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Cardiovascular disease and cancer: Evidence for shared disease pathways and pharmacologic prevention

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Abstract

Cardiovascular disease (CVD) and cancer are leading causes of mortality and morbidity worldwide. Strategies to improve their treatment and prevention are global priorities and major focus of World Health Organization's joint prevention programs. Emerging evidence suggests that modifiable risk factors including diet, sedentary lifestyle, obesity and tobacco use are central to the pathogenesis of both diseases and are reflected in common genetic, cellular, and signaling mechanisms. Understanding this important biological overlap is critical and may help identify novel therapeutic and preventative strategies for both disorders. In this review, we will discuss the shared genetic and molecular factors central to CVD and cancer and how the strategies commonly used for the prevention of atherosclerotic vascular disease can be applied to cancer prevention.

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Author contributions

FMK was responsible for writing the draft of the manuscript, creating the figure and tables and performing major revision of the manuscript. NS developed the idea, wrote some parts, edited the whole manuscript and supervised the whole project. CG edited the whole manuscript and wrote some parts. AI contributed in idea development and edited the manuscript. AK was responsible for editing the whole manuscript and writing some parts. MD wrote the cardio-oncology section. CF critically edited the whole manuscript and shortened the manuscript. AM was responsible for scientific support of the genetic and molecular pathways and did the major revisions.

1. Introduction

In 2012, two-thirds of global non-communicable disease deaths were attributable to cardiovascular disease (CVD) and cancer [1], both associated with significant morbidity and poor health-related quality of life [2,3]. The incidence of CVD and cancer is increasing in all socioeconomic classes worldwide [1,4]. According to the 2002 *World Health Report* [5] and 2011 *United Nations High-Level Meeting on Non-communicable Diseases* [6], the global reduction of four common modifiable risk factors including unhealthy diet, sedentary lifestyle, excess alcohol consumption and tobacco use can help prevent four prevalent diseases including CVD, cancer, type 2 diabetes (T2DM) and chronic obstructive pulmonary disease.

The importance of common modifiable risk factors for both CVD and cancer is reflected in our emerging understanding of the shared genetics and molecular mechanisms that are central to the pathogenesis of both diseases [7]. Mounting evidence supports the use of medications like aspirin, statins and inhibitors of the reninangiotensin-aldosterone system (RAAS) in the prevention of a variety of malignancies [8–11]. Understanding the significant biological overlap between CVD and cancer is crucial and may foster the development of novel therapeutic and preventive strategies for both diseases. In this review, we will discuss the shared genetics and cellular molecular pathways central to CVD and cancer to provide additional credence for the WHO's recommendation that health promotion and prevention programs should be directed jointly at CVD and cancer [1,5,6].

2. Shared molecular and genetic pathways in CVD and cancer

2.1. Systemic inflammation & oxidative stress

Atherosclerosis is a chronic inflammatory disease of the arterial wall and is the principal pathology leading to myocardial infarction, stroke, and peripheral vascular disease [12]. The continuous accumulation of lipid and inflammatory cells in the arterial intima is central to atherogenesis. Monocyte/macrophages and other inflammatory cells elaborate diverse pro-inflammatory cytokines such as interleukin-1 (IL-1), tumor necrosis factor- α (TNF- α), and interferon- γ (IFN- γ) which foster further cell recruitment and inflammation. The highly dynamic, lipid rich and chronically inflamed microenvironment of the plaque also contains an abundance of reactive oxygen species (ROS) and oxidized low-densitylipoprotein cholesterol (LDL), driving further inflammatory signaling and gene expression cascades including nuclear factor-kB (NF-kB) [13], hypoxia inducible factor-1 α (HIF-1 α) [14], and signal transducer and activator of transcription (STAT) [15] which drive cell recruitment, foam cell formation and angiogenesis.

Since Virchow's 19th-century hypothesis of an inflammationecancer relationship [16], accumulating evidence has supported a complex interplay between inflammation and carcinogenesis [17]. Epidemiological data suggest that over 25% of all cancers are triggered by chronic inflammation [18]. In most solid tumors, malignant cells interact in a complex, chronically inflamed extracellular microenvironment, enriched with macrophages, inflammatory cytokines, growth factors, and reactive oxygen species. This complex interaction activates a wide array of intracellular signaling pathways including Janus-

activated kinase (JAK), protein kinase B (Akt), and mitogen-activated protein kinase (MAPK). These cascades of events can in turn lead to transcriptional activation of pro-inflammatory, pro-survival and proteolytic programs via STATs, NF- κ B, and HIF-1 α [17,19–21]. Moreover, ROS and resultant reactive nitrogen species (RNS) can induce DNA damage and modulate the expression of oncogenes and tumor suppressor genes [17,20].

In summary, common intracellular signaling cascades lead to chronic inflammation, oxidative stress and the activation of cellular processes that underlie both diseases.

2.2. Adenosine 5' monophosphate-activated protein kinase (AMPK)

AMPK is a key regulator of cellular metabolism in most cells. Emerging evidence supports a pleiotropic and overall protective effect for AMPK in CVD. AMPK activation reduces ROS formation [22] and inflammation [23] by inhibiting immune cell adhesion [24], foam cell formation [25] and vascular smooth muscle cell (VSMC) proliferation [26], all central events in the development of atherosclerosis. Furthermore, pharmacological activation of AMPK reduces atherosclerotic plaque size in apolipoprotein E-deficient mice [25]. AMPK also plays a critical role in maintaining glucose homeostasis and improves insulin sensitivity [27]. Interestingly, medications such as metformin, thiazolidinediones (TZDs) and statins, may in part exert their vascular protective effects through activation of AMPK [24].

AMPK activation has also been demonstrated to prevent malignant growth in a variety of tumors, including glial [28], breast [29], lung [30], liver [31], stomach [32], and prostate [33]. AMPK activation inhibits tumorigenesis by regulating signaling pathways such as PI3K, mTOR, and p53, which are involved in cellular proliferation, cell cycle progression and cellular survival [26,34]. Metformin, activates the AMPK indirectly through inhibiting complex I of the mitochondrial respiratory chain, leading to an increased AMP:ATP ratio [35]. Multiple retrospective studies and metaanalyses in patients with type II diabetes showed that use of metformin was associated with overall 30% lower risk of cancer compared with other antidiabetic medications and this protective effect was more prominent in hepatocellular and colorectal cancers [36–38]. This retrospective evidence is further supported by animal studies reporting a delayed onset of malignant tumor growth in tumor-prone mice due to heterozygous mutations in PTEN, which inhibits PI3K/mTOR pathway. Interestingly, phenformin, another type of biguanide class of antidiabetic drugs, had an even more pronounced effect due to its greater membrane permeability [35]. Treatment of the mice with oral phenformin from 3 weeks after tumor initiation prolonged survival of the mice and delayed tumor progression as well as increasing expression of markers of necrosis and apoptosis in the tumors [39].

2.3. Peroxisome proliferator-activated receptor- γ (PPAR- γ)

PPAR- γ is a widely expressed ligand activated transcription factor, which regulates the expression of multiple genes involved in lipid and glucose homeostasis. It is also a major receptor for the TZD class of insulin-sensitizing drugs [23]. In addition to its effect on glucose metabolism and insulin resistance, PPAR- γ activation can reduce atherosclerosis [40,41] by improving endothelial function and inhibiting the production of pro-inflammatory cytokines, foam cell formation, and VSMC proliferation [23,42,43]. PPAR- γ activation also

lowers blood pressure by interfering with angiotensin-II mediated pathways [43,44]. PPAR- γ is also expressed in a number of solid tumors including colon, breast, bladder, lung, and gastric cancers [23] and acts as a tumor suppressor by reducing proliferation and angiogenesis and promoting differentiation. Moreover, TZD class of PPAR- γ agonists have been shown to inhibit the Wnt/ β -catenin signaling pathway [45], which functions in the self-renewal capability of cancer stem cells including prostate [46], bladder [47], colon [45], and breast [48] cancer, and also lymphoma [49]. TZD analogs have also recently been identified as potent inhibitors of IGF-1 receptors [50], which are aberrantly activated in several cancers [51]. The inhibition of pro-survival IGF-1 receptor signaling by TZDs may partially explain the observed anti-cancer effects of TZDs. The understanding of anti-cancer effects of TZDs still remains elusive and a careful re-examination of its chemistry and pharmacological effect is needed. In addition to anti-cancer effects [45–47,49,52,53], pioglitazone class of TZDs have the potential to attenuate atherosclerosis and reduce the risk of cardiovascular events [42,43]. A recent multi-center clinical trial in non-diabetic insulin resistant patients with a previous history of transient ischemic attack or stroke demonstrated that risk of stroke and myocardial infarction was lower among patients who received pioglitazone than those who received placebo. A meta-analysis of six randomized clinical trials (4 on pioglitazone and 2 on rosiglitazone) in diabetic and non-diabetic patients after coronary stent implantation demonstrated that those who received TZDs in addition to standard therapy were less likely to undergo revascularization due to stent restenosis at 6-month follow-up [54]. It is noteworthy that despite proven beneficial effect of pioglitazone in reducing myocardial infarction, stroke, and cardiovascular mortality in patients with type II diabetes [55–58], there is conflicting data regarding possible increased risk of myocardial infarction, with no change in cardiovascular mortality, with use of rosiglitazone [59]. Hence, only pioglitazone might be considered as a potential drug for joint pharmacologic prevention of CVD and cancer.

2.4. Fatty acid synthase

Fatty acid synthase (FAS), one of the key enzymes involved in de novo fatty acid synthesis, is abundant in atherosclerotic plaques and plays an important role in atherogenesis [23,60]. In experimental models of atherosclerosis, foam cell formation is reduced in FAS deficient macrophages due to increased cholesterol efflux and reduced uptake of oxidized LDL [60]. Palmitate, an end product of FAS activity, plays an important role by triggering proinflammatory effects in macrophages and VSMCs [61]. FAS is overexpressed in a variety of solid tumors including breast, ovary, endometrium, prostate, colon, esophagus, stomach, pancreas, thyroid and melanoma [23,62]. Overexpression of FAS in malignant tumors is proposed to provide an abundant alternate energy supply in the relatively hypoxic tumor microenvironment [23]. FAS can also affect signaling through the Wnt/ β -catenin pathway via palmitoylation of Wnt proteins and plays an important role in cancer stem cell renewal [63]. Moreover, FAS levels are inversely correlated with phosphatase and tensin homologue (PTEN), an important tumor suppressor [64] and its inhibition induces programmed cell death in human breast [65], prostate [64], and pancreas [66] cancer cells. Taken together, FAS is yet another example of the important biological overlap between CVD and cancer.

2.5. Plasminogen activator inhibitor-1

Plasminogen Activator Inhibitor-1 (PAI-1) is a multifunctional protein with the ability to regulate fibrinolysis and many other cellular processes [67]. Increased levels of circulating PAI-1 are associated with an elevated risk of atherogenesis and cardiovascular events, T2DM, and several cancers [67–69]. PAI-1 mRNA is increased in atherosclerotic plaques and may stabilize the fibrin matrix, providing a scaffold for migrating cells, stimulate VSMC proliferation and LDL uptake into the lesion [67]. The role of PAI-1 in malignant tumors has been primarily attributed to its proangiogenic function in the extracellular milieu that may contribute to tumor cell growth, invasion, and metastasis [70]. Moreover, it has been recently observed that PAI-1 protects tumor cells from Fas/Fas ligand-mediated apoptosis [70].

2.6. Obesity and adipokines

Epidemiological studies have demonstrated a robust link between CVD and obesity. Truncal obesity has been shown to be an independent modifiable risk factor for CAD as identified the INTERHEART Study [71]. Moreover, obese and overweight individuals may also be at increased risk of developing a variety of cancers including breast, uterus, esophagus, pancreas, colorectal, and kidney [72]. The causal link between obesity and both cancer and CVD is further strengthened by evidence of decreased incidence of MI, stroke and cancer in patients with weight loss following bariatric surgery [73]. Adipose tissue secretes numerous bioactive proteins including pro-inflammatory cytokines (e.g. TNF- α and IL-6), PAI-1, and adipokines (e.g. adiponectin and leptin) [74–77]. These in turn increase activities of PI3K, MAPK, and STAT3 pathways, which play important roles in atherosclerosis as well as angiogenesis and malignant growth [69]. Among the aforementioned adipokines, the role of leptin in connecting the obesity, CVD, and cancer is noteworthy. Except for in lipodystrophy, leptin levels are elevated in obese patients. Recent studies have shown that leptin dysregulation plays a critical role in the development and metastasis of different malignant tumors by modifying its microenvironment, promoting migration of endothelial cells, and recruitment of macrophages and monocytes, which secrete vascular endothelial growth factor and proinflammatory cytokines that will promote angiogenesis of tumors [78,79]. Leptin has been shown to promote endothelial dysfunction through decreasing the bioavailability of nitric-oxide, upregulating the endothelin-1 secretion, and activating JAK/STAT pathway and increasing ERK signaling [80]. The involvement of leptin in CVD is further supported by its induction of osteoblastic differentiation and calcification of vascular cells, promoting platelets aggregation and arterial thrombosis, and inducing the accumulation of cholesterol in macrophages in hyperglycemic conditions via activation of acylCoA: cholesterol O-acyltransferase (ACAT), and the release of monocyte colony-stimulating factor [80]. Although, PPAR- γ activators like TZDs are pro-adipogenic, they downregulate leptin gene expression [81] and therefore inhibit Akt-dependent migration of vascular smooth muscle cell through inhibition of eNOS [82]. These findings highlight the potential therapeutic role of TZDs in prevention of diabetes-associated vasculoproliferative disorders.

2.7. Wnt signaling pathway

Signaling by the Wnt family of secreted glycolipoproteins plays an important role in the regulation of cell proliferation, polarity, migration and cell fate determination [83]. In the 'canonical' Wnt/ β -catenin signaling pathway, binding of Wnts to the transmembrane Frizzled and lipoprotein receptor-related proteins (LRP5 and LRP6), prevents the cytoplasmic degradation of β -catenin. Translocation of β -catenin nucleus allows for interaction with members of the T cell factor/lymphoid enhancer factor (TCF/LEF) family including TCF7L2 to promote expression of genes involved in proliferation, and survival [84,85]. Aberrant Wnt signaling plays an important role in the pathogenesis of atherosclerosis [85–87]. Wnt and downstream signaling targets can promote endothelial dysfunction and inflammation [88,89], monocyte adhesion [7], and vascular calcification [90]. Wnt/ β -catenin pathway also plays a crucial role in proliferation of VSMCs [91]. Interestingly, impaired LRP6-TCF7L2 activity enhances VSMC plasticity, increasing neointimal thickening, in the absence of excessive lipid accumulation [85]. Aberrant Wnt signaling functions is also linked to a number of cancers including prostate [46], bladder [47], colon [45], breast [48] and lymphoma [49]. Using a drosophila model of insulin resistance Hirabayashi et al. [92] showed that the transcriptional upregulation of insulin receptor by Wnt/TCF7L2 in Ras/Src-transformed tumors may explain increased growth and metastatic capability of malignant tumors in patients with T2DM and/or obesity. Taking together, the Wnt signaling pathway is an emerging biological link between CVD, diabetes and cancer, and may be novel therapeutic target in the future.

2.8. LRP6 mutation

In 2007, a novel neomorphic missense mutation (R611C) in the LRP6 coding region on chromosome 12p was identified in an Iranian family with autosomal dominant premature CAD, metabolic syndrome (dyslipidemia, hypertension, and diabetes), and osteoporosis [87]. Further studies demonstrated that *LRP6^{R611C}* plays an important role in insulin resistance, hypertriglyceridemia and LDL, non-alcoholic fatty liver disease, and accumulation of ectopic fat [93–101]. The *LRP6^{R611C}* mutation promoted PDGF stimulated VSMC proliferation and [86], dedifferentiation and neointimal thickening via the non-canonical Wnt signaling pathway [85]. Recent studies have shown that overexpression of *LRP6* enhances cell proliferation and induces tumorigenesis in fibrosarcoma [102], hepatocellular carcinoma [103], and breast [104,105] and colorectal [106] cancer. In conclusion, aberrant activation of *LRP6* gene plays a major role in pathophysiology of both diseases and may be as one of the genetic links between CVD and cancer.

2.9. TCF7L2 polymorphism

The *TCF7L2* gene located on chromosome 10q25.3 is a transcription cofactor involved in canonical Wnt signaling pathway [107]. Single nucleotide polymorphisms (SNPs) of *TCF7L2* gene, in particular the T allele of rs7903146, have been associated with T2DM in diverse ethnic populations, making *TCF7L2*, one of the strongest diabetes susceptibility genes known to date [108–110]. Muendlein et al. [107] recently reported that rs7903146 and two other variants of *TCF7L2* are linked with angiographically evident coronary atherosclerosis, particularly in diabetic patients. Interestingly, polymorphisms of *TCF7L2*

are also associated with increased risk of breast, endometrial, colorectal, and recurrent prostate cancer [111–116]. Altogether, *TCF7L2* polymorphism is another example for genetic linkage of CVD and cancer, and their shared metabolic risk factors including T2DM and obesity.

2.10. DYRK1B mutations

DYRK1B is a member of the Dyrk family of proteins, a group of evolutionarily conserved protein kinases that are involved in cell differentiation, survival, and proliferation [117,118]. It is overexpressed in many types of human tumors, particularly ovarian, lung, and pancreatic cancers [119–121]. A gain of function mutation in *DYRK1B* gene (R102C) was recently identified through linkage analysis of three large families premature CAD, central obesity, hypertension, and T2DM [122]. Furthermore, R102C mutant cell lines demonstrate enhanced adipogenesis and glucose-6phosphatase expression in vitro [122]. DYRK1B may thus represent a novel biological overlap between cancer cell survival and premature coronary atherosclerosis.

2.11. Methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism

MTHFR is a key enzyme involved in the synthesis of methionine from homocysteine and folate. Increased plasma homocysteine is an independent risk factor for CAD [123–125]. Homocysteine has multiple effects on atherosclerosis including enhanced lipid peroxidation, endothelial dysfunction and reduced nitric oxide, as well as stimulating VSMC proliferation [126]. Moreover, homocysteine can lead to platelet activation and promote thrombosis [123]. C677T is the most common genetic variant of the *MTHFR* gene producing a less active, thermolabile mutant and increased plasma homocysteine and reduced folate levels [123–125,127]. Several recent meta-analyses have revealed that the C677T polymorphism is associated with increased risk of CAD [123,124], MI [125], peripheral arterial disease [128], and ischemic and hemorrhagic stroke [129–132].

Mounting evidence has also supported an association of the *MTHFR* C677T polymorphism with a variety of cancers including breast, prostate, colorectal, cervical, oral, ovarian, esophageal, gastric, pancreatic, lung, bladder cancer, hepatocellular carcinoma and acute lymphoblastic leukemia [127]. The C677T mutation can result in reduced folate levels and may increase the incidence of cancer [127,133]. Folate plays a key role in epigenetic processes by regulating DNA methylation [133]. Altered DNA methylation can lead to increased expression of various oncogenes [127] see (Fig. 1).

3. Joint pharmacologic prevention for CVD and cancer

Effective prevention strategies include both pharmacologic and non-pharmacologic components. In line with the significant effect of prevention strategies on global disease incidence, the WHO has identified global targets for major environmental and lifestyle related risk factors [1]. In addition are cornerstones of the prevention and management of CVD. A growing body of evidence supports a role for statins, angiotensin converting enzyme inhibitors/angiotensin receptor blockers, and aspirin in cancer prevention. Although currently no organization endorses widespread use of these drugs for primary prevention of

cancer, they may be considered among strategies for joint prevention of CVD and cancer as evidence for risks and benefits is established see (Table 1).

3.1. Statins

Lipid lowering therapy with statins is the cornerstone of medical therapy for primary and secondary prevention of CVD [134]. In addition to potent LDL lowering, statins can improve endothelial function, promote plaque stabilization, and exert antioxidant and anti-inflammatory effects [135]. Although not currently part of medical therapy for malignancy, a potential tumor-suppressor and anti-cancer role for statins thought to be independent of their lipidreducing properties is also emerging. Statin use is associated with reduced incidence of colorectal, liver, breast, skin, prostate, melanoma, head and neck, lung and pancreatic cancers [136–140]. Statins also inhibit production of the mevalonate pathway products involved in posttranslational modification of cell signaling proteins. This modulation of cellular signaling may have pro-apoptotic, antiproliferative, anti-invasive, and radiosensitizing effects [23,135,136]. Statins may also play a protective role against DNA damage which is a key factor in pathophysiology of both atherosclerosis and cancer [141]. Recent studies have shown that statins slightly increase the incidence of new-onset T2DM [142, 143] and the effect varies as per the dosage and type used [142]. However, most of the investigators are of the opinion that the risk of T2DM with statins can be outweighed by the long-term benefits in preventing complications [142,144]. Taken together, statins are interesting candidates for application in CVD and cancer prevention. In patients with high risk of T2DM, statins should be cautiously used and clinicians should vigilantly monitor for incident T2DM in patients on statins [142,144].

3.2. Angiotensin converting enzyme inhibitors (ACEIs)/angiotensinreceptor blockers (ARBs)

Evidence suggests that long-term exposure to ACEIs/ARBs is associated with decreased overall risk of cancer [9,145], with potentially stronger effects in colorectal, pancreatic, breast, prostate, and lung cancers [8,9,11,145–148]. The main effector peptide of the renin-angiotensin-aldosterone system, angiotensin II, induces angiogenesis [149,150], cell proliferation [151] and DNA synthesis [152]. Blocking angiotensin II decreases preneoplastic lesions, cell growth, angiogenesis, and VEGF levels in experimental models of cancer [8,146,153]. Moreover, it has been established that blockade of the RAAS exerts potent anti-atherosclerotic effects through anti-hypertensive effects and through anti-inflammatory, anti-proliferative and antioxidant properties [134]. Hence, the role of ACEIs/ARBs in joint pharmacologic prevention of CVD and cancer may have to be examined in clinical studies.

3.3. Aspirin

The role of aspirin in the secondary prevention of CVD is well established [154,155]. It reduces the risk of recurrent major coronary events and stroke by 20% and 19%, respectively [156]. Although uncertainties exist regarding the net beneficial effect (decreased MI vs. increased bleeding) of aspirin for primary prevention of CVD in low risk populations [155], guidelines of the American College of Cardiology, American Heart Association, American Diabetes Association, as well as a position paper of the European Society of Cardiology

Working Group on Thrombosis, recommend its use in individuals at high risk of CVD and not at increased risk of bleeding [155].

Aspirin may also reduce cancer-related mortality. The first and the most powerful preventive effect was observed in colorectal cancer and then extended to other malignancies, especially adenocarcinomas [157]. In long-term follow-up of participants in five randomized trials of cardiovascular prevention, Rothwell and colleagues [158] reported that daily aspirin at any dose reduced risk of colorectal cancer by 24% and reduced associated mortality by 35% after 8e10 years. Daily aspirin use was associated with a 21% reduced risk of cancer death during the trials, with benefit only apparent after 5 years, and reduced mortality due to several cancers during post-trial follow-up to 20 years [159]. These data were reinforced by a more recent meta-analysis of 11 RCTs, reporting that daily aspirin use significantly reduces risk of non-vascular death by 12% and of cancer death by 15%, with benefit seen within 3 years for high doses (≥ 300 mg/day) and after 5 years for low doses (<300 mg/day) [10]. Taken together, pending the results of several ongoing studies on efficacy of aspirin in primary prevention of CVD in high-risk patients [155], aspirin is considered a candidate drug for joint prevention of CVD and cancer in high-risk populations.

3.4. Polypill

The concept of combining multiple classes of cardiovascular medications (including aspirin, statins, ACEIs/ARBs) into a single pill, so-called “polypill”, has gained great interest in the past decade. There are several ongoing trials evaluating the short-term and long-term efficacy of a fixed-dose polypill strategy in primary and secondary prevention of CVD. Taking into account the promising effects of aspirin, statins, and ACEIs/ARBs on primary prevention of cancers, assessment of the efficacy of the polypill in the primary prevention of cancer in high-risk populations should be considered.

4. Conclusions

While diverse diseases, CVD and cancer have many similarities. These include common lifestyle-related risk factors, and shared cellular, signaling and genetic pathways. Moreover, the interaction between genetics and environment adds further complexity to both diseases and will be an important area for future research [160]. Clearly, multifaceted interventions to address these shared issues are needed and will include individual and population-level behavioral and policy strategies as well as novel pharmacologic approaches. Modifying common risk factors and targeting of common disease pathways may prove to be the most powerful strategy for prevention of both cancer and CVD.

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Conflict of interest

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Abbreviations:

CVD	cardiovascular disease
CAD	coronary artery disease
T2DM	type II diabetes mellitus
ACEIs/ARBs	angiotensin converting enzyme inhibitors/ angiotensin receptor blockers
RAAS	renin-angiotensin-aldosterone system
VSMC	vascular smooth muscle cell
AMPK	adenosine 5' monophosphate-activated protein kinase
PPAR-γ	peroxisome proliferator-activated receptor- γ
PAI-1	plasminogen activator inhibitor-1
TZDs	thiazolidinediones
WHO	World Health Organization.

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Fig. 1.

Interplay of shared molecular pathways, genetic alterations, metabolic disorders, and environmental life-style related factors in the dynamic process of developing cardiovascular disease and cancer.

AMPK, adenosine 5' monophosphate-activated protein kinase; PPAR- γ , peroxisome proliferator-activated receptor- γ ; PAI-1, plasminogen activator inhibitor-1; FAS, fatty acid synthase.

Table 1

Potential drugs for joint pharmacologic prevention of cardiovascular disease and cancer.

Drug	Direct Target	Indirect Targets	Action on CVD	Action on Cancer	
Statins	HMG-CoA-reductase inhibition	• AMPK activation	Improving endothelial function	Tumor-suppressor and anti-cancer role through:	
		• Inhibition of Cyclins & cycline-dependent kinases	Plaque stabilization	↑ Apoptosis	
			↓ Atherosclerosis progression	↓ Proliferation	
			↓ Myocardial infarction and stroke	↓ Invasion	
			↓ Cardiovascular mortality	↑ Radiosensitization	
ASA	Inhibition of COX1	• AMPK activation?	↓ Myocardial infarction and stroke	↓ Cancer incidence	
			↓ Cardiovascular mortality	↓ Cancer death	
			Improving endothelial function	↓ Cancer incidence	
			Plaque stabilization	Tumor-suppressor and anti-cancer role through:	
			↓ Atherosclerosis progression	↓ DNA damage	
ACEIs/ARBs	ACE inhibition/Angiotensin II receptor antagonism	• ↓ VEGF expression	Improving endothelial function	↓ Cancer incidence	
		• PPAR-γ activation	Plaque stabilization	Tumor-suppressor and anti-cancer role through:	
			↓ Atherosclerosis progression	↓ DNA damage	
			↓ Myocardial infarction and stroke	↑Apoptosis	
			↓ Cardiovascular mortality	↓ Differentiation ↓ Angiogenesis ↓ Cell growth	
Metformin	Unknown	• AMPK activation	↓ Cancer incidence	Tumor suppression by regulating cellular proliferation, cell cycle progression and cellular survival	
TZDs	PPAR-γ agonism	• AMPK activation	↓ Coronary and carotid atherosclerosis	Tumor suppression through:	
		• Wnt/β-catenin signaling pathway inhibition		↓ Angiogenesis	
			• IGF-1 inhibition	↓ Thrombus formation and acute	↑ Apoptosis
			• Inhibition of leptin gene expression	myocardial infarction and stroke	↓ Self-renewal of cancer cells
				↓ Blood pressure	↑ Differentiation

HMG-CoA-reductase, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase; AMPK, Adenosine 5' monophosphate -activated protein kinase; PI3K, phosphoinositide 3- kinase; NFκB, nuclear factor kappa-B; MAPK, mitogen-activated kinases; CVD, cardiovascular disease; COX1, cyclooxygenase 1; ACEIs/ARBs, angiotensin-converting enzyme inhibitors/angiotensin II receptor antagonists; ACE, angiotensin-converting enzyme; VEGF, vascular endothelial growth factor; PPAR-γ, peroxisome proliferator-activated receptor-γ; TZDs, thiazolidinediones.