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Cancer, An Underestimated Cardiovascular Risk Factor, Review Paper

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***Abstract*—** *Cancer is a disease in the rise all over the world. According to a report by the World Health Organization and the International Agency for Research on Cancer, the number of people affected by this disease is expected to reach 22 million annually in 2030, which is 8 million more than in 2012. Next to cancer, cardiovascular disease is the leading cause of death in the world. These two noncommunicable diseases together share several risk factors. Cancer from the tissue changes it causes, promotes vascular events. This article, a preamble to a prospective study, provides an overview of the different cardiovascular consequences of cancer. It appears that cancer dramatically increases cardiovascular risk even in patients without pre-existing risk factors. With these data which highlight the reality of the cardiovascular risk presented by cancer, we call on clinicians to take more time in the daily care of these patients, with multidisciplinary dialogue*.

***Keywords*—** *Cancer; cardiovascular disease; risk factor; outcome*.

I. INTRODUCTION

Non communicable diseases are the leading causes of death worldwide, with 36 million lives lost each year [1]. They have a constant epidemiological increase in the world and more precisely in developing countries [1].

The four main non-communicable diseases are cardiovascular disease (heart or stroke), cancer, chronic respiratory disease (such as chronic obstructive pulmonary disease or asthma) and diabetes [2]. These four groups of pathologies are responsible for 63% of global mortality and 80% of deaths in low and low- to middle-income countries [1, 3].

Cancers and cardiovascular disease have several risk factors in common despite different pathophysiological mechanisms. For example, smoking, alcoholism, lack of physical activity, overweight (or obesity) [4].

These different pathologies influence each other. Cardiovascular disease is a cause of death in patients with cancer and cancer survivors. With recent progress in screening, diagnosis, and treatment of many cancers, the population of cancer survivors is increasing. It has been shown that these cancer survivors have an increased risk for cardiovascular disease [5].

A recent observational study in the USA in patients with invasive cancer, diagnosed between 1973 and 2015, showed that the risk of death from CVD was highest within the first year following the diagnosis of cancer, and remained elevated throughout follow-up compared to the general population [6].

The occurrence of cardiovascular disease in cancer patients underlies several mechanisms including inflammation, disruption of lipid metabolism and chemotherapy treatment which will be clear up in our narrative review.

II. LITERATURE

We searched PubMed and Embase for the following terms and synonyms in English: “cancer”, “cancer survivor”, “cardiovascular disease”, “metabolic syndrome”, “inflammation”, “chemotherapy”, “radiotherapy”, and “outcome”.

III. CANCER AND INFLAMMATION

Inflammation is a process that involves activation, recruitment and action of cells of the innate and adaptive immunity. Cancers are characterised by the loss of cell-intrinsic tumor suppressor functions. One of the most commonly mutated tumor suppressors is (tumor protein 53) Tp53, encoding for p53 protein. P53 protein has multifaceted functions to regulate cellular homeostasis but one of them is its transcriptional antagonism with nuclear factor-kappa B (NF-κB) a key positive regulator of inflammation. As NF-κB activating signals are always present within the tumor microenvironment and even in normal tissue, loss of functional p53 results in increased expression of NF-κB dependent inflammatory genes [7]. Also, Cancerous cells produce pro-inflammatory cytokines and chemokines that promote endothelial damage and increase micro vascular permeability and leakage of procoagulant factors (platelet activating factors, tissue factor) in the extravascular space [8].

This inflammation will lead to a procoagulant state and vascular damage with clinical consequences such as stroke and myocardial infarctions.

Itzhaki Ben Zadok et al. in a one year follow up of patients with cancer presenting acute myocardial infarction, have shown that patients with cancer were more likely to present with high-risk acute coronary syndrome (ACS) characteristics, proven by the increased GRACE score and the worse Killip class [9].

In the OASIS-Cancer study, investigators prospectively evaluated extracellular vesicles among 155 patients with active cancer and ischemic stroke and 158 controls with cancer only, stroke only, or healthy subjects[10], They reported that cancer cell-derived extracellular vesicle levels correlated with D-dimer levels and that cancer cell-derived

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extracellular vesicle levels were highest among the cancer and the stroke group. Although cancer cells have been shown to express tissue factor, which can activate factor VIII and set off the coagulation cascade, the effects of these vesicles appeared to be mediated via tissue factor-independent mechanisms [11]. Cancers also increase the levels of other procoagulant factors, including factor X, and they can release mucins that activate platelets and endothelial cells [11]. Additionally, cancers stimulate neutrophils to release decondensed chromatin, leading to the formation of neutrophil extracellular traps (NETs), which promote inflammation and thrombosis [12].

IV. Cancer and Metabolic Disorder

Low-grade inflammation induced by obesity, hyperglycemia and excessive lipid accumulation is generally systemic, and as a result, can promote or increase the risk for many different cancers, including liver, pancreatic, colon, breast and other malignancies [13].

On the other hand, several epidemiological studies have reported an increased incidence of metabolic syndrome and cardiovascular disease in childhood cancer survivors.

The pathophysiology of the development of cardiovascular disease in childhood cancer survivors is a multifactorial process as in the normal population, but with additional treatment and disease-specific modulators [14].

Overweight, obesity and adiposity are frequently described phenomena in childhood cancer survivors. Being overweight has a negative influence on blood pressure, lipid metabolism and insulin resistance. A five kg/m2 BMI increase has been described to be associated with a 1.5- or 2-fold risk increase for coronary heart disease [14,15] and 4- or 8-fold for diabetes mellitus [16].

The most widely described mechanisms explaining these conditions in cancer survivors are growth hormone deficiency which occurs in brain tumors, brain surgery, cranial irradiation; corticosteroid therapy also, as used in lymphoma[14]. Further details on the effects of cancer treatment are discussed below.

Nevertheless, genetic susceptibility has been described. England et al. performed whole-exome sequencing in 209 ALL survivors and reported that variants in BAD and FCRL3 (Fc receptor-like 3) genes were associated with a phenotype of three or more cardiometabolic risk factors [17].

V. Cancer and Treatment

Cancer treatment modalities have been described as potential providers of cardiovascular disease in cancer patients. Be it chemotherapy, radiotherapy or surgery, these treatments increase the cardiovascular risk of cancer patients compared to the general population.

Chemotherapies frequently complicated by the onset of cardiovascular diseases such as heart failure (HF), myocardial infarction (MI), hypertension, thromboembolism, QT prolongation, and bradycardia [18].

The cardiotoxicity of chemotherapeutic, varies with the intensity of the treatment, the dose of drug administered, the cumulative dose, the route of administration, association with radiotherapy, and the interval of administration [19]. In some patients, the age, the preexisting cardiovascular risk factors, and CVD put them at greater risk of cardiotoxicity [20].

The four groups of antineoplasic drugs best recognized to be cardiotoxic are anthracyclines (doxorubicin, daunorubicin); antimetabolites (fluorouracil, capecitabine);antimicrotubule agents (paclitaxel, docetaxel) and tyrosine kinase inhibitors including monoclonal antibody-based (bevacizumab), and small-molecule tyrosine kinase inhibitors (erlotinib, sorafenib) [18,21].Production of reactive oxygen species (ROS) and the formation of iron complexes, resulting in intracellular damage have been implicated in anthracycline-mediated toxicity [22].

5-Fluorouracil (5-FU), capecitabine, docetaxel, paclitaxel, and sorafenib promote myocardial ischemia by vasospasm in patients with cardiovascular risk or not. They induce abnormal vasoreactivity leading to endothelial damage and alterations in the control of vascular smooth muscle tone [18,23]. Also, some chemotherapeutic agents like bevacizumab or cisplatin, cause acute coronary thrombosis, as a result of endothelial dysfunction, inflammation, platelet activation, and vascular remodeling [24].

In a population-based study, Fung et al evaluated CVD mortality after chemotherapy or surgery in patients with testicular cancer. It appears that no increased risk followed surgery alone, whereas a significantly increased risk (60% excesses) occurred after chemotherapy. Likewise, cerebrovascular disease mortality accounted for 16.3% of all CVD deaths, with significantly elevated risks after chemotherapy [25].

On the other hand, radiotherapy and surgery are other modalities of cancer treatment. The effect of radiation therapy may be directly related to radiation or related to damage of the treated organ. Surgery, on the other hand, is much more implicated by the ablation of organs, especially endocrine organs.

Brain tumors, cranial radiation therapy (CRT) and brain surgery have been associated with the occurrence of metabolic syndrome in childhood cancer survivors [14]. The primary mechanism is the damage of the hypothalamus and pituitary gland, which leads to several endocrine disorders, the most common being growth hormone deficiency (GHD) [14].

After radiotherapy growth hormone secretion may gradually and irreversibly decrease over the years in a dose-dependent manner [14,26]. In a meta-analysis by Mulder, the pooled prevalence of GHD after cranial radiation was 35.6% [27].

GHD induces the components of the metabolic syndrome, adiposity, insulin resistance, dyslipidemia and hypertension [28,29]. It is also linked to endothelial dysfunction and atherosclerosis [30]. All of these increase the risk of cardiovascular complications.

Radiation-related cardiovascular diseases are damages to cardiac structures or vessels due to radiation exposure. These damages, including heart valves, pericardium, and myocardium occur at the time of radiation and the effects become visible clinically either shortly after exposure (eg: radiation-related pericarditis) or later after radiotherapy (coronary artery disease, valvular disease) [18,31].

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In one retrospective study, Khakoo et al. found that 10.4% of patients treated with mediastinal radiotherapy for Hodgkin's lymphoma had radiation-induced coronary artery disease (CAD) at a mean of 9 years after treatment [32]. Thoracic radiation therapy is seen to be the most important cancer therapy-related cause of CAD and myocardial infarction not related to vasospasm [18,32]. Nimwegen et al. With their cohort of 797 patients with Hodgkin's lymphoma who underwent treatment with mediastinal radiotherapy and anthracyclines, reported a 40-year cumulative incidence of cardiovascular diseases of 50% [33].

The central mechanism of this radiotherapy-induced CAD seems to be the damage of coronary artery endothelium [34].

VI. Conclusion

Cancer is an ever-growing disease. Air pollution, changes in lifestyles and diet make it even easier to rise significantly. It has several risk factors in common with cardiovascular disease. From the data in the literature today, it is clear that cancer itself predisposes to cardiovascular disease even in patients without standard cardiovascular risk factors. This calls on us to take a meticulous clinical approach and methodical screening for cancer in patients with cardiovascular pathologies, especially if they do not have the standard risk profile, if they have a family or personal history of cancer or if we do not immediately find the cause as in a cryptogenic ischemic stroke for example.

Competing interests

The authors declare no competing interests.

Author's contributions

Study conception: EGA; manuscript writing: EGA; critical revision: GN, NVN, AS; supervision: AS.

All the authors have read and agreed to the final manuscript.

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