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Review article

Reverse cardio-oncology: Exploring the effects of cardiovascular disease on cancer pathogenesis

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ABSTRACT

The field of cardio-oncology has emerged in response to the increased risk of cardiovascular disease (CVD) in patients with cancer. However, recent studies suggest a more complicated CVD-cancer relationship, wherein development of CVD, either prior to or following a cancer diagnosis, can also lead to increased risk of cancer and worse outcomes for patients. In this review, we describe the current evidence base, across epidemiological as well as preclinical studies, which supports the emerging concept of 'reverse-cardio oncology', or CVD-induced acceleration of cancer pathogenesis.

1. Introduction

The field of cardio-oncology has evolved from observations of increased risk of cardiovascular disease (CVD) following a cancer diagnosis [1]. The increased CVD risk is linked to both direct (e.g. cardiotoxic) and indirect (e.g. sedentary lifestyle) complications of cancer treatments [2], and the cardio-oncology field continues to grow with the introduction of new immunotherapies, with various cardiotoxic sequelae, and expansion of their clinical use [3]. This expansion, alongside the evolving management and treatment of CVD in patients with cancer, has also led to an adjacent line of investigation: can the presence of CVD reciprocally influence cancer pathogenesis? Indeed, recent studies suggest that the CVD-cancer relationship may be more complex than previously appreciated, leading to a new concept of CVD-induced cancer risk and progression that has been termed 'reverse cardio-oncology' [4].

Cardiovascular disease (CVD) is now well established as a systemic disease [5–8]. CVD-induced dysregulation of systemic inflammation, immunity, and metabolism have been shown to have direct effects on both CVD (e.g. pre-existing atherosclerotic plaques) [8] and non-CVD tissues (e.g. adipose tissue) [6], leading to increased morbidity and mortality (e.g. recurrent myocardial infarction (MI), insulin resistance and diabetes). It is therefore plausible that the systemic effects of CVD can also drive other disease entities, including cancer. Cancer and CVD, the two leading causes of death in developed countries, share numerous modifiable and non-modifiable risk factors, including smoking, obesity, physical inactivity, hypertension, dyslipidaemia, aging, and genetic predisposition [9,10]. Over the last decade, observational data have shown a positive relationship between CVD and pan-cancer incidence [11–13], with emerging support from preclinical studies [14,15]. Whether this relationship is causal or due to shared risk factors remains in debate [16], but evidence continues to mount that the systemic changes associated with CVD can have pro-tumorigenic effects [17]. Further, recent work that suggests incident CVD following a primary cancer diagnosis may drive cancer progression [18] has spurred further interest in understanding the impact of this bi-directional relationship on disease progression and clinical practice [19].

In this review, we outline the emerging data exploring how the development of CVD, either prior to or following a cancer diagnosis, relates to cancer initiation and progression. First, we briefly overview a number of selected CVD risk factors that have cancer-promoting effects. We next describe the extant observational data outlining the role of established CVD on cancer incidence and progression, as well as post-cancer diagnosis CVD on cancer outcomes. We then provide a detailed overview of recent mechanistic studies that draw causal connections in preclinical models between CVD and cancer pathogenesis. Finally, we propose future directions, across basic, translational, and clinical levels for the field.

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2. 1. Common risk factors in CVD and cancer

The growing recognition of the interplay between CVD and cancer is placed on the background of the increased prevalence of CVD in patients with cancer, and vice versa [9,20]. Today, it is acknowledged that these two diseases have various similarities, including risk factors that explain, at least in part, their co-occurrence. This section aims to summarize select CVD modifiable and non-modifiable shared risk factors [21] and the potential biological pathways by which such risk factors contribute to cancer incidence and progression. A more comprehensive overview of these and other risk factors are provided in recent reviews [9,10].

2.1. The link between modifiable CVD risk factors and cancer

2.1.1. Smoking

Smoking, like CVD [22], is an indisputable risk factor for cancer [23]. Beyond the elevated risk in lung cancer, where 80–90% of cancer deaths are due to smoking, chronic smoke exposure also increases cancer risk in up to 17 other cancer subtypes, and current estimates suggest that ~30% of all cancer deaths are due to smoking [23–25]. A multitude of pro-tumorigenic mechanisms of smoking have been identified, centring on the direct carcinogenic effects of smoke exposure on mutagenesis, epigenetic modifications and inflammation [23].

2.1.2. Obesity

Obesity is also a CVD risk factor that is associated with cancer risk and progression [26]. A recent analysis of ~1000 observational studies identified that high body mass index (BMI) is associated with increased risk of 13 different cancers [27]. Further, a prospective study of ~1 million adults identified that high BMI is associated with increased risk of cancer-specific mortality across 10 different cancers in men and 12 different cancers in women [28]. Mechanistically, obesity is associated with increased levels of various circulating factors including leptin, glucose, insulin, and insulin-like growth factor 1, all of which activate numerous growth factor signalling pathways resulting in tissue microenvironments primed for cell growth, proliferation, and survival [23]. Obesity also promotes the production of chronic inflammatory cytokines, increases oxidative stress through production of mutagenic reaction oxygen species, and induces immune suppression [29–31]. Collectively, these alterations can reduce the barrier to oncogenic transformation [29,32], as well as promote disease progression [29–31].

2.1.3. Physical inactivity

Mounting evidence suggests that physical inactivity, a CVD risk factor [33], also increases risk of cancer incidence and progression. Pooled data from 12 prospective cohort studies demonstrated that high levels of self-reported physical activity are associated with reduced risk of cancer incidence across 13 cancer subtypes compared to those reporting low levels of physical activity [34]. Further, pooled estimates across 26 prospective studies of breast, colorectal, and prostate cancer show that high levels of post cancer diagnosis self-reported physical activity are also associated with reduced risk of recurrence and cancer-specific mortality compared to those reporting low levels [35]. The mechanisms by which physical inactivity drives cancer incidence and progression are multifactorial and several emerging mechanisms by which its inverse, physical activity, may protect from cancer and its progression have been identified, including modulation of immunity, metabolism, and angiogenesis [36–40].

2.1.4. Hypertension

The causal role of hypertension (i.e., chronically elevated blood pressure) in cancer remains ambiguous. A prospective study of seven population-based cohorts totalling more than half a million adults identified a small increased risk of cancer incidence in patients with elevated blood pressure across several cancer types in men, but not women, yet increased risk for cancer-specific mortality across both men and women [41]. Hypertension also independently predicts cancer-specific mortality in women with early-stage breast cancer [42]. While speculative, several mechanistic links between CVD and carcinogenesis have been proposed, including hypertension-induced increases in vascular endothelial growth factor and angiotensin II, as well as oxidative stress [9].

2.1.5. Dyslipidaemia

Dyslipidaemia, a well-established CVD risk factor [43], has also been implicated as a risk factor for cancer, although evidence is mixed [44]. In prostate cancer, low levels of total cholesterol are associated with decreased risk of high-grade prostate cancer [45,46], and high levels are associated with increased recurrence risk [47]. In breast cancer, while conflicting reports have yielded it unclear whether total, low density lipoprotein (LDL), or high density lipoprotein (HDL) cholesterol impact risk of cancer incidence [48], a prospective study of 520 women with early-stage breast cancer showed that high circulating total cholesterol and low density lipoprotein cholesterol levels were correlated with recurrence risk [49]. Preclinical studies have identified that high cholesterol levels, and particularly the primary cholesterol metabolite 27-hydroxycholesterol, which acts as a selective estrogen receptor modulator, drives estrogen receptor positive breast cancer [50–52] through pro-metastatic shifts in both innate and adaptive immunity [50,51]. Further, given that intracellular cholesterol homeostasis and dysregulation is implicated in cancer development and progression across a variety of cancers [44], future studies that continue to resolve equivocal epidemiologic data alongside mechanistic studies of systemic and/or intracellular cholesterol dysregulation are warranted.

2.2. Shared non-modifiable risk factors in cancer and CVD

Non-modifiable CVD risk factors including genetics, age, and sex also influence the incidence and progression of cancer. For example, genetic mutations related to the Wnt/b-catenin pathway play a role in both the development of CVD by mediating hypertrophy, fibrosis, and ischemia [53], as well as malignant transformation and cancer cell proliferation in many cancer types [54]. Further, mutations in the protein kinase dual specificity tyrosine phosphorylation-regulated kinase 1B (DYRK1B) gene are associated with individual CVD risk factors, namely obesity, coronary artery disease (CAD), hypertension, and diabetes [55], while in cancer, DYRK1B regulates cellular quiescence and survival [56]. Age-associated mutations in hematopoietic stem cells also contribute to a condition known as clonal haematopoiesis of indeterminate potential (CHIP), which has been linked to both CVD and cancer [57–59]. In CVD, clinical and preclinical data show CHIP carriers of specific mutations have increased coronary-artery calcification and overexpression of several chemokines and cytokine genes that are known to induce atherosclerosis [58]. In cancer, CHIP is a major risk factor for haematologic malignancy [57].

3. Increased cancer incidence and worse cancer-specific outcomes in patients with prevalent CVD

Beyond common risk factors between CVD and cancer that may drive their co-occurrence, a growing body of clinical evidence also demonstrates that prevalent CVD is itself associated with higher cancer incidence. While these studies are of substantial hypothesis-generating value, they should also be critically assessed for their limitations and validity.

One of the central outstanding issues is if prevalent CVD can initiate new cancer formation (tumorigenesis), or that rather the internal milieu in CVD patients is such that it accelerates early existing tumors to grow or metastasize. Preclinical models mostly have focused on tumor acceleration and growth. So, in the literature, when incident cancer is described, it may be that cancer already existed, but remained occult and only started to manifest after CVD ensued.

Having said that, an abundance of data has hinted at an association between heart failure (HF) and cancer incidence. A cohort study showed that patients who develop HF within one month after MI were more prone to develop cancer in comparison to participants with no HF [11]. Four Danish registries (The Danish Civil Registration System registry, the NPR (Danish National Patient Registry), the National Causes of Death Registry, and the Danish National Prescription Registry) evaluated cancer risk and cancer death in patients with MI. All age groups of patients demonstrated higher incidence rates of cancer after 1 year from the diagnosis of MI [12]. A long-term prospective study evaluated the clinical features and prevalence of malignant neoplasm in patients with acute coronary syndrome (ACS) during a 17-year follow-up. This group reported a higher malignancy risk in ACS patients, and those who developed malignancies after the ACS diagnosis demonstrated a worse prognosis [13].

Utilizing the PREVEND study, a community-based cohort study of middle-aged participants, Meijers et al. identified that NT-proBNP, which is the gold standard biomarker for HF detection, was also associated with incident cancer [14]. Specifically, with a median follow-up of 11.5 years ($n = 8319$), where 13.2% of participants developed cancer ($n = 1132$), higher levels of NT-proBNP were associated with new-onset cancer (HR: 1.06, 95%CI 1.00–1.12) after adjustment for age, smoking and body mass index (BMI). Similar adjusted analyses showed comparable effect sizes (although not significant possibly due to limited power) for incident colorectal cancer, but interestingly, high levels of NT-proBNP were associated with female reproductive cancer incidence (adjusted HR: 1.30, 95%CI 1.08–1.56). In addition to natriuretic peptides, high-sensitivity troponin, as well as the pro-inflammatory cytokines pro-adrenomedullin, pro-endothelin, and C-reactive Protein (CRP) were also associated with incident cancer, the latter with the strongest association (HR 1.08; 95%CI 1.04–1.13).

Cancer risk in other CVD, including stroke and cardiac arrythmias, has also been assessed. The Swedish Inpatient Register found that 4% of patients with venous thromboembolism were diagnosed with cancer within the first year after enrolment [60]. In the Vitamin Intervention for Stroke Prevention study, ischemic stroke survivors demonstrated a higher annual rate of age-adjusted cancer risk compared to the general population [61]. Moreover, it appears that atrial fibrillation can also predict cancer. In the Women's Health Study, 10% of patients who had new-onset AF developed subsequent cancer [62]. Similarly, the investigators of the Danish population-based cohort study found that 11.1% of women and 15% of men who presented with new-onset AF were diagnosed with cancer later [63]. In a study that analysed echocardiographic data from more than 80,000 patients, of which nearly 5000 patients had aortic stenosis and over 8000 patients developed non-haematological cancers during a median follow-up of 5.4 years, Avraham et al. [15] showed that the crude incidence rate and death of non-haematological cancer were higher in patients with moderate to severe aortic stenosis. However, when adjusted for covariates, including age, ethnicity, alcohol abuse, smoking, obesity, diabetes, history of cancer, and aspirin and statin use, the association between aortic stenosis and cancer only held in patients between 40 and 60 years of age.

It should be noted that CVD patients are more exposed to medical surveillance in comparison to the general population. Consequently, the increased cancer risk in these patients can be due to detection bias, and regular lab tests, chest X-rays, CT scans, PET scans, and MRI scans may unmask occult malignancies [64]. In the Swedish Inpatient Register and Women's Health Study, the increased short-term cancer prevalence (within one year after venous thromboembolism diagnosis) confirms this assumption [60,62]. Nevertheless, the longer-term increase in the relative risk of cancer in patients with atrial fibrillation and venous thromboembolism cannot be explained by surveillance bias exclusively. In addition, CVD management, like anticoagulants administration to treat atrial fibrillation, may contribute to the earlier detection of cancers due to bleeding.

In sum, while these provocative studies suggest a relationship between prevalent CVD, incident cancer, and worse cancer outcomes, it is important to acknowledge their limitations. Primarily, many of these associations are identified in retrospectives analyses, in which causality is not guaranteed. Also, these studies are hampered by their design not being powered toward specific cancer outcomes in CVD patients. Thus, targeted and independent analyses are needed to reach clinically relevant conclusions.

4. Increased risk of recurrence and cancer-specific mortality in patients with incident (post-cancer diagnosis) CVD

A more recent line of investigation has been understanding the relationship between the onset of CVD following a cancer diagnosis and progression of underlying malignancy. Koelwyn et al. [18] performed a retrospective analysis of two prospective case cohort studies in early-stage breast cancer, the LACE and Pathways studies, interrogating the relationship between a post diagnosis CVD event (i.e., MI, CAD, stroke, HF, and arrythmia), and cancer outcomes (i.e. recurrence and breast cancer-specific mortality) ($n = 1724$, median follow-up 11.7 years). Patients were excluded if they had established CVD, or CVD risk factors (i.e., dyslipidaemia, hypertension, and diabetes). After adjustment for multiple covariates, including age, race, smoking status, body mass index at diagnosis date, tumor stage and adjuvant therapy (chemotherapy, radiation, endocrine therapy), patients who experienced a CV event had an adjusted 59% increased risk of cancer recurrence (95% CI: 1.23–2.06) and 60% increased risk cancer-specific mortality (95% CI: 1.16–2.22) compared to patients who did not experience a CV event. These data suggest that CV events drive progression of breast cancer. Mechanistic studies in pre-clinical models of breast cancer suggest that MI may reprogram subsequent immune responses leading to a pro-tumorigenic environment (described further below). However, validation of this relationship in independent and larger trials, as well as in other cancer populations at high risk of CVD post-cancer diagnosis are warranted.

5. Mechanisms of CVD-induced cancer pathogenesis in preclinical models

Given the growing body of observational data describing the effects of CVD on cancer incidence and outcomes, a new field has emerged exploring the causal mechanistic links that may enable cross-disease communication between CVD and cancer. These studies have combined observational findings in patients (discussed above) with relevant preclinical models of CVD, including surgical models of MI and subsequent HF, as well as aortic stenosis/constriction, identifying a number of candidate systemic factors that drive CVD-induced acceleration of colon, breast, and lung cancer.

5.1. MI-induced heart failure and colon cancer pathogenesis

In the first study to assess the role of CVD in cancer pathogenesis, Meijers and colleagues [14] discerned the effects of MI-induced HF on intestinal polyp formation in the APC^{min} model of colon cancer. This model forms spontaneous intestinal adenomas, developing ~30 adenomas throughout the intestinal tract, which lead to colon obstruction and mortality starting at ~17 weeks of age. The researchers performed surgical MI by permanent ligation of the left anterior descending coronary artery at 6 weeks of age. HF was confirmed at 12 weeks of age by MRI or echo imaging, and post-mortem by increased LV fibrosis and atrial, spleen and liver weight, as well as elevated cardiac and plasma levels of fibrosis and inflammatory-associated gene and protein products. Intestinal tissue taken at the same time point (6 weeks following MI) showed that MI-induced HF increased polyp number, size, and cumulative tumor volume. Interestingly, cumulative tumor volume positively and negatively correlated with LV fibrosis and LVEF, respectively, suggesting a dose response effect. Further, measures of proliferation by immunostaining for Ki67 in the gut showed greater proliferation in HF mice compared to sham control.

The authors subsequently investigated if the cancer-promoting effects of HF were driven by the presence of a failing heart, independent of the hemodynamic changes induced by HF (i.e., 'forward failure' due to reduced systolic blood pressure or 'backward failure' due to congestion from increased filling pressures). To experimentally test this question, hearts were excised from donor APC^{min} mice one week following surgical MI or sham surgery and transplanted into the cervical region of recipient APC^{min} mice at 7 weeks of age, and connected to the circulation via the external jugular vein and carotid artery. This enabled recipient mice to maintain hemodynamic function via their native (endogenous) heart but be exposed to the secretome of a failing heart (or sham control). In support of the hypothesis that the systemic effects of HF drove cancer outgrowth, the presence of a failing heart increased polyp number, size and tumor volume, as well as spleen weight, compared to sham transplant. Proliferation as measured by Ki67 was also increased, and similar positive and negative correlations of LV fibrosis and LVEF with tumor volume were observed. Such evidence showed that systemic factors released from the failing heart were a central driver of colon cancer outgrowth, independent of HF-associated hemodynamic changes.

To discern relevant candidate factors released from the failing heart that promote colon polyp formation and outgrowth, the authors next performed a literature search of HF-associated circulating factors (ligands) with corresponding intestine-specific receptors, identifying 5 potential circulating candidates: SerpinA1, SerpinA3, Fibronectin, Ceruloplasmin and Paraoxonase 1. The authors identified elevated levels of all 5 proteins in the plasma of 101 patients with chronic HF compared to 180 age and sex matched controls, and validated increased cardiac-specific gene expression of these factors in the failing hearts of mice compared to sham control, as well as three genes (*SerpinA3, Fibronectin, Paraoxonase1*) in transplanted hearts. In vitro, only SerpinA3 exerted consistent proliferative effects on HT29 cells, a human colorectal cancer cell line, which was shown to occur via activation of the AKT pathway.

In sum, this study provided the first causal evidence in a preclinical model that the systemic effects of HF directly regulate colon cancer pathogenesis. These effects were independent of hemodynamic changes, implicating the HF-induced cardiac secretome as a driver of colon cancer, of which a number of candidate factors in mice were identified and shown to also be upregulated in HF patients, most notably SerpinA3.

5.2. Transverse Aortic constriction and breast cancer and lung cancer progression

Avraham and colleagues [15] investigated the effect of transverse aortic constriction (TAC), a model of pressure overload-induced cardiac hypertrophy and HF, on tumor growth and metastasis in mouse models of breast and lung cancer. First, the researchers performed TAC 10 days prior to orthotopic injection of tumor cells isolated from the genetically engineered MMTV-PyMT mouse model of breast cancer. Characterization of heart function 9 days post TAC showed that fractional shortening was decreased, heart to body weight ratio was elevated, and cardiac expression of hypertrophic genes including *Anp, Bnp, bMHC and Acta1* were increased in mice exposed to TAC compared to sham or control. No changes in LV fibrosis were noted, suggesting mild cardiac remodelling and hypertrophy with reduced contractile function, without overt signs of HF. In this model, TAC accelerated breast cancer tumor growth over 25 days compared to sham and control mice. Using a second cancer model, the Lewis Lung Carcinoma (LLC) model, the authors similarly found that TAC accelerated subcutaneous tumor growth in the flank over 20 days compared to sham and control. Cell proliferation, as assessed by Ki67 immunostaining, was greater in tumors from mice with TAC compared to sham in both the PyMT and LLC models; however, no differences were noted for tumor angiogenesis. Further, delaying PyMT tumor injection to 30 days post TAC compared to 10 days post, where cardiac remodelling was more pronounced (e.g., further reductions in fractional shortening, greater heart weight/body weight ratio), lead to greater acceleration of tumor growth, suggesting that more advanced cardiac remodelling conferred a larger primary tumor growth advantage. Next, the authors sought to investigate the effects of TAC on metastasis using an experimental metastasis model in which TAC was performed (or no surgery control) on mice 45 days prior to tail vein injection of PyMT or LLC cells. TAC resulted in a greater number of lung metastatic lesions, as well a greater average lesion area, in both the PyMT and LLC models after 10 days. Together, these models show that TAC, resulting in varying levels of early cardiac remodelling, has tumor- and metastasis-promoting effects in models of breast and lung cancer.

To explore the factors and/or processes that may be responsible for TAC-accelerated tumor growth, the authors investigated the requirement of an intact immune system using NOD/SCID mice, which lack T and B lymphocytes, and have reduced natural killer and myeloid cell function. In these experiments, TAC similarly accelerated PyMT primary tumor growth compared to non-surgery control mice, suggesting the effects were independent of effects on a fully functioning immune system. The authors also performed TAC in the maladaptive-cardiac remodelling-resistant (MCRR) mouse model, which failed to result in significant differences in cardiac function and remodelling, or TAC-accelerated tumor growth. To identify potential candidate factors of TAC-induced tumor growth, the authors next investigated whether the systemic (circulating) milieu associated with TAC altered tumor cell behaviour. Both PyMT and LLC cells cultured in vitro with serum from mice exposed to TAC showed increased proliferation compared to serum from either sham or non-surgery control mice. Using bulk RNA sequencing of the TAC-hearts 55 days following surgery the authors identified 520 differentially expressed genes, of which 33 were upregulated and encoded for secreted proteins. Two of those, *CTgF* and *Periostin,* which are known regulators of cancer progression [65], were upregulated in TAC-operated hearts of both tumor (PyMT and LLC) and non-tumor bearing mice, as were protein levels in the serum. Finally, periostin increased proliferation of PyMT and LLC cells in vitro, and periostin-depleted serum from TAC-operated mice failed to increase cell proliferation in vitro. Together, these data suggest that periostin may be a candidate driver of tumor growth following TAC via its effects on cancer cell proliferation. In sum, this study supports the concept that early cardiac remodelling in response to aortic constriction, similar to models of HF, has cancer promoting effects through altering the systemic host milieu.

5.3. Myocardial infarction accelerates breast cancer

While the aforementioned studies discerned the role of pre-existing CVD (early and late-stage HF) on cancer pathogenesis, Koelwyn et al. [18] interrogated whether incident CVD events, such as MI, following primary cancer could alter cancer progression. To address this question in preclinical models, the authors first implanted syngeneic E0771 cancer cells into the mammary fat pad of C57BL/6 J mice, then subjected to surgical MI or sham surgery 3 days following implantation. Over 17 days, MI accelerated tumor growth compared to sham, resulting in increased tumor volume and tumor weight. MI also increased intratumoral cell proliferation at the tumor border, as assessed by Ki67 immunostaining, which occurred in both the non-immune (CD45-) and immune (CD45+) cell fractions. The authors validated that MI-accelerated tumor growth in MMTV-PyMT mice – a transgenic mouse model of spontaneous breast cancer on the C57BL/6 background. Surgical MI, performed upon palpable tumor formation, accelerated tumor growth and metastasis to the lung over a period of 18 days, compared to sham surgery. Together, these experiments identified in mouse models of breast cancer that MI following primary breast cancer accelerates disease progression.

To discern how MI accelerates cancer outgrowth, the authors performed intratumoral immune profiling by flow cytometry. In the E0771 model, MI increased the proportion of $CD45^{+}$ immune cells in tumors compared to sham, which was driven by an increased accumulation of $CD11b^{+}Ly6C^{hi}$ monocytes. Monocytes, as well as monocyte-derived

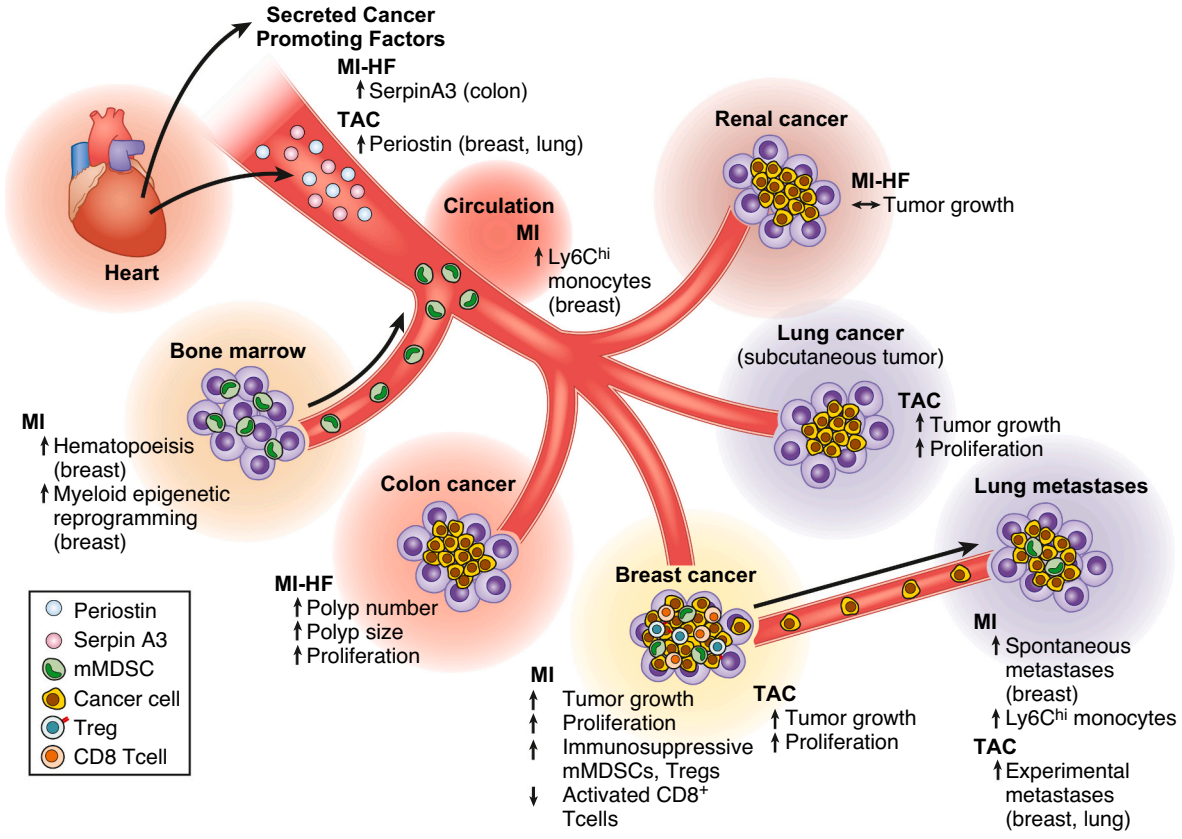

Fig. 1. Graphical summary of preclinical studies [14,15,18,71] interrogating the effects of cardiovascular disease on cancer pathogenesis. MI: myocardial infarction; HF: heart failure; TAC: transverse aortic constriction, a model of pressure overload-induced cardiac hypertrophy and heart failure; mMDSC: monocytic myeloid-derived suppressor cell; Treg: regulatory T cell.

tumor associated macrophages, have numerous cancer-promoting functions, including immune suppression [66]. MI also decreased tumoral $CD3^+$ T cells as a percentage of $CD45^+$ cells, but induced a proportional increase in immunosuppressive $CD3^+FoxP3^+$ regulatory T cells in the tumors. These MI-induced alterations in the tumor immune landscape were also noted in the MMTV-PyMT model, wherein MI increased levels of monocyte-derived $CD11b^{lo}MHCII^{hi}$ tumor associated macrophages and $CD3^+FoxP3^+$ regulatory T cells in primary tumors, as well as increasing $Ly6C^{hi}$ monocytes in metastasis-bearing lungs.

High circulating monocyte levels are known to correlate with worse cancer outcomes across multiple cancers [67,68]. Following MI, E0771 tumor-bearing mice had a sustained monocytosis within the circulation compared to sham mice. This may be due to increased haematopoiesis, as the proportion of common myeloid progenitors within the bone marrow, a precursor of $Ly6C^{hi}$ monocytes, was increased after MI. Using adoptive transfer experiments, the authors showed that MI also increased recruitment of monocytes to tumors during early tumor growth. These increases in the systemic availability and recruitment of $Ly6C^{hi}$ monocytes to tumors were required for MI-accelerated tumor growth, as depletion of monocytes 10 days following E0771 tumor injections using the CCR2-diptheria toxin receptor mouse model abrogated the MI-induced tumor growth advantage. Intriguingly, removal of intratumoral $Ly6C^{hi}$ monocytes reversed the MI-induced immunosuppressive microenvironment in the tumor, by reducing the proportion of regulatory T cells and increasing the proportion of activated (Granzyme B^+) $CD8^+$ T cells. To explore how MI altered monocyte phenotypes in the tumor, the authors isolated tumor $Ly6C^{hi}$ monocytes and tested their ability to alter $CD8^+$ T cell activation and proliferation. While no differences were noted for $CD8^+$ T cell proliferation, monocytes from MI mice more potently suppressed $CD8^+$ T cell activation (as measured by GrB^+, $iFN\gamma^+$, and $TNF\alpha^+$) compared to tumoral monocytes from sham controls. Consistent with this, RNA sequencing of tumoral $Ly6C^{hi}$ monocytes isolated 17 days following MI identified pathways associated with immunosuppression, including inhibition of lymphocyte activation, adaptive immune responses and IFNg signalling. In support of the central role of $CD8^+$ T cell-induced immunosuppression in tumor growth, depletion of these cells using anti-CD8 accelerated tumor growth in sham mice, while no tumor growth differences were noted in mice with MI, consistent with the established dysfunctional phenotype of $CD8^+$ cells following MI.

Given that MI dysregulated systemic immune processes, the authors next investigated whether the immunosuppressive transcriptional signature noted in tumor $Ly6C^{hi}$ monocytes was also observed in monocytes in the circulation and bone marrow reservoir, prior to tumor recruitment. Indeed, geneset analysis of the top 1000 differentially expressed genes in tumor monocytes showed that these changes correlated with those observed in circulating and bone marrow monocytes, suggesting that MI reprograms systemic monocytes and these changes are maintained upon tumor entry. Further, transposase-accessible chromatin with high-throughput sequencing (ATAC-seq) analysis performed on bone marrow monocytes identified that MI reduced chromatin accessibility at loci associated with immune and inflammatory responses, lymphocyte activation and cytokine production. Analysis of transcription factor binding motifs in these regions of less accessible chromatin after MI identified the pioneer factors PU.1 and CEBP, as well as the interferon regulatory factor (IRF)-8, which is known to regulate myeloid cell differentiation. Interestingly, repression of IRF-8 has previously been shown to induce a myeloid-derived suppressor cell phenotype [69,70], which is consistent with the immunosuppressive phenotype of monocytes observed after MI. Subsequent integration of ATAC- and RNA-seq monocyte datasets found

numerous genes regulated by PU.1, CEBP and IRF-8 that showed both less accessible chromatin in the bone marrow and reduced gene expression in the tumor, including genes involved in T cell activation (e.g. *Cd40, Cd86*), *Il12*, and *Irf8* itself. To confirm that changes in the bone marrow were driving MI-accelerated tumor growth, the authors performed a bone marrow transplant from tumor-bearing mice exposed to MI or sham surgery to wildtype donor mice, and assessed monocyte levels and tumor growth 14 weeks later. Strikingly, mice with MI-donor bone marrow exhibited a circulating monocytosis compared to mice with sham-donor bone marrow, and accelerated growth of E0771 tumors upon implantation. These data suggest long-term alterations to the chromatin (e.g., epigenetic) status of monocyte precursors following MI, which drives sustained haematopoiesis and an immunosuppressive phenotype that accelerates tumor growth. Together, this study highlights that post-cancer CVD events such as MI, similar to prevalent HF prior to cancer, can promote a pro-tumorigenic systemic host milieu.

In sum, this emerging collection of mechanistic studies highlights numerous candidate mechanisms by which CVD (e.g. models of MI, MI-induced heart failure, and aortic stenosis/constriction) accelerates cancer, including cardiac-specific circulating factors (e.g. SerpinA3, Periostin) and innate immune-specific changes (Fig. 1). However, given the pleotropic effects that CVD exerts on the systemic host milieu, these changes likely explain only part of this complicated cross-disease interaction. It is plausible that a combination of changes across systemic regulatory networks (e.g. autonomic function, inflammatory and immune responses, metabolism) as well tissue-specific alterations (e.g. bone marrow, spleen, heart, lung, muscle, adipose, liver, kidney) that occur in both CVD and cancer are leading to deleterious interactions that potentiate risk for cancer cell transformation, proliferation and cancer progression. Such interactions, however, will likely be dependent both on CVD and cancer type. In a recent study, Shi and colleagues found that MI-induced HF did not accelerate renal cancer progression in the RENCA mouse model, and tumor weights were comparable between the MI and sham groups [71]. These outcomes suggest that the effects of HF on tumor growth are not generic, and likely the underlying mechanisms might be specific for HF etiologies, cancer types, and animal models. Further, as basic and translational scientists continue to explore the systemic, tissue, and cell-specific factors that enable CVD-induced cancer pathogenesis, it will be essential to consider the appropriate development and utilization of CVD and cancer model systems that are designed to recapitulate clinical observational findings and subsequent translation to patients.

6. Future directions and clinical implications

Cardio-oncology for a long time has been exclusively focused on CVD development during or after cancer and cancer treatment. Just recently, it has been appreciated that CVD may also be accompanied or complicated by incident cancer. As described, epidemiological studies show that the presence of CVD is associated with higher incidence and worse outcomes for cancer patients, which has been backed by compelling experimental studies, which identify various CVD-specific secreted factors and alterations to host immunity, which in turn induce a pro-tumorigenic milieu that is favourable to cancer outgrowth. Such interrogation provides a window into the mechanistic underpinnings of such clinical observations.

We are now at the stage where we need scientific expansion of this field to allow clinical translation. Clearly, the first studies, that we have contributed to and have reviewed in this article, are a simplification of the complex human (patho-) physiology, yet at the same time, have explored several very attractive mechanistic pathways. Circulating factors may be employed for detection of cancer risk, that may be CVD specific, or generic. And as has recently been discussed by several groups [72–74], biomarkers may be further developed into biotargets. The observed changes in the immune system obviously are also very feasible and attractive targets for treatment, in the era that immune therapy is becoming the mainstay of cancer treatment.

Table 1
– Future areas of research in the field of 'reverse cardio-oncology'.

Future Area of Research	Lines of Investigation
1. Epidemiological Discovery	*Prevalent CVD and Cancer Incidence, Recurrence, Cancer-specific Mortality* • Design of prospective studies, using cardiac imaging or established markers of disease, that are powered based on cancer outcomes in CVD patients • Discern specific cancers that may be more sensitive to prevalent CVD • Discern how CVD risk factors influence the relationship between prevalent CVD and cancer incidence/progression *Post Cancer Diagnosis Incident CVD and Cancer Recurrence, Cancer-specific Mortality* • Validate in larger trials the relationship between post-diagnosis CVD and cancer outcomes (e.g. recurrence, time to recurrence, cancer-specific mortality) • Explore relationships in specific cancer populations at high risk of CVD post-cancer diagnosis (e.g. due to age, cardiotoxicity and/or longevity post cancer diagnosis) • Discern relationship between specific post diagnosis CV events (e.g. MI, HF, stroke) and cancer outcomes
2. Molecular Epidemiology	• Creation and merging of CVD and cancer databases, biobanks and repositories to enable deep phenotyping of CVD-cancer interactions • Connect established as well as novel systemic/tissue-specific CVD factors with cancer outcomes • Discern if CVD relationships differ based on tumor intrinsic properties (e.g. do associations differ across specific tumor subtypes, such as estrogen receptor +/− breast cancers, or with certain molecular markers? Does mutational status/burden alter risk?)
3. Preclinical Studies	• Validate identified CVD-specific mechanisms in preclinical models of breast, colon, lung in other disease relevant models of cancer (e.g. genetically engineered mouse models, spontaneous models of metastasis), as well as extend to models of other cancers • Establish CVD-cancer phenotypes in mouse backgrounds other than C57BL6/J, as response to CVD events (e.g. MI, HF) can differ across mouse lines. • Explore CVD-induced pro-tumorigenic effects in other models of HF and MI (e.g. ischemia/ reperfusion injury), other CVD conditions with early epidemiological CVD-cancer signals (e.g. stroke, arrythmias) and models of cardiotoxicity • Establish how comorbidities influence the CVD-cancer pathogenesis link (e.g. MI or HF in mice with established atherosclerosis, obesity) • Connect how CVD-induced systemic/tissue- (e.g. heart, vascular, liver, lung, kidney) specific changes relate to tumor/tissue microenvironment-specific alterations

What needs to be done? In Table 1, we provide three overarching areas of future investigation. First, we will need cardiologists and oncologists who are dedicated to move outside their comfort zone, and systematically and precisely map the scope of the problem. Cancer trials need meticulous CV phenotyping, and CV trials need meticulous cancer phenotyping. In reality, this rarely happens. Second, databases, biobanks and repositories coming from such concerted actions will prove invaluable in deep phenotyping of the intimate relationship, and generate insights into potential pathways. Third, translational and basic researchers should become involved to test the pathways. Ultimately, this should improve the understanding of the complex interplays between cancer and CVD and improve outcomes for patients.

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Declaration of Competing Interest

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