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INVITED EDITORIAL

Cancer and cardiovascular mortality risk: is the die cast?

Patrizio Lancellotti[1,2]*, Mai-Linh Nguyen Trung[1], Cécile Oury[1], and Marie Moonen[1]

[1]University of Liège Hospital, GIGA Cardiovascular Sciences, Department of Cardiology, CHU Sart Tilman, Liège, Belgium; and [2]Gruppo Villa Maria Care and Research, Maria Cecilia Hospital, Cotignola, and Anthea Hospital, Bari, Italy

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This editorial refers to 'Long-term cardiovascular disease mortality among 160 834 five-year survivors of adolescent and young adult cancer: an American population-based cohort study', by L. Wang *et al.*, doi:10.1093/eurheartj/ehaa779.

Among the causes of death worldwide and, in particular, in developed countries, cardiovascular diseases (CVDs) and cancer remain in the lead. In 2017, there were 108.7 million people living with CVD in the 54 European Society of Cardiology (ESC) member countries. In 2018, there were 3.91 million new cases of cancer in Europe and 1.93 million deaths from cancer. CVD remain the leading cause of death within ESC member countries (4.1 million deaths) but, in several individual countries, cancer now causes more deaths than CVD.[1,2]

In recent years, the links between these two entities have aroused growing interest. More and more data reveal common risk factors (age, obesity, sedentary lifestyle, diabetes, tobacco, alcohol, unbalanced diet, low-grade chronic inflammation, and clonal haematopoiesis of indeterminate potential) and, as a corollary, some shared or similar pathophysiological mechanisms.[3,4] In addition, continual improvement and development of new anticancer therapies has led to an ever-increasing number of cancer survivors. This population, however, shows an increase of cardiovascular (CV) morbidity and mortality compared with the general population. This excess risk is due to a combination of pathophysiological processes in connection with the cancer itself, patient initial comorbidities, and toxicity of anticancer therapies.[5] These last were divided by the ESC into nine categories: myocardial dysfunction and heart failure; coronary artery disease; valvular disease; arrhythmias, especially those induced by QT-prolonging drugs; arterial hypertension; thrombo-embolic disease; peripheral vascular disease and stroke; pulmonary hypertension; and pericardial complications.[6] Studying and understanding the toxicity of anticancer therapies is a large, complex, and constantly evolving subject. Indeed, side effects are many and varied, new treatments involving different mechanisms and therapeutic targets are constantly emerging, and toxicity of anticancer therapy can appear early but also very late, several years after cancer remission.

These findings have led, in recent years, to the emergence of a new integrative medical discipline devoted to this problem, namely cardio-oncology. Multidisciplinary staff who work in cardio-oncology teams are dedicated to prevention, detection, monitoring, and treatment of cancer patients at risk of cardiotoxicity and/or with concomitant CVD. In other words, their ultimate goal is to provide cancer patients with the optimal treatment while minimizing their CV risk.[7] Despite all these innovations, much progress remains to be made; among them, establishment of effective strategies for CV surveillance and prevention in cancer survivors is crucial. For this purpose, it is essential to collect strong and varied epidemiological data concerning this particular population.

In this issue of the *European Heart Journal*, Zhen Chen *et al.* retrospectively studied long-term CVD mortality among 160 834 adolescent and young adult (AYA) patients who had survived cancer for 5 years by leveraging data from the SEER9 (Surveillance, Epidemiology, and End Results programme) US nationwide registry recording incident cancer cases since 1975.[8] Eligibility criteria were defined as follows: diagnosis of an initial primary malignant neoplasm at 15–39 years of age; diagnosis during the period from 1975 to 2011; and survival for 5 years or more following the first diagnosis of malignancy. They also collected a contemporaneous cohort of patients surviving childhood malignancies for 5 years aged under 15 years at diagnosis. The aim of the study was to compare the risk of CVD mortality among the selected population compared with the US general population and 5-year survivors of childhood cancer. Standardized mortality ratios (SMRs) and absolute excess risks (AERs) were used to compare CV mortality in AYA cancer survivors and the US general population. SMRs reflects the risk of CVD mortality relative to that

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* Corresponding author. Department of Cardiology, University of Liège Hospital, Domaine Universitaire du Sart Tilman, B.35, 4000 Liège, Belgium. Tel: +32 4 366 71 94, Fax: +32 4 366 71 95, Email: plancellotti@chuliege.be

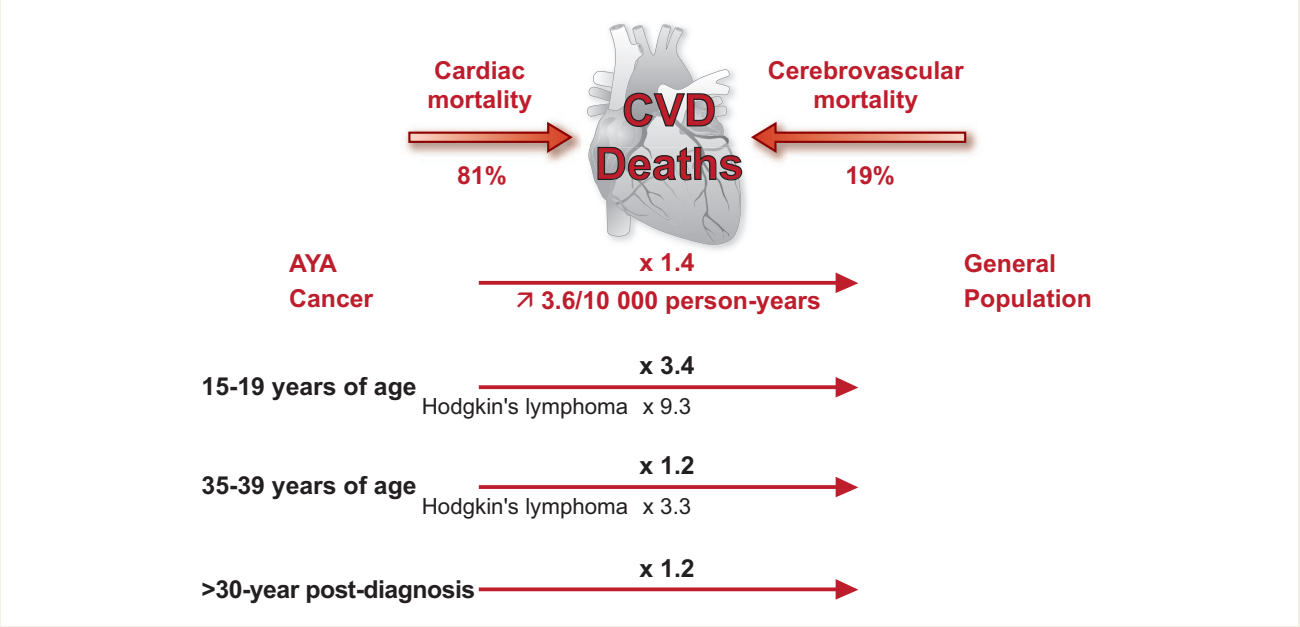

Figure 1 Standardized mortality ratio used to compare cardiovascular disease (CVD) mortality in adolescent and young adult (AYA) cancer survivors and the US general population.

of the general US population and were determined as the ratio of the number of CV deaths observed among 5-year AYA cancer survivors to that expected in the general population with the same distribution of sex, age, and ethnicity and in the same calendar year. To compare AYA and childhood cancer survivors, they conducted analysis with a competing risk model. The average follow-up period was 13.9 years from 5-year survival and the median attained age was 53.9 years.

The present study, with a large cohort of cancer patients and nearly 40 years of follow- up, is the largest one to assess late CVD mortality risk among childhood and AYA cancer survivors in the USA. It is based on the SEER9 database, a strong and well-conducted registry, and provides comparative data with childhood cancer survivors while most studies focus on a single age category. Overall, the authors observed 1.4 times more CVD deaths in AYA cancer survivors than expected in the general population, corresponding to 3.6 excess deaths per 10 000 person-years (*Figure 1*), which was consistent with the results of a previous study concerning >200 000 UK 5-year survivors of AYA cancer.[9] However, the number of CV events and the number of female deaths from CVD were higher in the current American cohort. It is noteworthy that radiotherapy, known to further damage cardiac and vascular function when combined with chemotherapy, was associated with a higher CVD mortality rate in both populations. The highest risk of cardiac mortality was found among survivors of Hodgkin lymphoma, while the highest risk of cerebrovascular mortality was observed with central nervous system (CNS) tumours. Hence, CVDs were mainly due to heart disease (81%) and cerebrovascular disease (14%). The risk excess was attenuated with the increase of attained age but, even at more than 30 years post-diagnosis or in survivors over 60 years of age, the CVD risk remained significantly elevated (SMR 1.3). In the UK cohort, among survivors of Hodgkin lymphoma aged over 60 years, almost 30% of the total excess number of deaths observed were due to heart disease. Regarding survivors of childhood cancer, they were 490% (SMR 5.9) more likely to die from CVD than expected in the general population, with the greatest risk in acute myeloid leukaemia survivors (SMR 19.9) and CNS tumour survivors (SMR 8.4). Their cumulative risk of CVD during the total follow-up period was lower than in AYA cancer survivors, probably reflecting continued efforts to maximize CV health among survivors of cancer in recent years.

Although these data could be used to refine long-term risk-based surveillance strategies for CVD, the lack of detailed information on CVD cause (heart failure, ischaemic cardiopathy, arrhythmia, valvular heart disease, etc.), the types of chemotherapy, and radiation doses call for additional large-scale registries specifically examining these points. Performing similar studies in different geographic areas may also be useful to evaluate the impact of environmental factors on CVD mortality of cancer survivors. Despite these unknowns, the present study represents a valuable contribution to the identification of at-risk patient groups requiring close follow-up care, as well as to the understanding of a major health issue.

Conflict of interest: none declared.

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