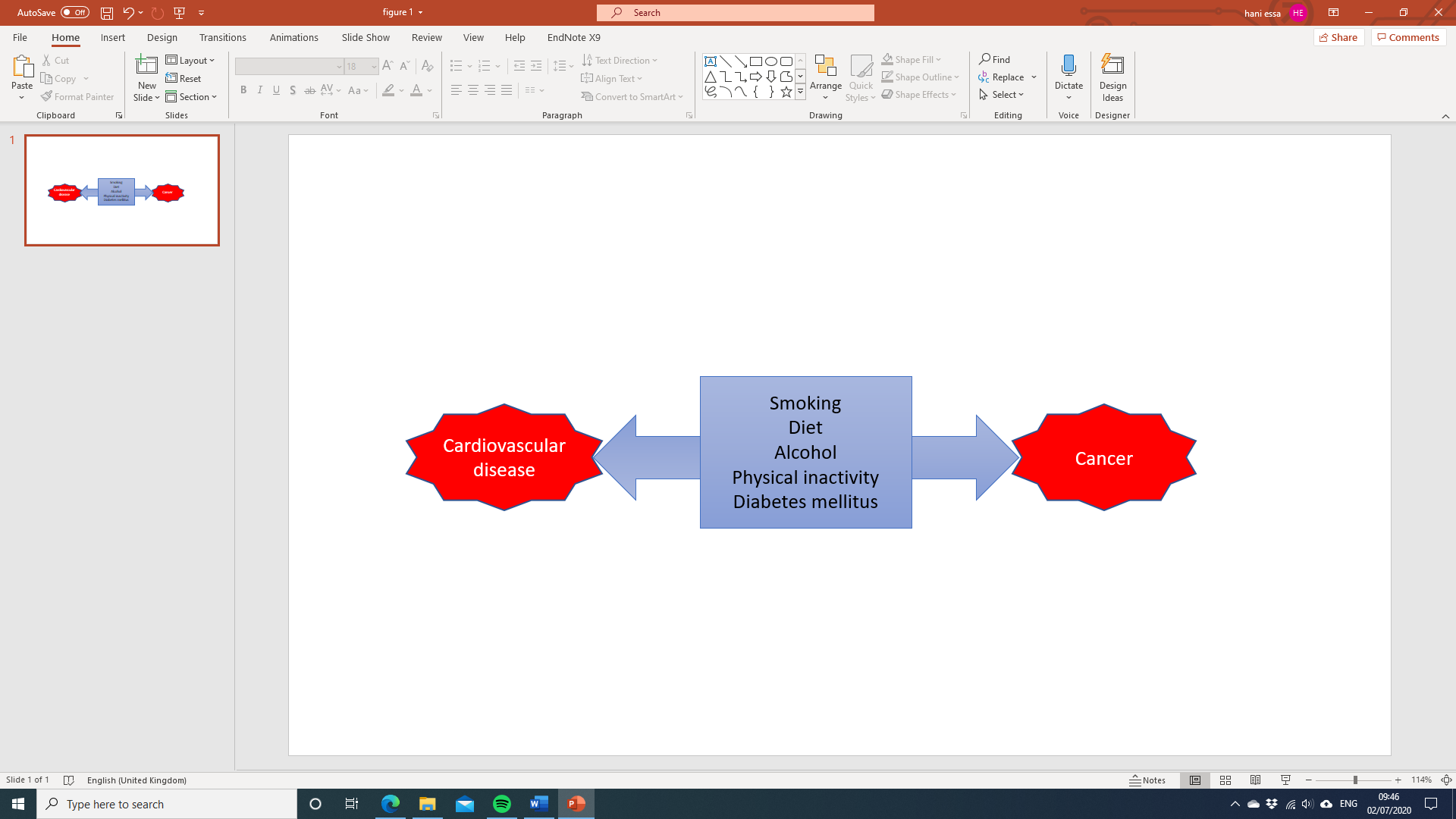
Hypertension is one of the most common CVD risk factors in cancer patients11. The aetiology of hypertension in this cohort is complex and multifactorial based on the type of cancer treatment, type of malignancy and intrinsic patient factors such as age and pre-existing comorbidities. Therefore, prevalence is difficult to estimate as it is often context specific and therefore difficult to generalise to all oncology situations. A large variety of anti-neoplastic agents have been linked to hypertension, none more so as angiogenesis inhibitors. All angiogenesis inhibitors have been linked to hypertension12. A 2017 meta-analysis of 77 studies looking at 11 different angiogenesis inhibitors demonstrated an odds ratio of 5.28 (95% Confidence interval (CI) of 4.53 – 6.15) for new onset hypertension. The issue with angiogenesis inhibitors is so prevalent as to have resulted in a consensus document of expert recommendations by the Cardiovascular Toxicities Panel of the National Cancer Institute regarding the assessment, surveillance and management of hypertension when utilising this class of medications13. However, hypertension has been linked to multiple other agents including but not limited to antimetabolites such as Gemcitabine, mitotic agents such as vincristine, Proteasome inhibitors such as Carfilzomib, and adjuvants such as steroids & non-steroidal anti-inflammatorys14.

Cancer patients are more likely to suffer CV risk factors such as hypertension, diabetes, and dyslipidaemia and when these are adjusted for, have higher rates of progression to CVD as compared to the general population5. This is in keeping with the biological plausibility that cancer and CVD share some underlying processes. Inflammation is one such factor implicated in both cancer and CVD15. Inflammatory pathways have been implicated in the initiation and progression of both neoplasm and atherosclerosis. Prognostically, oncology patients with CV risk factors have worse outcomes compared to their peers5. Cigarette smoking, obesity, lack of exercise, alcohol, increasing age, diabetes and diet have all been implicated in causing both CVD and cancer2. This highlights the importance of active risk factor management in this cohort, even more so than in the general population.

Given the large body of evidence demonstrating that CVD is more common in patients with cancer, one may wonder if this relationship is bidirectional, i.e do CVD patients suffer a larger burden of cancer than would be expected. Whilst the data in this area is more sparsely populated, there is strong evidence for a relationship demonstrating that CVD patients are more likely to suffer from cancer. A 2016 prospective study looking at 1,081 patients who suffered heart failure after myocardial infarction found that they were at a higher risk of cancer compared to patients who suffer myocardial infarction but do not progress to heart failure (adjusted Hazard ratio 1.92, 95% CI, 1.11-3.11)16. This has also been replicated in data published from the Framingham heart study, this looked at 12,712 participants free from CVD and cancer at baseline. These participants were followed up and the data shows that in those who developed subsequent CV events there was a >7-fold higher risk of subsequent cancer17. There is also evidence that interventions that focus on reducing CV risk factors also reduce the risk of incipient cancer18. Figure 1 demonstrates the shared CV risk factors inherent to both cancer and CVD.

The overlapping risk factors for CVD and cancer suggest that there is an element of shared underlying aetiology. Chronic inflammation is one such pathway, however there are likely to be others at play. The knowledge that oncology patients are at a substantially higher risk of CV risk factors should mean that this cohort undergoes targeted screening to prevent downstream CVD. This is already the case with angiogenesis inhibitors, where a position document by the European Society of Cardiology in 2016 advocated for a CV risk factor assessment for all patients prior to treatment19. Moving forward, this practice should be extended to all cancer patients at all stages of their treatment.

Figure 1. Theoretical model of bidirectional relationship of cardiovascular disease (CVD) and cancer. There is strong evidence that cancer patients suffer an excess burden of CVD and in turn that CVD patients are more likely to suffer cancer.



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