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# Current Problems in Cardiology

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Invited Review Article

## Evolving perspectives in reverse cardio-oncology: A review of current status, pathophysiological insights, and future directives

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### A B S T R A C T

Cardiovascular disease (CVD) and cancer are leading causes of mortality worldwide, traditionally linked through adverse effects of cancer therapies on cardiovascular health. However, reverse cardio-oncology, a burgeoning field, shifts this perspective to examine how cardiovascular diseases influence the onset and progression of cancer. This novel approach has revealed a higher likelihood of cancer development in patients with pre-existing cardiovascular conditions, attributed to shared risk factors such as obesity, a sedentary lifestyle, and smoking. Underlying mechanisms like chronic inflammation and clonal hematopoiesis further illuminate the connections between cardiovascular ailments and cancer. This comprehensive narrative review, spanning a broad spectrum of studies, outlines the syndromic classification of cardio-oncology, the intersection of cardiovascular risk factors and oncogenesis, and the bidirectional dynamics between CVD and cancer. Additionally, the review also discusses the pathophysiological mechanisms underpinning this interconnection, examining the roles of cardiokines, genetic factors, and the effects of cardiovascular therapies and biomarkers in cancer diagnostics. Lastly, it aims to underline future directives, emphasising the need for integrated healthcare strategies, interdisciplinary research, and comprehensive treatment protocols.

### Introduction

Cardiovascular disease (CVD) and cancer, as leading causes of mortality worldwide, have traditionally been linked through the adverse cardiovascular effects of cancer therapies, such as radiotherapy and chemotherapy.<sup>1</sup> However, the field of reverse cardio-oncology, emerging from specialised cardio-oncological care, shifts this perspective. It investigates the impact of cardiovascular diseases on the modulation of cancer onset and progression.<sup>2</sup> This novel approach has revealed that patients with pre-existing cardiovascular conditions are more likely to develop cancer compared to the general population, a correlation largely attributed to shared

*Abbreviations:* CVD, Cardiovascular Disease; MI, Myocardial Infarction; HF, Heart Failure; COS, Cardio-oncology Syndrome; CI, Confidence Interval; ECM, Extra-cellular Matrix; DVT, Deep Vein Thrombosis; RCC, Renal Cell Carcinoma; PREVEND, Prevention of Renal and Vascular End-Stage Disease; TAC, Transverse Aortic Constriction; EMT, Epithelial to Mesenchymal Transition; CANTOS, Canakinumab Anti-Inflammatory Thrombosis Outcome Study; VEGF, Vascular Endothelial Growth Factor; HIF-1, Hypoxia-Induced Factor 1; CHIP, Clonal Haematopoiesis of Indeterminate Potential; TAM, Tumour-associated Macrophages; TME, Tumour Microenvironment; TTN, Titin; IGF-1, Insulin-like Growth Factor 1.

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risk factors such as obesity, a sedentary lifestyle, and smoking.<sup>3</sup> Additionally, underlying mechanisms like chronic inflammation and clonal hematopoiesis, alongside shared risk factors mentioned before, highlight the deep-seated connections between cardiovascular ailments and various cancers.

The growing prevalence and mortality rates associated with these conditions underscore the urgency of this research. Prevalent cases of total CVD nearly doubled from 271 million in 1990 to 523 million in 2019, and the number of CVD deaths steadily increased from 12.1 million in 1990, reaching 18.6 million. In parallel, the global burden of cancer is also escalating significantly.<sup>4</sup> There were an estimated 18.1 million new cases of cancer worldwide in 2020, and projections suggest that the global incidence of cancer will rise to 28 million cases by the end of this decade.<sup>5</sup> These alarming statistics not only reflect the growing impact of these diseases on public health but also highlight the critical need for integrated approaches in healthcare. In fact, reverse cardio-oncology was a focal point at the 2023 Global Cardio-Oncology Summit (GCOS) in Madrid, with a dedicated session exploring its nuances. Scholars and researchers at the summit placed particular emphasis on the association between heart failure and oncogenesis.<sup>6</sup> The discourse focused on delineating how heart failure, beyond its shared epidemiological risk factors with cancer, may act as a catalyst for oncogenic processes through the induction of physiological stress and systemic alterations.

Consequently, by exploring how CVDs contribute to increased cancer risk and understanding the shared mechanisms, reverse cardio-oncology not only offers insights into the reciprocal relationship between these two disease states but also opens the door to innovative therapeutic strategies and improved patient outcomes. This paper aims to outline the relationship between cardiovascular diseases and cancer, emphasising the importance of addressing these interconnected health challenges in a holistic manner.

## Methodology

This literature review on reverse cardio-oncology, conducted from November 15th to November 28th, 2023, encompassed a broad spectrum of studies, including observational, case-control, cohort, and randomised controlled trials, to ensure a comprehensive understanding of the field.

The literature search spanned several databases, including PubMed, EMBASE, Google Scholar, the Cochrane Library, CINAHL, SCOPUS, and Scielo, with publications covered up to December 16th, 2023. Key search terms were selected to align closely with the focus of reverse cardio-oncology, incorporating phrases such as "cardiovascular diseases and cancer," "cardio-oncology," "cardiac and cancer interplay," "cardiovascular impact on cancer," and "reverse cardio-oncological mechanisms." An additional manual search complemented the electronic database exploration and involved reviewing reference lists of key articles to capture any significant studies potentially missed during the initial search. The review was restricted to articles in English and excluded stand-alone abstracts, unpublished studies, and trial protocols. Each identified paper underwent a thorough screening for relevance and quality following the SANRA framework.

## Current knowledge

### Syndromic classification

The classification system conceptualised by Boer and colleagues, delineating a 5-tier framework, offers a scholarly lens for examining the field of cardio-oncology in its entirety.<sup>7</sup> Specifically, Types 3 and 4 within their proposed system, as illustrated in Fig. 1, correlate to the study of reverse cardio-oncology.

Type 3, or COS Type III, directly corresponds to reverse cardio-oncology. It is characterised by the pro-oncogenic environment created by the release of cardiokines and hypoxia in patients with cardiovascular dysfunction.<sup>3,7,8</sup> This classification acknowledges how the physiological changes and biochemical releases associated with heart diseases can contribute to the development and progression of cancer. Conversely, Type 4 (or COS Type IV) encompasses cardiovascular disease therapies and diagnostic procedures that

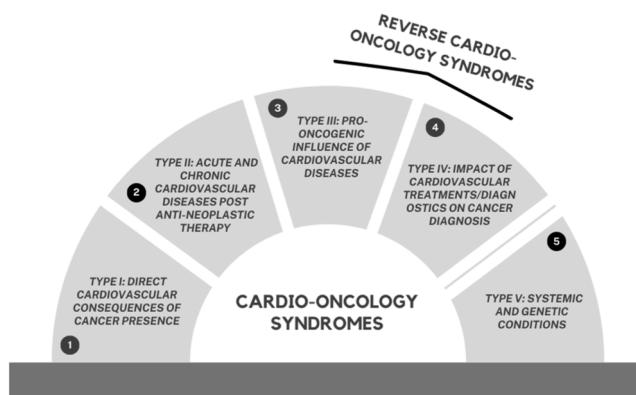


Fig. 1. Cardio-oncology syndrome classification framework (with Types 4 and 5 marked as being related to reverse cardio-oncology).

are associated with promoting or unmasking cancer.<sup>7</sup> This classification addresses the issue of how certain interventions for heart diseases like diagnostic radiation and medications might inadvertently contribute to the development or revelation of oncological conditions.<sup>9,10</sup>

Here, it's important to note that although Type 5 steps beyond the traditional scope of reverse cardio-oncology, its focus on shared risk factors, genetic predispositions, and overlapping pathophysiological aspects is integral to understanding the interrelationship between cardiovascular health and cancer.<sup>7</sup> It extends to a broader analysis of systemic and genetic factors that predispose individuals to both cardiovascular and oncological diseases.

### *Intersection of cardiovascular risk factors & oncogenesis*

The confluence of cardiovascular risk factors, such as hypertension, smoking and obesity, with oncogenic processes forms a critical area of study in reverse cardio-oncology. Therefore, understanding this intersection is key to understanding the shared pathways that exacerbate both cardiovascular and cancer risks, underscoring the need for integrated prevention and treatment strategies.

#### *Hypertension*

In examining the shared risk factors between CVD and cancer, hypertension has gained prominence as a notable contributor to an increased risk of malignancy. This association, while a subject of ongoing research, has seen varied findings. Satpathy et al (2023) references a prospective analysis revealing a connection between hypertension and higher cancer incidence, with a hazard ratio of 1.12 (95% CI: 1.08 - 1.15) per 10-mmHg increment, for male subjects and 1.06 (95% CI: 1.02 - 1.11) for female subjects.<sup>2</sup> In addition, their review consolidates findings from various meta-analyses, showing heightened risks of renal cell carcinoma (RCC), colorectal, endometrial, prostate, and breast malignancies among hypertensive patients. Similarly, Sinha et al. (2022) underscores hypertension's role in increasing breast cancer risk, specifically in post-menopausal women.<sup>11</sup> Han et al's comprehensive systematic review and meta-analysis further corroborates this, noting a 15% increased risk of breast cancer in post-menopausal women with hypertension.<sup>12</sup> They suggest that the difference in risk between pre and post-menopausal women could be attributed to varying levels of circulating oestrogen.

Overall, researchers posit several mechanisms by which hypertension might elevate cancer risk, including alterations in the cell cycle and disruption of apoptosis. Additionally, the pro-inflammatory states caused by excess adipose tissue and hypertension-induced changes in the extracellular matrix (ECM) are considered significant contributors.<sup>13</sup> Likewise, hypertension is also believed to cause arterial wall hardening, which in turn affects the ECM by disrupting its cellular metabolism, thereby creating a conducive environment for tumour growth.<sup>13</sup>

#### *Smoking*

Smoking has long been established as a risk factor for various cancers, extending beyond its well-known association with lung cancer. Chronic exposure to smoke is linked with an elevated risk of 17 different types of cancers, with studies indicating that smoking accounts for 30% of all cancer-related deaths.<sup>14</sup> The scope of cancers impacted by smoking includes those of the oesophagus, trachea, oral cavity, oropharynx, kidney, bladder, liver, pancreas, stomach, cervix, colon, and rectum.<sup>15</sup> As such, the risk of dying from lung cancer increases up to 40 times in individuals smoking 35 cigarettes per day. In a comprehensive genomic analysis of 5243 cancer samples, 2490 of which were from tobacco smokers, researchers identified five distinct mutation cancer signatures predominantly elevated in smokers.<sup>15</sup> These findings illustrate the direct mutational burden of smoking, especially noted in the TP53 tumour suppressor gene commonly mutated in lung cancer. Similar patterns have been noticed in other smoking-related cancers, with the pharynx being a prime location due to its proximity. These mutational abnormalities can be attributed to smoking by the effect tobacco may have on spontaneous cytosine deamination and deficient mismatch repair. This can lead to errors in nucleotide conversions and hence, resulting in abnormal DNA production.<sup>16</sup>

#### *Dyslipidaemia*

Cholesterol and lipid metabolism have long been an established risk factor for the predisposition to cardiovascular diseases. In recent years, however, reverse cardio-oncology has expanded this sphere to investigate the role that is played by lipids in the development of cancer pathogenesis.<sup>2,11</sup> However, and similar to hypertension, the evidence to substantiate the role played by cholesterol in cancer development has not been fully clarified, given the conflicting findings.<sup>2</sup> In mice, it has been shown that breast cancer is potentiated by the presence of excess cholesterol. This occurs due to the abnormal lipid metabolism which alters the internal stability of liver lipoproteins.<sup>2</sup> As a result of this, LDL cholesterol promotes tumour evolution and elevated cholesterol levels have also been linked to differentiated malignancy of the thyroid gland.<sup>2</sup>

In juxtaposition of the aforementioned findings, it has been reported by a number of UK-based longitudinal cohort analyses that abnormal lipid metabolism is in fact protective against breast malignancy.<sup>2</sup> However, the link between excess cholesterol potentially causing breast cancer maintains a strong one.<sup>11</sup> The pathway by which this occurs is thought to be primarily via 27-hydroxycholesterol, allowing for the production of oestrogen receptor positive breast cancer. Some proposed mechanisms for this are the inhibition of cytotoxic CD8+ T cells and tumour suppressor genes, as well as the initiation of growth-promoting component.<sup>11</sup> Dietary cholesterol is also linked positively to a risk in several different malignancies. In one instance, elevated levels of plasma cholesterol (superior to 160 mg/dL) increased the risk of prostate and bowel malignancy for male subjects, while female subjects were at an increased risk of breast malignancy.<sup>17</sup>

### Obesity

Obesity is a risk factor associated with CVD and cancer risk and progression. Obesity is also a major risk factor for hypertension, which indicates obesity, both directly and indirectly increases the risk of cancer.<sup>18</sup> An analysis of approximately 1000 observational studies revealed that high BMI is linked with a heightened risk of 13 types of cancers.<sup>13</sup> Furthermore, another study with around 1 million participants found that high BMI was linked to an increased risk of cancer-specific mortality across 10 and 12 different cancers across men and women, respectively. A different study of 16 years by Calle et al. revealed that patient with a BMI greater than 40 in men had a relative risk of cancer death of 1.52 (95% CI=1.13-2.05) and 1.62 (95% CI=1.40-1.87) for women.<sup>19</sup> It was also shown that the risk of cancer increased by 10% for every 5% increase in BMI.<sup>2</sup> Obesity enhances the generation of inflammatory cytokines, increases oxidative stress, and initiates immune suppression. Conjointly, the above can lead to oncogenic transformation and disease progression.<sup>13</sup> This oncogenic transformation creates an environment for cell growth, proliferation, and survival by primarily altering the signalling pathway due to many reactive oxygen species.<sup>2</sup>

### Physical inactivity

Yet another major risk factor for the development of cancer is the lack of physical activity. Satpathy et al. report a study with 1.44 million test subjects, in which the lack of physical activity augments the risk of 13 kinds of malignancy.<sup>2</sup> A proposed solution suggests that 2.5 hrs of regular intensity movement produces a 13% decrease in mortality from cancer.<sup>2</sup> Physical inactivity has a closer link to increasing the risk of breast and colon cancers. The link to breast cancer has been established by the theory that reduced exercise results in higher serum oestradiol, lower hormone-binding globulin, greater fat masses and higher serum insulin levels.<sup>20</sup> The connection to colon cancer has been justified by a study that states that reduced physical activity increases the FI transit time and, therefore, increases the exposure to potential carcinogens.<sup>20</sup> It remains unclear as to how physical activity directly can reduce the risk of cancer, some supported mechanisms are modulation of immunity, metabolism, and angiogenesis.<sup>14</sup>

### Bidirectional dynamics between cardiovascular diseases and cancer

Previously, treatment-related adverse effects were thought to be the only link between cardiovascular disease (CVD) and various cancer types. However, specialist care provided by cardio-oncologists and key observational studies have indicated a deeper physiological connection between certain cardiovascular conditions (such as myocardial infarction, heart failure and atrial fibrillation) and cancer. Research into the expansive interplay between these fields is a key step for the formulation of therapies and treatment protocols.

### Myocardial infarction

Myocardial infarction (MI) is caused by a reduction or cessation in the blood flow to a section of the myocardium. MI and cancer share risk factors but it is essential to substantiate if MI can cause cancer via pathophysiological processes such as specific cell reprogramming pathways and promoting the adaptation of the body's milieu to a pro-tumorigenic environment. A nationwide cohort study in Denmark involving a 30-99 year old population from 1996 to 2012 found a higher incidence rate of cancer, 19.1/1000 person-years, in the MI population in all age groups, compared to the reference population which was 18.2/1000 person-years. The incidence rate of cancer was higher after the first year following MI diagnosis.<sup>21</sup> Following on, the Tromsø study in Norway showed a hazard ratio of 46% of cancer in participants compared to those without MI and the highest cancer incidence rate of 29.0/1000 person-years was at 6 months.<sup>22</sup>

Furthermore, a preclinical study involving a mouse model of breast cancer highlights the tumour growth and progression in MI as well as exploring the immune suppression and genetic mechanisms in the MI model which ameliorates tumour growth.<sup>14</sup> The MI model had an accelerated breast cancer tumour growth (approximately 2-fold more) at 20 days compared to the sham model. Tumour volume and weight in the MI model at 20 days had expanded more compared to the sham model. Immunologically, higher proportions of CD45<sup>+</sup> leukocytes were present in the MI model than the sham model at 30% vs 16% of live cells; moreover, CD11b<sup>+</sup>Ly6G-Ly6C<sup>high</sup> monocyte levels were higher in the MI model.<sup>14</sup> Ly6C<sup>high</sup> monocytes have the same surface markers as myeloid derived suppressor cells which play a role in suppressing T-lymphocytes' immune response against tumour cells.<sup>23</sup> *CXCL13* is a gene linked with the progression of breast cancer and this gene along with its receptor, *CXCR5*, were both increased in the MI mouse model.<sup>14,24</sup>

In addition, a 2019 meta-analysis investigated the presence of an increased risk of cancer following MI found that the increase in cancer risk is statistically significant in females (95% CI=1.01-1.20,  $P=0.025$ ) and not in males (95% CI=0.99-1.10,  $P=0.124$ ).<sup>25</sup> The increased cancer risk was significant in lung cancer (male: 95% CI=1.05-1.19,  $P<0.01$ ; and female: 95% CI=1.15-1.99,  $P<0.01$ ) and not for breast (female: 95% CI=0.86-1.04,  $P=0.222$ ) and prostate (male: 95% CI=0.85-1.09,  $P=0.546$ ) cancers. In addition, this meta-analysis observed an increased cancer risk is significant at 0-6 months period ( $P<0.01$ ) and not in the 6-12 months ( $P=0.627$ ) or >12 months ( $P=0.585$ ).<sup>25</sup>

Therefore, the current evidence reveals a relationship between MI and cancer formation and growth in the preclinical models and with the incidence rate of cancer in cohort trials and meta-analyses. The highest incidence of cancer seems to be at 6-12 months after the MI, which is where findings of multiple studies align. However, there are some important factors to consider in the cohort trials; most of the data comes from countries in the north of Europe such as Denmark and Norway. This means that the data is not representative of populations in the other parts of the world. The number of studies where the investigation into the main mechanism(s) of MI causing cancer formation and growth are limited and need further preclinical and cohort studies from different populations to establish any causal relationships.

### Heart failure (HF)

Recent studies have elucidated a direct relationship between heart failure (HF) and cancer, notably in how HF can influence tumour onset and progression through secreted circulating factors and immune cell reprogramming. Meijers et al. (2018) demonstrated this connection by reporting increased intestinal polyp growth in precancerous mice induced with HF brought on by large anterior MIs.<sup>26</sup> Interestingly, this effect was independent of blood flow or circulation changes, as shown using a heterotropic heart transplantation model, resulting in a significant 2.4-fold increase in intestinal tumour burden. Further evidence comes from the PREVEND (Prevention of Renal and Vascular End-Stage Disease) study, which linked higher levels of inflammatory and cardiac biomarkers such as NT-proBNP (N-terminal pro-B-type natriuretic peptide) in healthy individuals (n=8319) were found to forecast the occurrence of new cancer cases (n=1124), irrespective of cancer risk factors.<sup>26</sup> Koelwyn et al further explored this link, demonstrating that HF can promote breast cancer growth via immune cell reprogramming.<sup>27</sup> Their research highlights the pivotal role of monocytic myeloid-derived suppressor cells in facilitating HF-induced tumour progression, suggesting a potential therapeutic target in the CCL2/CCR2 axis. In fact, the use of CCR2 inhibitors, currently under investigation, could offer a novel approach in tackling tumour growth in the context of HF. However, contrasting findings from studies like Avraham et al (2020) introduce a new layer of complexity. Their research showed no significant tumour growth changes in HF pre-clinical models, including transverse aortic constriction (TAC)-operated NOD/SCID and C57BL/6 mice.<sup>28,29</sup> TAC itself leads to pressure overload-induced hypertrophy which has led to increased tumour growth in certain mouse models for lung and breast cancer.<sup>29</sup> Consequently, these varied findings reflect the multifaceted and sometimes contradictory nature of the relationship between HF and cancer. There are several other mechanisms involved in the progression of both diseases, including angiogenesis, which require further exploration to effectively address the issue.

### Atrial fibrillation

Atrial fibrillation (AF) is the most common cardiac arrhythmia among patients and there has also been a global increase in cancer survivorship, due to advanced cancer therapies and screening tools.<sup>30</sup> Similar to other cardiovascular conditions, there is a complex multifactorial interplay between the 2 conditions. A systematic review indicated a substantial increase in cancer diagnoses within 3 months of an AF diagnosis in patients.<sup>31</sup> Furthermore, a large prospective study (n = 3461 women), with a cancer incident rate of 3.8 per 100 person-years (HR 3.54; p <0.001) within 3 months of AF was carried out.<sup>32</sup> Higher rates of cancer cases were discovered within the first three months of diagnosing AF. Similar findings were derived in a study with 270,000 participants with newly diagnosed AF.<sup>33</sup> The mechanism behind this association is unclear however this could be explained by the shared risk factors between AF and cancer (diabetes, obesity and smoking).<sup>34</sup>

Additionally, this review emphasises that antiarrhythmic interventions, such as amiodarone are linked with an increased risk of cancer. The use of amiodarone has been specifically linked to higher discovery of cancer by incident, especially in male patients. (95% CI, 1.02 to 1.36).<sup>35</sup> It is also associated with a heightened risk of malignancies in liver and intrahepatic bile ducts.<sup>36</sup> Apart from amiodarone, other antiarrhythmic drugs such as quinidine and propafenone were shown to have an associated increased risk but the respective adjusted ratios were not statistically significant.<sup>31</sup> Current literature suggests a strong association between AF and cancer, especially within the first three months of the AF diagnosis, hinting that it could be an essential tool in tackling undetected early cancers. However, detection bias is a key factor to consider. The increased frequency of medical surveillance among individuals with recently diagnosed AF could lead to increased cancer diagnosis due to imaging being more common in patients with AF.<sup>31</sup> Presently, optimising control of risk factors in patients with AF is a sufficient approach in the clinical setting. To determine the legitimacy of a direct relationship between AF and tumour growth, extensive research will be required.

### Thromboemboli and strokes

While cardio-oncology research has already established that cancer and its therapies can cause a state of hypercoagulation and lead to thromboemboli, it's important to establish whether thromboemboli and strokes have a causal/correlational effect on cancer. For this purpose, Sorensen et al., 1998 investigated the cancer diagnosis risk after a PE or DVT. In the patients with DVT (n=15,348), 1737 cancer cases were found (95% CI 1.21 to 1.33). In patients with PE (n= 11,305), 730 cancer cases were found (95% CI 1.22 to 1.41).<sup>37</sup> Therefore, a standardised incidence ratio (SIR) is 1.3 for both the DVT group and the PE group. Additionally, the SIR was highest at 3.0 (95% CI) for both the DVT and PE groups at the 0 to <6 month period after which there was a reduction in SIR to around 1.0. Furthermore, cancers of the ovary, pancreas, liver and brain were associated with DVTs and PEs in the first year. However, this study concluded that due to the lack of cost effectiveness of "extensive" cancer screening as early detection does not change the prognosis.<sup>37</sup>

In another study focused on uncovering the relationship between venous thromboembolism (VTE) and cancer, Baron et al. (1998) data was utilised from the Swedish Inpatient Registry spanning 1965 to 1983. The study assessed cancer incidence in 1989 among patients who had a history of VTE and no prior cancer diagnosis.<sup>38</sup> The Standardized Incidence Ratio (SIR) within 0-12 months post-VTE was reported at 3.2 (95% CI 3.1-3.4). Notably, polycythemia vera, a rare cancer type, exhibited an SIR of 12.9 (95% CI 8.6 to 18.7), significantly higher than the SIR for cancers of other organs such as the pancreas, ovary, brain, and liver, all of which had an SIR above 5.0.<sup>38</sup> Over the long term, there was observed a 30% increase in overall cancer incidence 10 years or more after the VTE event. This study suggests that VTE is not only associated with an increased incidence of cancer but also indicates that neoplastic and pre-malignant changes might contribute to thromboembolism formation.<sup>38</sup>

Slot et al, 2009, (n=7710), used cohorts from the Oxfordshire Community Stroke Project, the Lothian Stroke Register and the International Stroke Trial. 33 patients died as a result of cancer, making cancer the primary cause of death in 3% of all the patients who died after 6 months (n= 1001).<sup>39</sup> On the other hand, a randomised control trial (RCT), Qureshi et al. 2015 (n=3247), found that the new cancer incidence increased as time passed: 0.15/100 patients at 1 month, 0.80/100 patients at 6 months and 2.0/100 patients at 2 years.<sup>40</sup> The cancer incidence rate was higher in stroke patients than the general population at 1 year with 581.8/100,000 people vs



486.5/100,000 people respectively and at 2 years with 1,301.7/100,000 people vs 911.5/100,000 people respectively. 23 died due to cancer out of 166 deaths during the following up period, hence, 13.9% of the deaths were due to cancer.<sup>40</sup> Therefore, due to factors such as cohort size and patient aetiology, there is a large contrast between these two studies between the percentage of death due to cancer. However, this RCT showed an increase in SIR over time and a higher SIR in stroke patients which may be due to shared risk factors between the stroke and cancer. Hence, underlying pathophysiological processes need to be further analysed to see if stroke causes cancer.

### **Pathophysiological mechanisms**

#### *Inflammation as a central mechanism in disease pathogenesis*

The role of inflammation is paramount in the pathophysiological overlap between CVD and cancer, with its involvement in disease initiation, progression, and influencing prognosis.<sup>34</sup> Inflammatory pathways, particularly through the process of epithelial to mesenchymal transition (EMT), are also critical in malignant transformation and metastatic behaviour.<sup>41</sup> For instance, myocardial infarction triggers an intensified inflammatory response, characterised by the release of danger signals from necrotic cells. This cascade activates mitogen-activated protein kinases and nuclear factor- $\kappa$ B, culminating in the overexpression of proinflammatory genes.<sup>42</sup> These genes, in turn, instigate inflammatory cell activation, oxidative damage, DNA alterations, and tissue microenvironment modifications, potentially leading to oncogenesis. Ischemic conditions further exacerbate this by inducing cytokines like tumour necrosis factor, a potent activator of nuclear factor- $\kappa$ B and a key inflammatory mediator in cancer development.<sup>42</sup> At the same time, the Canakinumab Anti-Inflammatory Thrombosis Outcome Study (CANTOS) highlighted the efficacy of targeting inflammatory pathways in managing CVD. Canakinumab, an interleukin-1 $\beta$  neutralizing monoclonal antibody, significantly reduced cardiovascular events and demonstrated a marked decrease in cancer mortality, particularly lung cancer, underscoring the interplay of inflammation in both CVD and cancer.<sup>43</sup>

#### *Tumour angiogenic mechanisms (Angiotensin II, VEGF, Hypoxia-mediated, Hypercoagulability)*

Angiotensin II significantly influences the link between hypertension and cancer by promoting vascular endothelial growth factor (VEGF) release, crucial for both tumour angiogenesis and cardiovascular disease progression.<sup>44</sup> Elevated VEGF levels in hypertensive patients establish this connection to increased cancer risk. Concurrently, cardiovascular diseases create a hypoxic environment, leading to hypoxia-inducible factor 1 (HIF-1) stabilisation, which not only contributes to atherosclerosis but also elevates VEGF production, enhancing angiogenesis central to both vascular and cancerous growth.<sup>8</sup> Adding to this, recent findings in thrombosis research indicate its role in cancer development. Thrombosis, often seen in patients after stroke or venous thromboembolism, has been associated with higher cancer incidence. Shorter anticoagulation treatments like warfarin are linked to increased cancer risks, as thrombin, a key factor in thrombosis, promotes metastasis and vascular growth factors, activating dormant cancer cells.<sup>42</sup> Moreover, ischemia-reperfusion injury in the heart triggers fibroblast growth factors production, aiding cardiac recovery and also promoting tumour angiogenesis and progression, further illustrating the shared pathogenic pathways between cardiovascular disease and cancer.<sup>45</sup>

#### *Clonal haematopoiesis*

Clonal hematopoiesis of indeterminate potential (CHIP) represents a key intersection in the pathophysiology of cardiovascular disease (CVD) and cancer. CHIP occurs when somatic mutations accumulate in the DNA of hematopoietic stem cells within the bone marrow, leading to the expansion of blood cell clones with these mutations.<sup>46</sup> While not immediately cancerous, CHIP is a critical precursor state, potentially evolving towards leukaemia if further mutations accumulate in cancer driver genes.

In the context of cardiovascular health, CHIP has several implications. Studies have demonstrated that certain genetic mutations common in CHIP, particularly in genes like Ten-Eleven Translocation-2 (TET2) and DNA methyltransferase 3A, are associated with an increased incidence and poorer prognosis of heart failure.<sup>47</sup> Research has shown that these and other genetic aberrations in CHIP are associated with accelerated heart failure progression and reduced left ventricular ejection fraction (LVEF), regardless of aetiology. Furthermore, the absence of the CHIP driver gene TET2 in animal models results in accelerated atherosclerosis progression and heightened susceptibility to cardiac dysfunction.<sup>42</sup> Not only this but CHIP also plays a notable role in patients with valvular diseases. In cases like aortic stenosis, the presence of CHIP accelerates valve sclerosis, often resulting in a poor prognosis and increased mortality, even after interventions such as aortic valve replacement.<sup>48</sup> Finally, the CANTOS trial also offers insights into addressing CHIP-related risks. The study demonstrated that canakinumab, an interleukin-1 $\beta$  antibody, not only decreased cardiovascular events but also proved particularly beneficial for CHIP-positive patients, especially those with TET2 mutations.<sup>42</sup>

These findings suggest that CHIP not only marks a haematological risk but also signifies a substantial cardiovascular risk, potentially altering the clinical management of patients with cardiovascular diseases.

#### *Macrophages - CVD & breast cancer link*

Post-MI, an array of macrophages, including resident and monocyte-derived types, are central to myocardial healing and remodelling. These macrophages, through their involvement in inflammation and tissue remodelling, might have systemic

implications that extend beyond the heart.<sup>49</sup> In particular, their role in inflammatory response and tissue remodelling post-injury could be a crucial factor in influencing breast tissue environment. In the context of breast cancer, tumour-associated macrophages (TAMs), derived from similar macrophage populations, play a pivotal role in tumour initiation, growth, and metastasis.<sup>50</sup> They exhibit diverse functions, from promoting tumour growth to facilitating metastasis. This is due to their adaptability, shaped by the tumour micro-environment (TME), where they express a mix of pro- and anti-tumoral characteristics. The potential link between MI and breast cancer via macrophages lies in the systemic influence of these cells.<sup>27</sup> The same macrophages involved in myocardial healing and remodelling could, through their systemic inflammatory activities, contribute to creating an environment conducive to breast cancer development. This suggests that cardiovascular health and its associated immunological responses might inadvertently influence breast tissue, setting a potential stage for breast cancer.<sup>51</sup>

### Cardiokines

With regards to oncogenesis, the role of cardiokines—specialised proteins secreted by cardiac cells including fibroblasts, cardiomyocytes, and vascular smooth muscle cells—is gaining recognition for their influence beyond cardiovascular pathology.<sup>42</sup> Notably, osteopontin, a cardiokine predominantly produced in response to ventricular hypertrophy, has been implicated in the progression of various solid tumours, highlighting the broader oncogenic impact of heart-derived proteins through pathways influencing cell proliferation and survival.<sup>52</sup> Concurrently, Apelin, synthesised in ischemic heart conditions, alters colon cancer cell behaviour, rearranging their actin cytoskeleton and enhancing proteolytic and migratory capacities, thus establishing a direct correlation between cardiac stress and oncological advancement.<sup>42</sup> Furthermore, growth arrest-specific gene 6 (GAS6), linked to atherosclerotic plaque formation, plays a critical role in facilitating epithelial-to-mesenchymal transition (EMT), a key process in cancer metastasis, by activating mitogen-activated protein kinase and Slug pathways.<sup>42</sup>

### Genetic & cellular basis

Titin (TTN), a key protein in the heart, is closely linked to cardiomyopathy. Its truncation mutations are notably prevalent in dilated cardiomyopathy and also associated with other forms like hypertrophic and arrhythmogenic right ventricular cardiomyopathy.<sup>53</sup> Notably, these TTN mutations are found in about 30% of solid tumours, suggesting a genetic overlap between cardiovascular diseases and cancer.<sup>7</sup> Additionally, the relationship between insulin-like growth factor 1 (IGF-1) levels and BRCA1/2 mutations further illustrates this connection. Altered IGF-1 levels in individuals with BRCA1/2 mutations, particularly higher levels in those with breast cancer, are linked to increased insulin resistance risk, a common factor in cardiovascular diseases.<sup>54</sup> This highlights a shared genetic underpinning that influences both cancer and cardiovascular health. Adding to this complexity is the gene expression analysis in chronic HF patients, as a study identified elevated levels of proteins such as serpin A1 and A3, paraoxonase 1 and fibronectin in diseased individuals compared to healthy controls.<sup>26</sup> Notably, these candidate-secreted proteins, particularly serpin A3, showcased significant proliferative effects on HT-29 colon cancer cells, potentially through the Akt-S6 phosphorylation pathway.<sup>26</sup>

## Therapeutic interventions and diagnostic advances

### Role of biomarkers in diagnostics

Biomarkers that are typically associated with one of the conditions have also been found to play a crucial role in the other one. Increased amounts of CVD biomarkers have predicted a higher risk of cancer mortality and certain tumour biomarkers have been successful in forecasting CV mortality. Jovani et al. (2022) investigated 71 different cardiovascular biomarkers in the Framingham Heart Study, where the participants were cancer-free (n = 5032).<sup>55</sup> Multivariable-adjusted Cox models were used to determine the strength of the association between protein biomarkers and the risk of cancer incidence. Key markers such as Growth Differentiation factor-15 (GDF-15), Stromal Cell-Derived Factor-1 (SDF-1), and Fibroblast Growth Factor-23 (FGF-23) were identified to significantly increased risk of incident gastrointestinal, colorectal cancer and cancer-related death.<sup>55</sup> For clarity purposes, these biomarkers have been summarised in [Table 1](#) below.

### Growth differentiation factor-15

Also known as macrophage inhibitory cytokine-1, it is pleiotropic cytokine and is an indicator of inflammation and cellular injury.

**Table 1**

Association of various biomarkers with cancer and related mortality risks.

Biomarker	Association with Cancer	Risk Increase
Growth Differentiation Factor-15	Linked to gastrointestinal, colorectal, and overall cancer <sup>56,57</sup>	HR 1.85 (GI), HR 1.94 (CRC) <sup>55</sup>
Stromal Cell-Derived Factor-1	Associated with decreased cancer-related mortality <sup>58-60</sup>	HR 0.75 (decreased mortality) <sup>55</sup>
Fibroblast Growth Factor-23	Specifically linked to colorectal cancer <sup>62</sup>	HR 1.55 (CRC) <sup>63</sup>
Carcinoembryonic Antigen (CEA)	Predicts cardiovascular and all-cause mortality <sup>64,65</sup>	HR 1.28 (CV), HR 1.60 (all-cause) <sup>65</sup>
Cancer Antigen 15-3 (CA15-3)	Predicts heart failure and all-cause mortality <sup>66</sup>	HR 1.67 (HF), HR 1.58 (all-cause) <sup>66</sup>
CYFRA21-1	Independent predictor of cardiovascular morbidity (females) <sup>64</sup>	HR 1.82 (CV) <sup>64</sup>



This cytokine reduced the response of macrophages in immunosurveillance, thus promoting early cancer progression.<sup>56</sup> It has also been shown to play a role in pro-neoplastic activity via the promotion of tumour progression, invasion and immune evasion.<sup>57</sup> It consistently demonstrated a significant link to the risk of incident gastrointestinal (GI), colorectal (CRC) and overall cancer. GDF-15 was also determined to have an increase of 85% in the risk of incident GI cancer per 1-standard deviation change (HR 1.85, 95% CI 1.37–2.50).<sup>57</sup> Additionally, GDF-15 was associated with CRC (HR 1.94, 95% CI 1.29–2.91).<sup>55</sup>

#### Stromal cell-derived factor-1

Also known as CXCL12, stromal cell-derived factor-1 (SDF-1) was associated with a lesser risk of cancer-related mortality. A 1-standard deviation increase in SDF1 levels led to a 25% decrease in hazard ratios of cancer death (HR 0.75, 95% CI 0.65–0.86).<sup>55</sup> Experimental data also suggests that this factor inhibits metastasis in colonic and pancreatic tumours.<sup>58</sup> Contradictory data suggests that SDF1 could lead to worse clinical outcomes due to its potential role in angiogenesis promotion, metastasis and leukocyte trafficking.<sup>59,60</sup>

#### Fibroblast growth factor-23

This growth factor is part of the endocrine FGF subfamily, with normal expression present on osteocytes and plays a crucial role in the regulation of phosphate levels.<sup>61</sup> The data from the Framingham Heart Study link FGF23 specifically to CRC (HR 1.55, 95% CI 1.20–2.00). Prior studies have also linked FGF-23 to an increased risk of incident prostate cancer and worse patient outcomes with bone metastases.<sup>62,63</sup>

#### CEA

Carcinoembryonic antigen, also known as CEA, is a glycoprotein situated on epithelial cells of the colon and is shown to play a role in tumour metastasis and invasion. It is used both as a diagnostic and prognostic tool in colorectal cancer. Mechanisms involve cell adhesion and deimination of intestinal cancer for metastasis via direct monocyte binding. Such cellular interactions could explain the potential link between tumour biomarkers and CVD.<sup>64</sup> Elevated CEA levels have been shown to have higher leukocyte count, suggesting a possible link between CEA levels and inflammation.<sup>65</sup> Levels of CEA were shown to significantly predict cardiovascular mortality (HR 1.28 (95% CI 1.08–1.53)). It also exhibited statistical significance in all-cause mortality prediction (HR 1.60 (95% CI 1.30–1.96)).<sup>65</sup>

#### CA15-3

Cancer antigen 15-3 is a transmembrane glycoprotein and is a soluble form of the mucin 1 transmembrane protein (MUC1). MUC1 is elevated in conditions such as acute MI due to the presence of this protein on the surface of many organ systems. Additionally, the strong correlation between CA15-3 and HF severity has been reported as well.<sup>66</sup> It was presented as a statistically significant predictor of heart failure (HR 1.67 (95% CI 1.15–2.42)). Similar to CEA, CA15-3 exhibited statistical significance in predicting all-cause mortality (1.58 (95% CI 1.18–2.12)).<sup>66</sup>

#### CYFRA21-1

Cytokeratin fragment 21-1 is a pan-carcinoma biomarker, which measures levels of cytokeratin 19 fragment levels. It is also used as a marker for prognosis in over 30 different cancer types. It has been suggested that elevated CYFRA21-1 levels are due to abnormal mitosis and apoptosis, processes often observed in CVD and tumour growth.<sup>64</sup> CYFRA21-1 was shown to be an independent predictor of cardiovascular morbidity and mortality in females only (HR 1.82 (95% CI 1.40–2.35)), suggesting that certain tumour biomarkers are gender-specific.

**Table 2**

Cardiovascular therapies and diagnostic avenues associated with cancer risk and research directions.

Cardiovascular Therapy	Association with Cancer Risk	Further Research Needed
Angiotensin Converting Enzyme Inhibitors (ACEIs)	Associated with increased lung cancer risk and breast cancer recurrence <sup>68,69</sup>	Mechanisms underlying effects on proteins synthesised in the lung
Angiotensin Receptor Blockers (ARBs)	Increased overall cancer risk, particularly lung cancer <sup>70,71</sup>	Further study on potential amelioration of pro-tumorigenic conditions
Antiplatelets	Potential to decrease cancer risk, recurrence, and mortality <sup>74–77</sup>	Explore pathways (e.g., COX-1, P2Y12) for optimum cardio-oncology treatments
Anticoagulants	Demonstrate anti-cancer properties in various cancer types <sup>79–82</sup>	Investigate anti-cancer effects and prevention potential
β-blockers	Strong evidence for use in cancer therapies along with chemotherapy <sup>86,88</sup>	Research in clinical cohorts for optimal use in cancer treatments
Calcium Channel Blockers (CCBs)	Conflicting results; recent studies show increased survival in cancer <sup>91–96</sup>	Expand knowledge into effects on different types of cancer
Digoxin	Cardioprotective effects and anti-cancer properties <sup>97,98</sup>	Further research on drug repurposing in cancer treatment
Percutaneous Coronary Intervention (PCI)	Reduces mortality and hospitalisation costs in cancer patients with acute coronary syndrome <sup>99–101</sup>	Research into effects on cancer formation and growth specifically due to PCIs
Diagnostic Radiation	Increases cancer risk; risk varies with dose and type of imaging <sup>9, 102–107</sup>	Caution in frequent imaging; explore techniques to reduce radiation exposure

Several other tumour biomarkers have shown diagnostic potential in terms of being important predictors of cardiovascular disease outcomes. Bracun et al., 2021 measured six tumour biomarkers (CEA, CA15-3, CYFRA21-1, CA19-9, CA125 and AFP) and investigated their respective predictive value for CVD in the PREVENT study.<sup>67</sup> There were 8592 participants in the original study, but only 8116 participants were included in this analysis as excluded participants had prevalent cancer or missing values within the original study. All six biomarkers demonstrated prognostic value for CVD events but CEA, CA15-3 and CYFRA21-1 exhibited the strongest associations.<sup>67</sup>

### *Cardiovascular disease therapies and cancer*

Cardiovascular therapies are becoming increasingly common to prescribe, owing to the growing numbers of patients being diagnosed with CVD, sometimes more than one type. Furthermore, polypharmacy is a necessity for patients whose CVD is unable to be controlled or if there is more than one condition to be managed. The effect of cardiovascular therapies on cancer have been classified as Type 4 of the reverse cardio-oncology syndromes. Table 2 showcases salient points from these therapeutic interventions and diagnostic avenues.

#### *Angiotensin converting enzyme inhibitors (ACEIs)*

Numerous studies have investigated ACEIs and cancer. Wu et al., 2022 conducted a systematic review and meta-analysis on ACEIs and lung cancer using a total of 11 studies from Asia, Europe and North America.<sup>68</sup> The results showed an odds ratio (OR) of 1.19 (95% CI 1.05-1.36) and therefore associated with an increased lung cancer risk. The cohort studies did not show statistical significance of ACEIs and increased lung cancer but the case-control studies were statistically significant (95% CI 1.04-1.16).<sup>68</sup> As angiotensin converting enzyme is synthesised in the lungs, a potential direction of research would be to explore the effects of ACEI on other proteins synthesised in the lung and if there is any link to cancer. In another study, Ganz et al., 2011, ACEIs were shown to have a statistically significant impact on the recurrence of breast cancer (95% CI 1.02 - 2.39).<sup>69</sup> Additionally, combined ACEI and beta blocker therapy was significant for mortality (95% 1.22 - 3.10). Thus, further research is needed to investigate the mechanisms underlying the effect of the ACEIs on breast cancer recurrence and any cancers linked to breast cancer such as those caused by BRAC1 and BRAC2 mutations.

#### *Angiotensin receptor blockers (ARBs)*

The renin-angiotensin-aldosterone system (RAAS) has been shown to participate in cell proliferation and tumour growth. The Sipahi et al., 2010 meta-analysis showed an increased cancer risk in the ARB group compared to the control group of 7.2% vs 6.0% respectively.<sup>70</sup> Lung cancer was significantly higher in the ARB group, 0.9% compared to 0.7% in the control group. Sipahi et al., 2022 was a meta-regression which showed a significant correlation between ARBs and risk of cancers with a slope of 0.07 (95% CI 0.03 to 0.11).<sup>71</sup> ARBs therefore have a cancer risk and further study has to establish the potential of ARBs to ameliorate pro-tumourigenic conditions.

#### *Antiplatelets*

Platelets have been shown to promote cancer, hence, antiplatelets have been postulated to have the ability to decrease cancer risk as well as promoting tumour growth, making this drug-class a topic of debate in cardio-oncology.<sup>72</sup> Wojtukiewicz et al., 2017 analysed preclinical and cohort studies; preclinical studies with pancreatic and colon cancer cells demonstrated aspirin inhibited the expression of c-MYC, an oncoprotein and a decrease in the cancer cells' ability to proliferate.<sup>73</sup> Data combined from 8 RCTs reduction in deaths caused by cancer (OR 0.79, 95% CI 0.68 to 0.92) due to aspirin along with significance in benefit due to aspirin in a 5 year follow up with gastrointestinal cancers showing the best results (95% CI 0.50 to 0.87). Aspirin has demonstrated a decreased breast cancer recurrence and death when taken for 12+months and lowering the incidence of prostate cancer.<sup>74-77</sup> Therefore, strong evidence is found for the use of antiplatelets to lower cancer risk, recurrence and mortality. A further analysis into pathways such as COX-1 and P2Y12 and their effect on cancer is needed to determine the optimum treatments for cardio-oncology.

#### *Anticoagulants*

Due to the links between cancer and coagulation, anticoagulants are being researched to establish whether they have anti-cancer properties. Ling et al., 2022 studied effects of anticoagulants on oral squamous cell carcinoma.<sup>78</sup> In vitro, the anticoagulants except heparin had anti-proliferative effects on the OKF6 cancer cell line. Warfarin, heparin and direct oral anticoagulants (DOACs) when combined with other DOACs e.g. apixaban and edoxaban also impeded cancer cell migration. In a review article, anti-cancer effects such as reduction in cancer spread and reduced cancer proliferation were shown by dabigatran, apixaban, rivaroxaban which was also discovered to be antiangiogenic, edoxaban and low molecular weight heparin.<sup>79-85</sup> Therefore, research into the use of anticoagulants for the prevention of cancer should also be conducted to add to the current evidence about their anti-cancer effects.

#### *β-blockers*

β-adrenergic pathways promote tumours via mechanisms such as vascular remodelling. Therefore β-blockers can be postulated to decrease cancer progression via interfering with the β-adrenergic pathways. β-blockers have shown to decrease cancer growth in preclinical models.<sup>86,87</sup> In a preclinical model of sarcoma, propranolol slowed tumour growth and survival rate. Tumour weight was lower in the propranolol group than the control. However, the same found similar levels of Ki67 from the control and treatment groups in the tumour, making it less likely that there was any direct blocking of cancer cell proliferation. This study concluded that

propranolol increases T cells and modulates the immune system, hence, propranolol should be used with chemotherapy to treat cancer.<sup>88</sup> Additionally, an association between  $\beta$ -blockers and triple negative breast cancer survival showing a hazard risk of 0.66 (95% CI 0.47 - 0.91) was shown in a meta-analysis and cohort study.<sup>89</sup> Another review investigated the benefits of  $\beta$ -blockers in cancer treatment and found that  $\beta$ -blockers blocked the formation and progression of cancer along with being therapeutic in preventing cachexia and chemotherapy-related cardiotoxicity.<sup>90</sup> Therefore,  $\beta$ -blockers have a strong evidence base to suggest use in cancer therapies along with chemotherapy which is an area to research further in clinical cohorts.

#### *Calcium channel blockers (CCBs)*

Studies conducted on the cancer and CCB relationship have had conflicting results with some suggesting a positive correlation between CCB use and increased cancer risk and others have suggested that there is no association.<sup>91-94</sup> A Taiwan-based retrospective cohort study found that breast cancer risk was significantly lower in CCB use compared to ACEIs/ARBs after >5 years of treatment (95% CI 0.33 - 0.98) in a Taiwanese population.<sup>95</sup> In pancreatic cancer, CCBs have been shown to significantly increase survival (95% CI 0.297-0.827) and the CCB group had a median survival of 15.3 months compared to 10.1 months in the non-treatment group.<sup>96</sup> Hence, CCBs were previously associated with an increase in cancer but recent studies have increasingly shown that CCB therapy is related to an increased survival rate in cancer. Future studies should aim towards expanding the knowledge into the effect of CCBs in different types of cancer as most studies only focus on breast cancer and pancreatic cancer as well as their effects on tumours.

#### *Digoxin*

Chemotherapy drugs such as adriamycin are known to be cardiotoxic which leaves a gap for the need to have a drug which has cardioprotective effects and anti-cancer properties which is the evidence centred around digoxin. Wang et al., 2020 used digoxin on its own and in combination with adriamycin to see the effect on small cell lung cancer in preclinical models.<sup>97</sup> In vitro, digoxin increased cancer cell mortality by inhibiting DNA repair pathways and increasing reactive oxygen species; in combination with adriamycin, antiproliferative effects were observed. Digoxin also inhibited cancer cell growth *in vivo*; anticancer effects increased and cardiotoxicity decreased when digoxin was used with adriamycin as a co-therapy.<sup>97</sup> Similarly, Yokoyama et al., 2019 analysed the specific anti-cancer properties of digoxin to find an inverse relationship with digoxin and cancers; digoxin's anti-cancer property may be via the peroxisome proliferator receptor  $\alpha$  and apoptosis caspase cascade pathways via clinical and bioinformatics databases.<sup>98</sup> Therefore, due to its cardioprotective niche when used with chemotherapy drugs, there is evidence to suggest further research into drug repurposing with digoxin in cancer.

#### *Percutaneous coronary intervention (PCI)*

PCI, colloquially known as stenting, is one of the definitive managements for MI in order to preserve the myocardium and prevent further ischaemia, damage and complications. The importance of preserving cardiac muscle in cancer patients is essential due to risk factors that affect the myocardium such as hypercoagulable states and cardiac muscle atrophy in cancer. However, there is not a lot of research into the effect of PCI on cancer. Monlezum et al., 2021 found that PCI reduced mortality and hospitalisation costs in cancer patients who have acute coronary syndrome as opposed to using medication alone.<sup>99</sup> Likewise, a meta-analysis conducted in 2022 also had similar results with patients with cancer having a significantly higher in-hospital mortality (95% CI 1.33-2.70) and 30 day mortality (95% CI 1.24-3.27) compared to patients without cancer.<sup>100</sup> In patients with stents, 60% of deaths were noncardiovascular and cancer was the most common cause of noncardiovascular death.<sup>101</sup> Hence, cancer, due to its pathophysiological effects on the body, may be the reason for the higher mortality when hospitalised. On the other hand, the current body of evidence suggesting that PCIs have any effects or relationship on cancer is very poor. The main area for further research is whether PCIs have effects on reducing the formation and growth of cancer in both preclinical models and cohort studies. In addition, any adverse effects of PCIs on the formation of cancer is essential to understand in determining future therapies in cardio-oncology.

#### *Diagnostic radiation*

Diagnostic radiation in cardiac imaging via modalities such as chest radiographs and interventional radiotherapy (such as angiography) has been important in visualising the heart and its structures in order to determine treatment course. However, ionising radiation, namely X-rays, can have detrimental effects on the body through overexposure. Radiation can cause mutations, giving rise to cancers in the body. Therefore, an exploration into the radiation exposure via cardiac imaging and cancer are important to establish to determine the risk vs benefit particularly when there is a need to perform cardiac imaging multiple times. A cardiac radiograph has a radiation dose of 0.02-0.1mSv, a chest CT has 6.2mSv and coronary angiography has 25mSv. Einstein., 2012 looked at 3 cohorts who received radiation doses similar to those undergoing cardiac imaging.<sup>9</sup> The excess relative risk of cancer in atomic bomb survivors and nuclear power plant workers was 0.02 and babies undergoing in-utero x-rays was 0.39.<sup>102-106</sup> The Quebec Post-MI study looked into a cohort (n = 82,861) from 1996 - 2006 in Quebec where 77% had undergone at least one cardiac imaging or procedure where they received a low dose of ionising radiation in the first year after an MI. Their results showed an incident cancer risk of 3% for every 10mSv of radiation received over a 5 year follow-up period. The hazard ratio was 1.003 per 1mSv of radiation received (95% CI 1.002-1.004).<sup>107</sup> In coronary CT angiography, the lifetime attributable cancer risk was 0.103-0.137% for males and 0.227-0.370% for females retrospectively and 0.013-0.17 for males and 0.035-0.69% for females prospectively. These results were lower compared to a traditional coronary angiography.<sup>108</sup> Hence, cardiac imaging has shown to increase the risk of cancer with the risk increasing as dose increases. Therefore, cardiac imaging involving radiation should be used with caution in patients who need frequent imaging. Newer techniques of imaging need to find methods of reducing time exposed to radiation, reducing radiation dose or ways to improve scans that do not utilise radiation such as magnetic resonance imaging (MRI) such as reducing the time taken to do a scan.

Overall, the main goal in patient care is to plan further research into specific mechanisms of CVD drugs and their anti-cancer abilities in order to incorporate them into the field of cardio-oncology and allow them to become repurposed for managing cancer. Conversely, mechanisms that increase cancer risk or cancer progression need to also be explored. Practical procedures for CVD such as PCI and cardiac imaging need to be followed in order to establish the relationships between them and cancer.

### Future prospects and recommendations

The burgeoning field of reverse cardio-oncology requires an expansive and integrated approach to fully understand and effectively manage the complex relationship. This multidisciplinary domain is poised for significant advancement through the adoption of several key strategies. The most critical among these have been outlined in Fig. 2.

At the forefront is the necessity for comprehensive cohort studies and clinical trials that encompass a broad spectrum of patients with cardiac conditions involved in cancer research, and conversely, cancer patients in cardiac studies.<sup>109</sup> This inclusivity is vital to generate rich, diverse data, which can offer more insight into the bidirectional influences between these two disease spectrums. Complementing this, the establishment of specific, evidence-based guidelines for diagnosing and managing reverse cardio-oncology cases is crucial. These guidelines will serve as a framework to standardise and enhance patient care, ensuring consistency across various healthcare settings.

In addition, interdisciplinary collaboration will likely form the cornerstone of progress in this field. A synergistic partnership between cardiologists, oncologists, geneticists, and molecular biologists is imperative for a comprehensive understanding and an integrated treatment approach.<sup>110</sup> This collaboration extends beyond medical specialties to include patient education and involvement, ensuring that patients are well-informed about their risks and actively participate in their treatment plans. In lieu of this, advancements in genetic and phenotypic profiling are important. As it has with cardio-oncology, personalised medicine (through precise genotyping and phenotyping) promises to revolutionise treatment strategies, catering to individual patient profiles and targeting specific disease pathways.<sup>111</sup> Equally important is the integration of advanced technologies like artificial intelligence and machine learning. These technologies have the potential to analyse vast datasets, unveiling novel insights into disease mechanisms and potential therapeutic pathways.

Concurrently, there is an urgent need for increased funding and policy support dedicated to reverse cardio-oncology research.<sup>112</sup> Such support is critical for advancing our understanding and developing new treatment modalities. For this purpose, building global research networks for multicentric studies would offer a more comprehensive understanding of reverse cardio-oncology across different populations and healthcare systems.<sup>113</sup> Long-term surveillance and follow-up studies are also essential to comprehend the long-term impacts of treatments and disease progression in reverse cardio-oncology. These studies will help in understanding the chronic aspects of the disease and the long-term efficacy of treatments. Furthermore, preventive strategies for at-risk patients, emphasising lifestyle modifications, early detection, and preemptive therapies, should be prioritised to mitigate the onset of these interrelated conditions.<sup>114</sup>

### Conclusion

Looking ahead, reverse cardio-oncology is poised for groundbreaking advancements through multidisciplinary research and personalised medicine approaches. Novel concepts, such as the utilisation of biomarkers for early detection and the exploration of targeted therapies based on genetic and molecular profiling, are promising avenues. This review has added to the available literature by pinpointing the complex interplay between cardiovascular disease and cancer, highlighting shared risk factors and pathophysiological

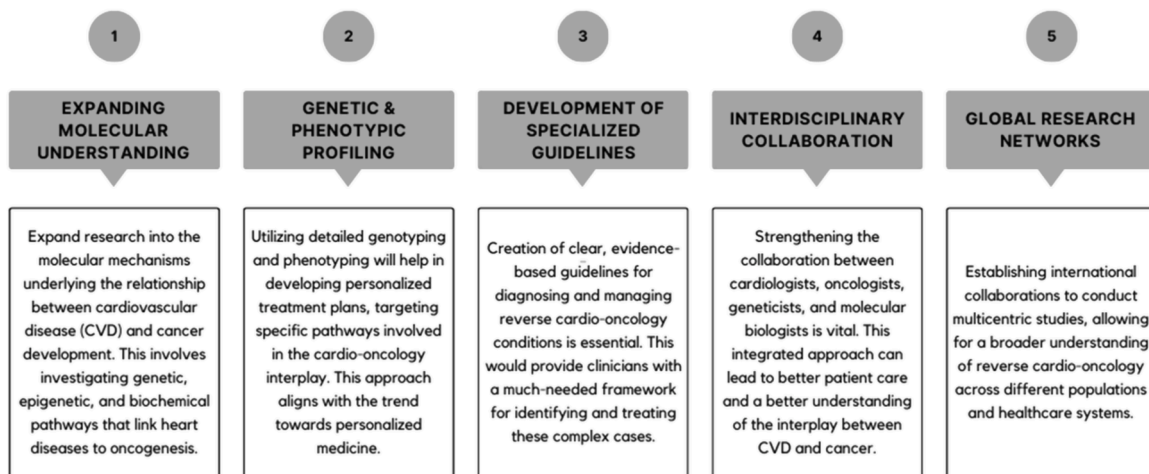


Fig. 2. Approaches to enhance the progress of reverse cardio-oncology.

mechanisms such as chronic inflammation and genetic predispositions. Future research should emphasise the development of integrated treatment protocols that address the co-occurrence and mutual influence of CVD and cancer, ultimately leading to enhanced patient care in this evolving field.

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## CRediT authorship contribution statement

**Shahzeb Imran:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Medha Sridhar Rao:** Writing – original draft, Writing – review & editing. **Muhammad Hamza Shah:** Conceptualization, Writing – original draft, Writing – review & editing. **Aditya Gaur:** Writing – original draft, Writing – review & editing. **Abderrahmane El Guernaoui:** Writing – original draft, Writing – review & editing. **Subham Roy:** Writing – original draft, Writing – review & editing. **Sakshi Roy:** Writing – original draft, Writing – review & editing. **Hareesha Rishab Bharadwaj:** Writing – original draft, Writing – review & editing. **Wireko Andrew Awuah:** Writing – original draft, Writing – review & editing, Supervision.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Muhammad Hamza Shah affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study planned have been explained.

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