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Linking Heart Failure to Cancer

Background Evidence and Research Perspectives

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ABSTRACT: Recent epidemiological analyses suggest that incident cancer may be more common among patients with preexisting heart failure (HF) than in patients without HF. Arguments against this notion have been the increased chance of co-occurrence of 2 high-prevalence conditions and increased tumor detection in patients with HF because of intensified medical observation. However, biological data lend support to the hypothesis that HF is an oncogenic condition. Neurohormonal activation has been related to cancer initiation, progression, and dissemination by studies not specifically focusing on HF, which are now reappraised in the light of the emerging evidence that tumors are diagnosed more often in HF than control cohorts. Furthermore, a thought-provoking scenario to be considered is that a systemically perturbed milieu, where low-grade inflammation plays a primary role, leads to both HF and malignancy, thus connecting 1 disease to another. Postischemic HF has been shown to promote tumor growth in an animal model. Exploring these and other pathways potentially linking HF to malignancy is a new and exciting field of research, with the ultimate goal of answering the question of whether HF does promote cancer.

Cardiovascular disease (CVD) and cancer intersect at multiple levels,[1] which has raised the question of whether this is a simple association or causation, and, if causation, in which direction.

In the past years, much emphasis has been given to the observation that oncological patients, especially long-term survivors, are prone to experience CVD. This susceptibility may be related to the cardiovascular toxicity of antineoplastic agents and chest radiation,[2] but also to clustering of cardiovascular risk factors in cancer survivors[3] and possibly a shared biology that primes both malignancy and CVD development. It is important to note that CVD in patients with tumors is associated with higher all-cause mortality than CVD alone, which may result in part from the fact that each disease hinders the optimal management of the other one, or that there is a gap of care when CVD occurs after cancer onset. Indeed, oncological patients presenting with acute myocardial infarction (AMI) were reported to be less likely to receive evidence-based treatment, and therefore face more in-hospital complications and deaths, than those without a history of malignancy.[4]

Recently, attention has moved to the opposite scenario, ie, cancer in individuals with preexisting CVD. Three groups independently reported a heightened risk of incident malignancy in heart failure (HF).[5–8] In a retrospective analysis comparing 596 patients who had HF with matched controls, HF with both reduced and

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preserved left ventricular ejection fraction (HF with reduced ejection fraction and HF with preserved ejection fraction, respectively) was associated with a 70% higher likelihood of cancer diagnosis.[5] The higher risk was independent of left ventricular ejection fraction and remained significant after excluding tumors discovered in the first 5 years of follow-up and after adjustment for predisposing factors.[5] Subsequently, a large prospective study reported a significantly higher cancer incidence in 9307 outpatients with HF, the vast majority (89.3%) having left ventricular ejection fraction <45%, in comparison with the general Danish population (5 million individuals).[6] The incidence rate of cancer in the HF cohort and in the background population was 189 and 63 per 10 000 patient-years, respectively, with an incidence rate ratio of 1.24 after multivariable regression adjustment. The risk of malignancy was increased for patients with HF even after excluding all tumors that occurred over the first year after HF diagnosis. The most frequent cancer sites in patients with HF were the lung and skin, but most common tumor types, including hematologic malignancies, were detected more often in the HF group, with the exception of prostate cancer.[6] Another group compared individuals with AMI complicated or not by HF in the following 30 days. Patients who developed HF after AMI had a 71% higher risk of incident malignancy in comparison with those without HF, this trend being more prominent in patients with HF with reduced ejection fraction.[7] A retrospective single-center study found a higher incidence of stomach, lung, prostate, breast, and colon cancer in 5238 patients with HF with reduced ejection fraction or HF with preserved ejection fraction than in matched controls.[8] In this cohort, tumor diagnosis was positively correlated with brain natriuretic peptide levels, but was independent of left ventricular ejection fraction.[8] In contrast, a single recent study of 28 341 participants free of HF and cancer at enrollment in the PHS studies (Physicians' Health Studies I and II) showed that HF was not associated with cancer incidence. This study had 2 major limitations: it was restricted to male participants, so observations may not be generalizable to women; and the determination of HF was based on self-reporting.[9]

Overall, these epidemiological data suggest that cancer is an important comorbidity complicating HF.[10]

WHAT LIES BEHIND THE ASSOCIATION OF HF WITH CANCER?

Shared risk factors, such as obesity, diabetes mellitus, and dyslipidemia, may be involved in the pathogenesis of both HF and malignancy. For instance, elevated cholesterol levels have long been known to promote atherosclerosis and coronary heart disease, but cholesterol and one of its primary metabolites, 27-hydroxycholesterol, have also been implicated in breast cancer progression.[11] In the studies exploring the incidence of malignancy in HF, however, patients with HF had a higher probability of receiving a tumor diagnosis than their counterparts after adjusting for cardiovascular risk factors. It is notable that HF was associated with cancer also when the tumor cases in the first years after HF diagnosis were not taken into account, making the possibility of surveillance bias unlikely, ie, early detection of otherwise asymptomatic malignancies because of intensified medical observation.

These considerations have led to 2 main hypotheses that are not mutually exclusive.

A complex and fascinating possibility is that systemic pathological processes, such as inflammation and oxidative stress, possibly superimposed on a background of genetic predisposition, may promote both HF and cancer and connect one to another (cancer and HF stemming from the same perturbed milieu, Figure 1). This scenario has been captured most convincingly by clinical investigations with translational insights.

Another intriguing hypothesis is that HF is an oncogenic condition (cancer as a consequence of HF, Figure 1). This paradigm is supported by 2 lines of evidence. First, experimental research links neurohormonal activation to tumorigenesis, and the use of neurohormonal inhibitors, especially blockers of the renin-angiotensin-aldosterone system (RAAS), was repeatedly associated with improved oncological outcomes. Second, a seminal basic science study showed that the postischemic failing heart stimulates colon tumor growth in a mouse model, purportedly via secreted factors among which SerpinA3 has been proposed as a mediator.[12]

COMMON MILIEU SUSTAINING HF AND CANCER

Inflammation and oxidative stress are powerful drivers of CVD and, specifically, HF. By initiating and maintaining atherosclerosis, they contribute to ischemic heart disease, which in turn is the main etiology of HF. Furthermore, they directly induce alterations in the myocardium that create a substrate for HF development. Microvascular endothelial inflammation may be pivotal to diastolic dysfunction leading to HF with preserved ejection fraction, by decreasing nitric oxide bioavailability and, thereby, reducing protein kinase G activity in cardiomyocytes.[13] Moreover, proinflammatory cytokines may impair contractility and drive remodeling of the left ventricle.[14] In fact, circulating levels of proinflammatory cytokines are elevated and correlated with negative outcomes in HF,[15] and portend an increased risk of incident HF in the general population.[16] Similarly, earlier studies indicate that oxidative stress, triggered by inflammation, cardiovascular risk factors, or aging, participates in HF pathogenesis.[17]

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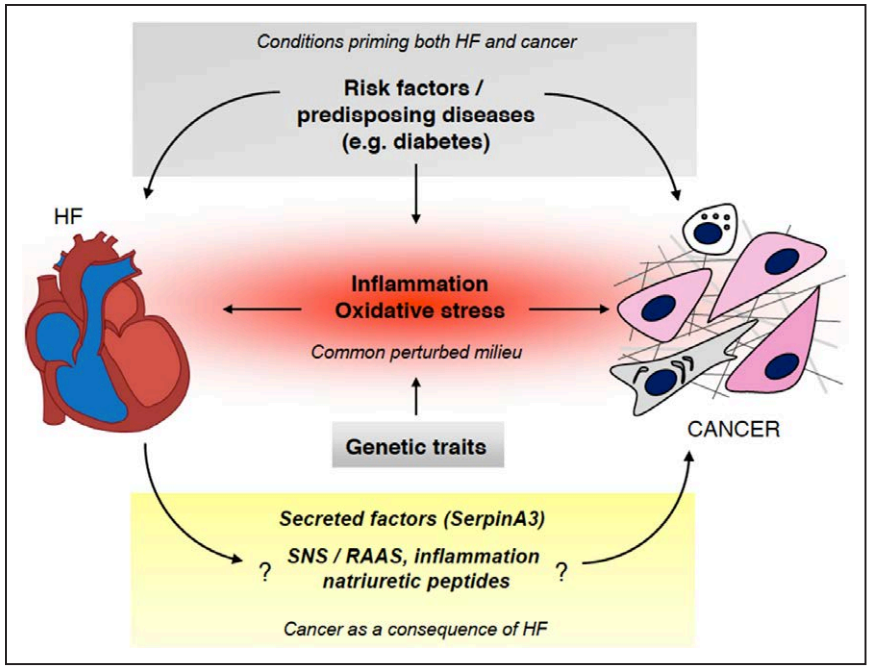

Figure 1. Possible pathways linking heart failure to cancer.
Shared risk factors and predisposing conditions may promote the development of both heart failure (HF) and cancer and, thereby, mediate their association, as depicted (**Upper**). On the other hand, they may fuel a pathological milieu fostering both HF and cancer, in which inflammation, oxidative stress, and likely other elements yet to be elucidated play a role (**Middle**). Genetic background may also contribute to such a milieu. HF may directly favor cancer initiation and progression, as presented (**Lower**). While there is experimental evidence that factors released from the failing myocardium, such as, in particular, SerpinA3, stimulate tumor growth, the oncogenic effects of HF-related neurohormonal activation, natriuretic peptides, and inflammation are plausible, but have not yet been demonstrated. RAAS indicates renin-angiotensin-aldosterone system; and SNS, sympathetic nervous system.

On the other hand, chronic inflammation with ensuing cellular oxidative stress may boost cancer initiation and progression, not only when it is organ specific, but also when it is diffuse.[18]

Against this background, inflammation and oxidative stress may constitute the chief elements of a pathological milieu that is genetically predisposed, fueled by common risk factors, and fosters both HF and cancer (Figure 1).

Recent ground-breaking clinical studies buttress this vision. Whole-exome sequencing has allowed identification of mutations in 4 genes that result in the expansion of hematopoietic clones of indeterminate immediate clinical significance, but carrying a 10-times higher risk of developing hematologic malignancies.[19] It is striking that these mutations are also strongly correlated with coronary artery disease and early-onset AMI, and atherosclerosis-prone *Ldlr* knockout mice whose myeloid cells lack one of these genes, *Tet2*, display inflammation in several organs and accelerated atherogenesis, ascribed to enhanced transcription of inflammatory chemokines by macrophages.[19] Based on the concept that inflammation causes CVD, the interleukin-1β–targeting antibody, canakinumab, was proposed to reduce recurrent cardiovascular events in patients with previous AMI and modestly elevated C-reactive protein levels. Results from the CANTOS trial (Canakinumab Anti-Inflammatory Thrombosis Outcome Study) have demonstrated that this approach is effective, and also demonstrated an unexpected decrease in lung cancer incidence on treatment with canakinumab, reinforcing the concept that inflammation may underlie both CVD and cancer.[20,21]

Further research is needed to solve the tangle of genetic traits, inflammation, oxidative stress, risk factors, HF, and cancer, and to understand whether, once HF is established, HF-elicited inflammation fosters cancer, as well (within the paradigm that HF promotes cancer; see Figure 1). For example, decreased naive T-cell numbers and increased effector and memory T cells were recently observed in patients with HF and causally related to elevated interleukin-6 levels.[22] These features are consistent with immunosenescence, which consists of the deterioration of both adaptive and innate immunity, and, given the role of the immune system in malignant cell elimination, might account for the increased cancer incidence in HF.

HF-RELATED NEUROHORMONAL ACTIVATION AND CANCER

Chronic and progressive hyperactivation of the sympathetic nervous system (SNS) and RAAS is a hallmark and major component of HF with reduced ejection fraction pathophysiology. These neurohormonal axes, and the natriuretic peptide system, as well, have also been shown to affect tumor biology. Hence, it has been conjectured that they may account for the increased risk of cancer in HF.[8]

Role of SNS Activation in Oncogenesis

The effects of the SNS on cancer have been explored extensively, mainly by means of cell systems exposed to β-adrenergic receptor (AR) agonists or antagonists and orthotopic tumor mouse models, in which a surge in SNS activity was elicited by chronic stress most often attributable to daily physical restraint,[23] but also to housing the animals at nonthermoneutral temperatures.[24] The results obtained with these stimuli were reproduced with β-AR agonists and inhibited by β-AR blockade, indicating that imposition of chronic stress is a valuable strategy to investigate the involvement of SNS-induced

β-AR signaling in tumor biology. It is important to note that β-AR activation in this context was mainly mediated by intratumoral norepinephrine, whereas a correlation with circulating catecholamines was not found.[25] Accordingly, in patients with ovarian cancer, high tumor norepinephrine concentration portends a dismal prognosis by promoting tumor metastasis.[26]

Several mechanisms have been proposed for the effect of SNS on cancer. Excess SNS activity may contribute to tumorigenesis via β-AR–dependent activation of stimulatory G protein-protein kinase A and β-arrestin-1 signaling, which promotes the accumulation of DNA damage and hampers its repair.[27] Although β-AR signaling has also been shown to induce cancer cell proliferation by activating downstream effectors such as CREB, NF-kB, and AP-1,[28] an indisputable β-AR–dependent increase in malignant cell proliferation has not been documented.[23] Nevertheless, a number of studies with mouse models reported increased tumor growth following chronic stress/SNS activation,[23,29,30] which may be explained by the inhibition of apoptosis of cancer cells, and by modulation of factors external, but crucial to neoplastic expansion, as well, ie, neoangiogenesis and lymphangiogenesis, the tumor microenviroment, and antitumor immunity (Figure 2). By acting on these components of cancer foci and by directly potentiating the migratory capacity of malignant cells, SNS activation may also stimulate metastatic spreading of cancer.

β-AR signaling confers resistance to apoptosis via several mechanisms, including β-arrestin-1–dependent degradation of the tumor suppressor gene p53,[27] phosphorylation of the proapoptotic protein BAD (BCL2-associated death promoter),[31] and inhibition of anoikis,[32] a form of apoptosis occurring when cells are detached from the extracellular matrix (Figure 2).

In a mouse model of ovarian cancer, Thaker et al[23] reported that stress-induced catecholamines promoted tumor growth, invasiveness, and vascularization by enhancing the expression of vascular endothelial growth factor (VEGF), a central mediator of neoangiogenesis. Furthermore, in pancreatic cancer, Src activation induces phosphorylation and subsequent nuclear translocation of signal transducer and activator of transcription-3, with ensuing synthesis of matrix metalloprotease (MMP)-2 and MMP-9 that degrade the extracellular matrix and facilitate neoangiogenesis.[30] Remodeling of the extracellular matrix by MMP is also pivotal to passage of malignant cells into blood and lymph vessels, which represent the first steps toward metastatic dissemination. In fact, β-AR signaling was shown to favor metastatization of ovarian cancer via upregulation of MMP-2 and MMP-9 in vivo.[33]

The SNS also shapes the microenvironment in which cancer is hosted and by which it is profoundly influenced.[25] In particular, the SNS has been demonstrated to act on tumor-associated macrophages in a way that fosters neoplastic dissemination. In a mouse model of ovarian cancer, β-AR signaling enhanced tumor-associated macrophage recruitment by increasing the production of monocyte chemoattractant protein-1, and this was associated with heightened cancer growth.[34] β-AR agonism was also observed to induce tumor-associated macrophages to release prostaglandin E_2, which in turn stimulates VEGF-C expression by neoplastic cells: local VEGF-C then causes an increase in intra- and peritumoral lymph vessel density, through which

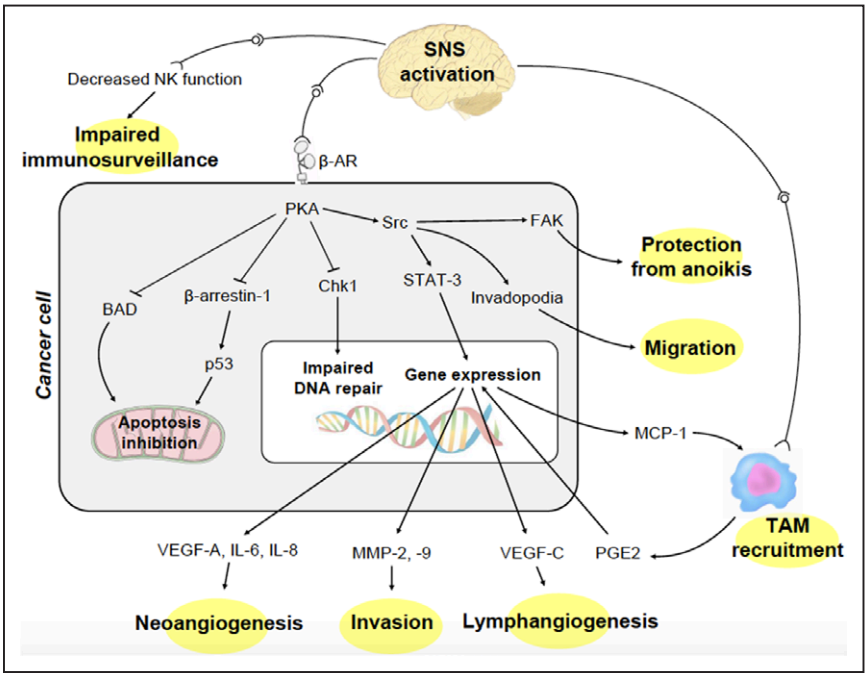

Figure 2. Effects of the sympathetic nervous system on cancer.
The sympathetic nervous system (SNS) may promote tumor development and progression by a variety of mechanisms, which are highlighted by yellow circles. Key underlying pathways are also presented. BAD indicates BCL2-associated death promoter; β-AR, β-adrenergic receptor; Chk-1, checkpoint kinase 1; FAK, focal adhesion kinase; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; MMP, matrix metalloprotease; NK, natural killer; PGE2, prostaglandin E2; PKA, protein kinase A; STAT-3, signal transducer and activator of transcription-2; TAM, tumor-associated macrophage; and VEGF, vascular endothelial growth factor.

malignant cells may spread to other organs. Moreover, aberrant nerve terminals may provide the substrate to the SNS to support tumor growth. In a mouse model of prostate cancer, newly formed autonomic nerve projections promoted malignant cell survival and dissemination, which were dramatically reduced by both sympathectomy and combined β_2- and β_3-AR silencing.[29]

Both innate and adaptive immune responses, in particular involving natural killer lymphocytes, can recognize and eliminate transformed cells before they can give rise to a macroscopically detectable tumor mass, and SNS hyperactivity can allow cancer to elude this immunosurveillance. Indeed, β-AR agonism transiently increases the number of circulating natural killer cells, but suppresses their activity, consequently favoring development and dissemination of natural killer-sensitive tumors.[35]

Catecholamines can accumulate in various tissues besides the myocardium in HF[36]; thus, it can be hypothesized that the SNS exerts tumorigenic actions in HF as it does in chronic stress conditions. Nonetheless, this has not yet been confirmed, and it cannot be excluded that the pattern of SNS activation in HF and thus the modulation of neoplastic behavior are somehow different from the ones in response to stress. Moreover, the literature about SNS and cancer almost exclusively concerns solid tumors, leaving uncertain whether hematologic malignancies are similarly affected by SNS signals.[36] Although β-ARs regulate the hematopoietic niche,[37] the only study in this regard argues against an effect of β-AR stimulation on leukemia cells.[38]

Role of RAAS Activation in Oncogenesis

A schematic of the RAAS and its relevant effects on cancer development and progression is presented in Figure 3. It is now established that the organ-specific local RAAS, with paracrine and autocrine functions, is as important as, or even more important than, the systemic endocrine RAAS. This concept is the cornerstone of the studies addressing the role of the RAAS in oncogenesis. A wealth of in vitro and in vivo investigations indicate that type 1 angiotensin receptor (AT1R) favors the growth, vascularization, and invasiveness of malignancies (Figure 3).[39] AT1R expression was documented in many types of cancer cells[39] and was related to a shift toward an aggressive phenotype.[40] Furthermore, in human ovarian carcinoma samples, AT1R levels were positively correlated with VEGF expression and tumor vessel density.[41] In agreement with these data, gene silencing and pharmacological antagonism of AT1R decreased tumor vascularization in animal models by reducing tumor-associated macrophage infiltration and VEGF levels in the subcutaneous tissue surrounding the tumor.[42] It is interesting to note that germline and somatic mutations in the genes encoding the RAAS components may influence the risk of cancer development in humans. For instance, the high-activity DD genotype of the insertion (I)/deletion (D) angiotensin-converting enzyme polymorphism was described to predispose to malignancy.[43]

The only study that has explored the activity of aldosterone on cancer so far found that both pharmacological blockade of the mineralocorticoid receptor and inhibition of aldosterone synthesis with a high-salt diet prevented pulmonary metastatic dissemination in mice with orthotopic renal cortical adenocarcinoma, whereas aldosterone administration favored tumor metastatization.[44]

Pharmacological Inhibition of the SNS and the RAAS and Cancer Outcomes

Results from a number of observational studies have shown that RAAS inhibitors are associated with more favorable cancer outcomes, such as recurrence and overall survival, whereas a smaller number of papers, especially investigating breast cancer, reported nonsignificant or unfavorable associations (Table I in the online-only Data Supplement).

Several investigators also assessed whether RAAS blockade affects cancer incidence, but the results have been inconsistent. Although a lower risk of cancer associated with angiotensin-converting enzyme inhibitors was initially reported,[45] a subsequent large controlled trial did not observe significant differences in tumor

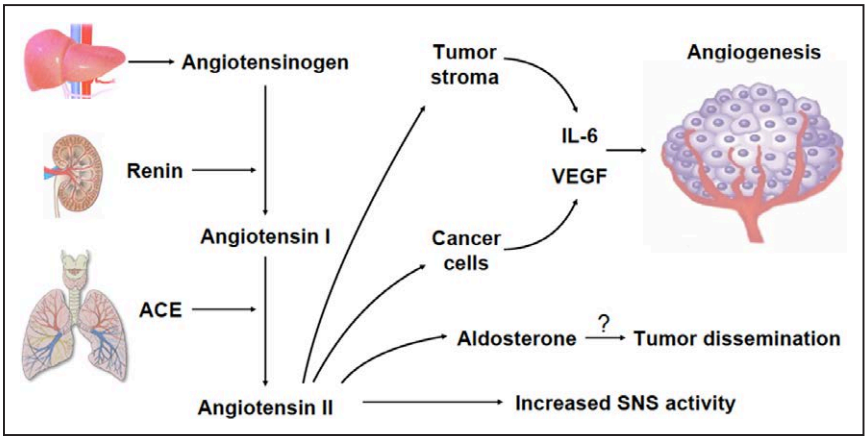

Figure 3. Effects of the renin-angiotensin-aldosterone system on cancer.
Angiotensin II may favor malignancy progression by promoting angiogenesis via induction of interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF) production by both cancer and tumor stroma cells. A single study reported that aldosterone may foster metastatic spread of renal cell carcinoma. ACE indicates angiotensin-converting enzyme; and SNS, sympathetic nervous system. The lung illustration is attributed to Patrick J. Lynch, medical illustrator; C. Carl Jaffe, MD, cardiologist, available under Creative Commons Attribution 2.5 License 2006.

risk between patients taking angiotensin-converting enzyme inhibitors or other antihypertensive medications.[46] Similarly, studies evaluating the effects of and associations between AT1R blockers and the risk of incident cancer have led to conflicting results.[47,48]

The impact of β-AR blockers on cancer outcomes is unclear. Although it was initially reported that these drugs improved the mortality of a number of malignancies, many subsequent studies attained neutral or negative results (Table II in the online-only Data Supplement).

Role of Natriuretic Peptides in Oncogenesis

In HF, the pressure- and volume-overloaded myocardium releases natriuretic peptides, especially atrial natriuretic peptide and brain natriuretic peptide. These peptides have recently been implicated in malignancy progression, but their role in cancer is actually still unresolved. Several tumor cell types express the natriuretic peptide receptor A, which binds both atrial natriuretic peptide and brain natriuretic peptide.[49] On the one hand, genetic deletion of natriuretic peptide receptor A attenuated tumor growth and neoangiogenesis in animal models of melanoma and lung and ovarian cancer.[49] On the other hand, atrial natriuretic peptide was observed to hinder extravasation of malignant cells, a key step in metastasis formation, by downregulating the adhesion molecule E-selectin. Consistent with this observation, treatment with atrial natriuretic peptide increased relapse-free survival of patients undergoing curative surgery for lung cancer.[50]

CONCLUSIONS AND PERSPECTIVES

Individuals with preexisting HF are more likely to be diagnosed with cancer, and ascribing this finding to mere coincidence appears reductive.

Is malignancy fostered by HF-induced pathways? A recent study indicates so.[12] Moreover, neurohormonal activation might stimulate tumor growth in HF, because it has already been shown in chronic stress. Another thought-provoking possibility to be considered is that a systemically perturbed milieu, where low-grade inflammation has a primary role, promotes both HF and cancer, thus lying underneath their association. It is remarkable that these hypotheses are not mutually exclusive.

Future investigations are needed to better gauge whether and how HF is linked to malignancy. While awaiting them, we are now aware that cancer should not be neglected as a comorbidity in HF and that, in this context, cardiology and oncology meet again.

ARTICLE INFORMATION

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Disclosures

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