Cancer and cardiovascular diseases: the long, winding and crossing roads

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According to the World Health Organization (WHO) global estimates, cancer is the second leading cause of death, accounting for 9.6 million, i.e. one in six, deaths in 2020.[1] For comparison, cardiovascular diseases (CVD) accounted for 17.9 million deaths, largely (85%) due to myocardial infarction (MI) and stroke.[2] In the same year, the WHO reported breast cancer (BC) as the most common site of new cancer (2.26 million cases), followed by lung (2.21 million) and colorectum (1.93 million).[1] Moreover, BC caused 685,000 deaths and 7.8 million women diagnosed with BC in the previous 5 years were alive,[1] making BC the world's most prevalent cancer.

More effective treatments and early detection in screening programs have contributed, in the past decades, to a substantial increase in the number of cancer patients surviving more than 5 years. Consequently, the risks of CVD and its mortality compete with the risk of cancer recurrences in long-term cancer survivors.[3,4] One of the underlying reasons is the shared risk factors between these two, highly prevalent, contemporary and multi-factorial diseases.[4] Consistently, among the global strategies to reduce cancer, the WHO recommends avoiding tobacco use, maintaining healthy body weight and diet, regular physical activity, avoiding or reducing alcohol consumption and reducing exposure to air pollution.[1] The very same interventions are recommended to prevent CVD and other non-communicable diseases.[1,2] Moreover, some pathogenetic pathways are shared between cancer and CVD. In particular, platelets known to be important in the aetiology of CVD, are increasingly recognized to contribute to cancer development and metastatization.[5] Large observational studies and long-term, post-hoc analyses from randomized controlled trials (RCT) of low-dose aspirin in CVD prevention, and RCTs in colorectal adenoma, show a chemo-preventative effect of aspirin on cancer onset and recurrence.[6] Aspirin is also being assessed in large RCTs enrolling patients with different cancer types in the adjuvant setting.[5] Recently, platelet-derived *in vivo* thromboxane A_2 generation has been found to be increased in cancer patients, especially those with gastrointestinal tract-derived cancers, again indicating a cross-talk between platelets and cancer.[7] This increased level of platelet activation in cancer patients may contribute to CVD and cancer-associated thromboembolism.

Common genetic factors have also been identified between cancer and heart disease.[8] These include mutations in Janus Kinase-2, titin, Tet methylcytosine dioxygenase 2, ATM serine/threonine kinase which regulates multiple cell damage response pathways, and several genes involved in the DNA damage repair and cell proliferation.[8]

In the current issue of this journal, Galimzhanov and colleagues add a new interesting piece of evidence to the clinical and epidemiological interplay between cancers, in particular BC, and CVD (Central Figure).[9] Their aim was to assess the incidence and risk of CVD mortality, coronary artery disease (CAD), MI, stroke, heart failure (HF) and atrial fibrillation (AFib) in BC survivors.

In 2,111,882 BC patients, the authors calculated the incidence per 1000 BC person-years of CVD death, MI, CAD, stroke, HF and AFib, which were 1.73 (95% CI 1.18, 2.53), 1.98 (95% CI 1.24, 3.16), 4.29 (95% CI 3.09, 5.94), 4.33 (95% CI 2.97, 6.30), 4.44 (95% CI 3.33, 5.92), and 12.95 (95% CI 12.60-13.31), respectively. Not surprisingly, the studies with a higher proportion of diabetic patients showed the highest incidence of CVD. BC women with smaller tumors at diagnosis had a higher incidence of CV death, possibly due to an excess of cancer-related deaths in patients with higher tumor burden at diagnosis, in whom the CVD risk was obscured by the oncological outcomes.

For the comparison with the general matched, cancer-free population – data was available from 26 studies totaling 836, 301 participants and were reported, if data were available, as a function of time from diagnosis. As compared to the control population, BC patients had a 13% relative increased risk for AFib for the first 3 years from diagnosis (Hazard Ratio [HR]=1.13; 95% Confidential Interval [CI]: 1.05, 1.21), a 9% increase in CV death within 5 years (HR=1.09; 95% CI: 1.07, 1.11), and a 20% increase in the risk for HF between 2 and 10 years (HR=1.21; 95% CI: 1.1, 1.33). The risk of CVD mortality decreased in subsequent years and became comparable to the control population, while data after year 3 and year 10 were not available for AFib and HF, respectively. These estimates in part may reflect the differences in the length of follow-up in the original studies, but some results e.g the early high risk of Afib and the 1-year lag in increased HF risk may also reflect the toxicity of the chemotherapeutic agents over time and/or the decreased activity of cancer-related effects such as inflammation, cardiotoxicity and endothelial dysfunction. Another relevant confounder could be the

age of the women, since an increased 3-year AFib risk would be age-dependent, and carries different implications for treatment in young versus older women.

Surprisingly, the risks for MI, CAD and stroke were not reported to be increased in this meta-analysis. These data are not consistent with a previous large, homogeneous cohort including different types of cancer, where the risk of both acute stroke and MI were increased in the first 1-2 years following diagnosis.[10] Moreover, recent data indicate a higher incidence of CVD, including MI and stroke in cancer survivors versus non-cancer subjects.[3,8] Chest irradiation and some chemotherapy agents are known to be associated with CVD during treatment and follow-up, possibly due to direct myocardial and/or vascular injury.[11] A recent registry of 627,702 long-term survivors of breast, prostate, or colorectal cancers, reported that the major cause of death in low-risk cancer patients was heart disease.[3] A relevant issue in interpreting the unexpected finding of a lack of association with MI, CAD and stroke in this new meta-analysis could be the heterogeneity of the chemotherapy and/or radiation regimens in the individual studies. This may explain the paradoxical lack of association with stroke even when an early increased risk of AFib is reported and the lack of a correlation between the risks of CAD and HF. Agreeing definitions and consistency of reporting are required to fully address these questions in future cohorts.

Another limitation of the current meta-analysis is the lack of meta-regression analyses to include type of oncological therapy, stage of cancer, presence of multiple CV risk factors (only some of these were in the original reports) and comorbidities. For example, anthracyclines and trastuzumab are known to cause long-term cardiotoxicity but this level of detail was not available in the meta-analysis. The lack of analysis for specific co-morbidities or other CVD risk factors also limits this study. Finally, the inclusion of venous thromboembolism as an early and late outcome would have been helpful to get

a broader estimate of the entire spectrum of thrombotic (arterial and venous) risk in BC patients with a view to defining more individualized prevention strategies.

While waiting for high-quality, possibly prospective, evidence, and for validation or intervention studies, the work by Galimzhanov and colleagues, together with similar studies on BC and other cancers highlights some important points. Lifestyle and/or pharmacological interventions to prevent modifiable risk factors and CV co-morbidities (diabetes, hypertension, high body weight, healthy lifestyle, low alcohol and tobacco use) recommended in the general population, should be maximally implemented in patients with BC. This would ensure that the benefit of longer survival rates achieved by improved oncological management over the past decades will not be blunted by a rise CVD morbidity and mortality. As the increase in CVD appears to be associated not only with BC, but also with gastro-intestinal and haematological cancers,[10,12] it will be important to consider whether cancer(s) should be included in novel risk stratification algorithms for arterial diseases, AFib and HF. The early high risk of AFib seen in this study suggests clinical and/or ECG investigations in cancer patients, even if asymptomatic could be warranted. It will also be important to understand how diagnostic and pharmacological strategies (i.e. low-dose aspirin, oral anticoagulation, HF pharmacological prevention) can be employed in asymptomatic cancer patients. This may be particularly relevant in the years immediately following the diagnosis of cancer and starting treatment, and/or as a function of the type and site of cancer and/or treatment received. Prophylactic diagnostic and therapeutic strategies should be part of a multidisciplinary cardio-oncology assessment aimed at improving overall outcomes.

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Legend to Central Figure: Cancer and cardiovascular diseases (CVD) share a number of risk factors. On the other hand, cancer, including breast cancer according to the meta-analysis work by Galimzhanov and colleagues, can favor CVD development and complications, in particular atrial fibrillation, heart failure and CVD mortality, while the associations with stroke and coronary artery disease (CAD) were not confirmed by the current study, as indicated by the '?' in the figure. MI: myocardial infarction.

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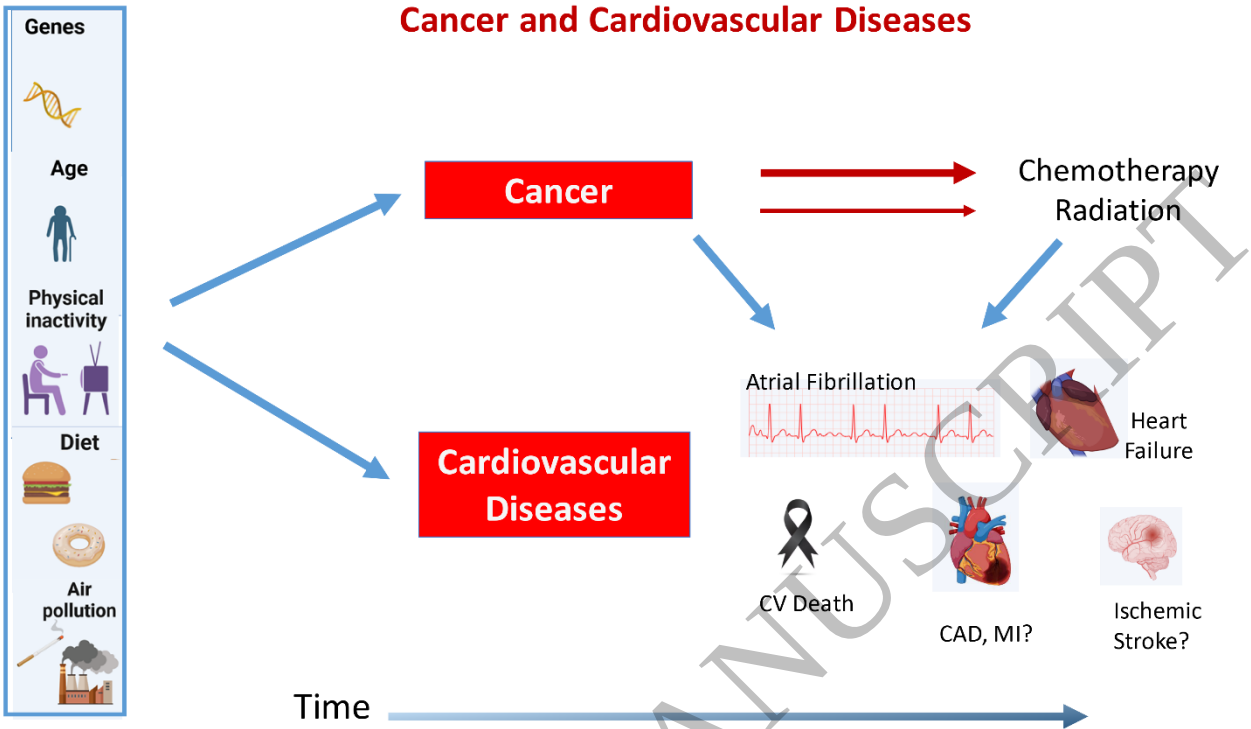

Figure 1
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