

BIDIRECTIONAL CARDIO-ONCOLOGY FOCUS ISSUE

Cancer and Cardiovascular Disease



Shared Risk Factors, Mechanisms, and Clinical Implications: *JACC: CardioOncology State-of-the-Art Review*

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ABSTRACT

Cancer and cardiovascular disease (CVD) remain the leading causes of morbidity and mortality worldwide, with emerging evidence highlighting their complex and bidirectional interplay. Shared risk factors, including aging, systemic inflammation, metabolic dysregulation, and lifestyle behaviors, can contribute to their co-occurrence while underlying biological mechanisms such as oxidative stress, chronic inflammation, and clonal hematopoiesis further reinforce their connection. These mechanisms drive pathophysiological changes contributing to disease progression, increasing susceptibility to both conditions. This review explores the epidemiology, overlapping biological pathways, and risk factors linking cancer and CVD, emphasizing key mechanisms such as epigenetic modifications, immune system dysregulation, and cellular senescence. Future research should aim to identify biomarkers, refine risk models, and develop targeted strategies to mitigate disease burden and improve outcomes. (JACC CardioOncol. 2025;7:453-469)

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Cardiovascular disease (CVD) and cancer are the leading causes of death worldwide, accounting for over half of global mortality.^{1,2} Although viewed as separate conditions, accumulating evidence reveals a complex and bidirectional relationship driven by overlapping risk factors and shared biological mechanisms (**Central Illustration**).³⁻⁵ Common risk factors such as aging, obesity, smoking, diabetes, and hypertension increase the likelihood of developing both diseases.⁵⁻⁸ Moreover, systemic inflammation, oxidative stress, epigenetic changes, cellular senescence, microbial

dysbiosis, and clonal hematopoiesis emerge as shared biological pathways, offering a mechanistic link between these two pathologies.⁹⁻¹⁵

Despite growing recognition of shared mechanisms, key gaps remain in understanding the full interplay between cancer and CVD. Their coexistence calls for integrated risk stratification and management focused on common biological pathways. This review examines the bidirectional relationship between cancer and CVD, emphasizing shared risk factors, biological mechanisms, and integrated prevention rather than treatment-related complications. We conducted

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

Manuscript received March 26, 2025; revised manuscript received July 11, 2025, accepted July 14, 2025.

**ABBREVIATIONS
AND ACRONYMS**

BMI	= body mass index
CAD	= coronary artery disease
CHIP	= clonal hematopoiesis of indeterminate potential
CVD	= cardiovascular disease
HDAC	= histone deacetylase
HIF	= hypoxia-inducible factor
IL	= interleukin
miRNA	= microRNA
ncRNA	= noncoding RNA
PM2.5	= particulate matter <2.5 μm in diameter
ROS	= reactive oxygen species
TME	= tumor microenvironment

a targeted literature review (2005–2025) focused on these themes (search strategy detailed in the *Supplemental Appendix*).

EPIDEMIOLOGIC OVERLAP AND DUAL BURDEN OF CANCER AND CVD

Cancer and CVD remain major global health burdens. In 2022, there were nearly 20 million new cancer cases and 9.7 million deaths worldwide.¹ In the United States, there are more than 18 million cancer survivors.¹⁶ The number continues to grow as cancer mortality decreases with better detection and treatment. CVD has become the top noncancer cause of death, accounting for up to 49% of such deaths in solid cancer survivors.¹⁷ Much of the data on cancer and CVD epidemiology come from U.S.-based registries, limiting global applicability, especially in low- and middle-income areas.¹⁸

Cancer survivors with CVD fare worse than those without, with 5-year survival rates of 75% vs 87% and 8-year rates of 60% vs 81%.¹⁹ Childhood cancer survivors are particularly vulnerable, facing a 15-fold higher lifetime risk of heart failure and a 7-fold increased risk of premature cardiac death compared with the general population.^{20,21}

Conversely, patients with existing CVD face a heightened likelihood of developing cancer. **Table 1** summarizes how specific CVD subtypes (eg, atrial fibrillation, heart failure, stroke, atherosclerotic disease) correlate with subsequent cancer incidence and mortality.^{22–31}

SHARED RISK FACTORS FOR CVD AND CANCER

Cancer and CVD frequently arise from overlapping demographic, clinical, and lifestyle risk factors. This section outlines these shared contributors and their role in disease development, with implications for integrated prevention and risk reduction strategies.

DEMOGRAPHIC AND SOCIOECONOMIC SHARED RISK FACTORS. **Advancing age.** The incidence of CVD rises from approximately 40% in adults 40 to 59 years of age to 75% in those 60 to 79 years of age, and to 86% in those over 80 years of age.³² Similarly, cancer risk increases exponentially with age, with nearly 60% of invasive cancer diagnoses occurring in adults 65 years of age and older, despite this group comprising only 17% of the population in the United States.³³

HIGHLIGHTS

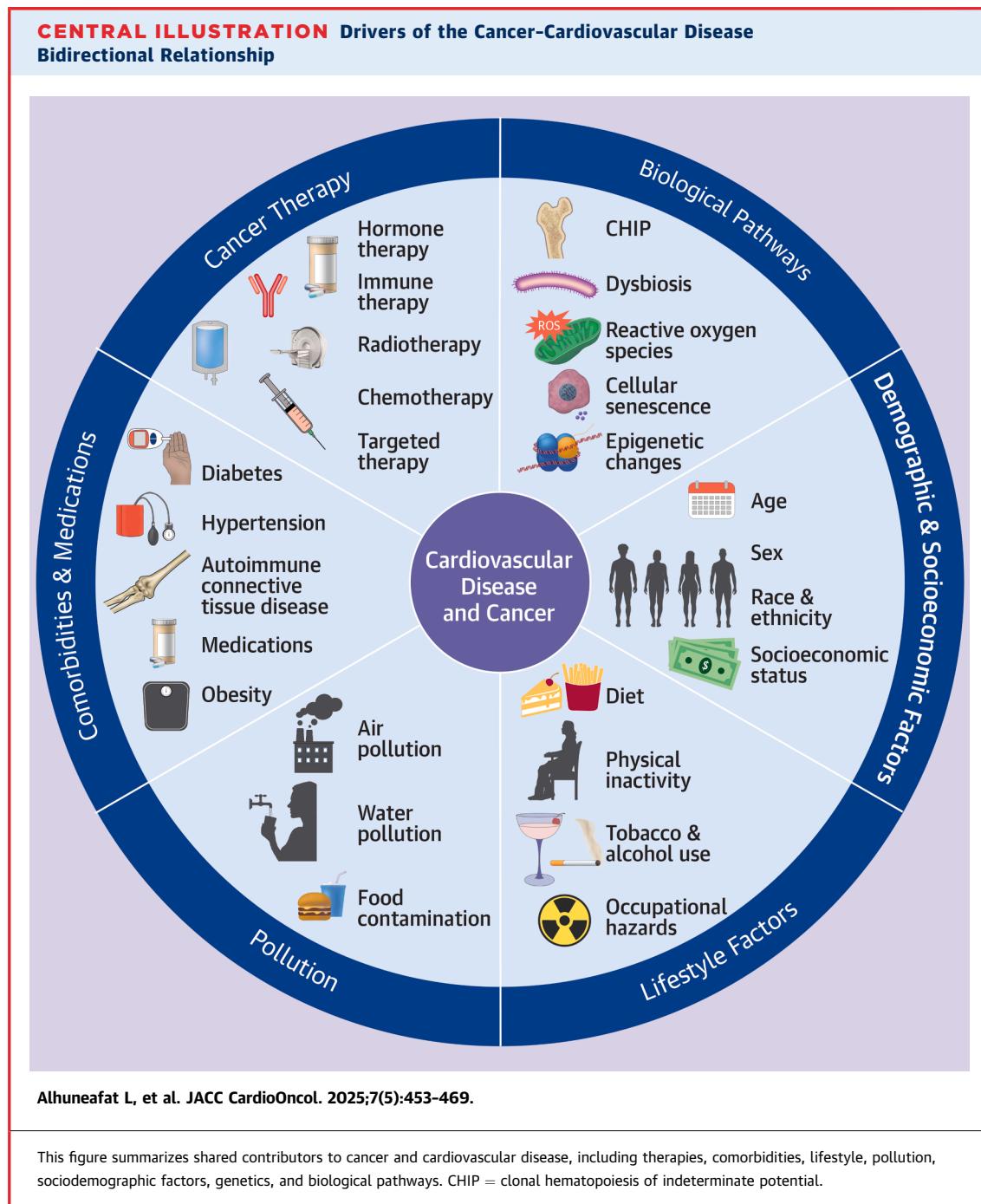
- Cancer and cardiovascular disease are leading causes of death with shared risks and biology.
- Common risk factors include age, comorbidities, lifestyle, and sociodemographic traits.
- Disparities in outcomes of both cancer and cardiovascular disease are shaped by social and environmental determinants.
- Shared pathways offer targets for integrated prevention and dual risk reduction.

Aging contributes to both diseases through shared mechanisms, including chronic low-grade inflammation, cellular senescence, mitochondrial dysfunction, genomic instability, epigenetic alterations, telomere attrition, and cumulative environmental exposures, reflecting biological aging processes that influence disease risk beyond chronological age alone.³⁴ Notably, molecular markers of biological aging may offer more risk prediction and inform preventive strategies.³⁵

Sex. Sex influences cancer and CVD risk and outcomes through hormonal differences, treatment responses, and disease patterns, and is recognized by the National Institutes of Health as a critical biological variable in research.^{36,37} Sex chromosomes and hormones influence immune, neuroendocrine, and vascular function, contributing to differences in stress response, inflammation, and treatment outcomes.³⁸

Sex differences significantly shape CVD epidemiology, with women generally developing CVD later in life than men, yet experiencing worse outcomes after events such as myocardial infarction.³⁹ Overall, breast cancer is the most common cancer in women, while prostate cancer is the most common in men, highlighting the prominence of sex-related malignancies and their inherent differences in oncological epidemiology.³³

Race and ethnicity. Race and ethnicity may influence the incidence and outcomes of cancer and CVD. A longitudinal analysis of over 3,100 U.S. counties found that counties with a higher percentage of Black residents experienced persistently higher cardiovascular mortality rates over a decade, even as national mortality declined.⁴⁰ A large cohort study demonstrated that American Indian and Alaska Native populations have a high burden of cardiometabolic



Alhuneafat L, et al. JACC CardioOncol. 2025;7(5):453-469.

This figure summarizes shared contributors to cancer and cardiovascular disease, including therapies, comorbidities, lifestyle, pollution, sociodemographic factors, genetics, and biological pathways. CHIP = clonal hematopoiesis of indeterminate potential.

risk factors and CVD, with a 5-year CVD mortality rate of 25%.⁴¹

American Indian and Alaska Native populations also have the highest overall cancer mortality, with kidney, liver, stomach, and cervical cancer rates 2 to 3 times higher than among White individuals.³³ Similarly, Black Americans experience double the

mortality rates for prostate, stomach, and uterine cancers and face disproportionately high CVD prevalence and mortality.^{33,42,43} Disparities may stem from systemic inequities, with structural racism and social determinants of health impacting access to care, housing, socioeconomic status, and quality of care.^{44,45}

TABLE 1 Epidemiologic Studies Demonstrating Cancer Risk Among Individuals with CVD

CVD Type	Study/Setting	Key Measures	First Author
AF	Danish population-based cohort (26,222 men, 28,879 women)	<ul style="list-style-type: none"> HR (men, all cancer type): 1.41 (95% CI: 1.26-1.58) HR (women, all cancer type): 1.15 (95% CI: 1.02-1.32) HR (lung cancer, men): 1.66 (95% CI: 1.19-2.30) HR (colorectal, men): 1.37 (95% CI: 1.02-1.85) 	Vinter et al ³¹
	Danish population (1980-2011; 269,742 patients with new onset AF)	<ul style="list-style-type: none"> SIR: 5.11 (95% CI: 4.99-5.24). Very strong associations for lung, kidney, colon, ovary, and non-Hodgkin's lymphoma 	Ostenfeld et al ²²
	Women's cohort (1993-2013; 34,691 women ≥45 y, free of AF, CVD, and cancer at baseline)	<ul style="list-style-type: none"> Age-adjusted HR: 1.58 (95% CI: 1.34-1.87); $P < 0.001$ Multivariable HR: 1.48 (95% CI: 1.25-1.75); $P < 0.001$ Early spike: 3-mo HR: 3.54 (95% CI: 2.05-6.10) Beyond 1 y: HR: 1.42 (95% CI: 1.18-1.71) 	Conen et al ²³
	RE-LY trial (18,113 patients with AF)	<ul style="list-style-type: none"> Greater than one-third of all AF patient deaths were non-CV Malignant tumors major cause of these non-CV deaths 13.93% cancer mortality 	Marijon et al ³⁰
HF	Meta-analysis (9 papers, 7,329,706 total patients; 515,041 with HF vs 6,814,665 without)	<ul style="list-style-type: none"> Primary endpoint: incidence of any cancer HR (HF vs non-HF) for all cancer: 1.43 (95% CI: 1.21-1.68) Secondary endpoints: incidences of breast, lung, hematological, colorectal, prostate cancers Breast HR: 1.28 (95% CI: 1.09-1.50) Lung HR: 1.89 (95% CI: 1.25-2.85) Hematologic HR: 1.63 (95% CI: 1.15-2.33) Colorectal HR: 1.32 (95% CI: 1.11-1.57) Prostate HR: 0.97 (95% CI: 0.66-1.43) 	Jaiswal et al ²⁹
Stroke	VISP trial (3,680 adults with nondisabling cerebral infarction)	<ul style="list-style-type: none"> Incidence of cancer per 100 patients: 1 mo: 0.15 6 mo: 0.80 1 y: 1.2 2 y: 2.0 SIRs 1 year: 1.2 (95% CI: 1.16-1.24) 2 year: 1.4 (95% CI: 1.2-1.6) Patients who developed cancer had an increased risk of death (OR: 3.1; 95% CI: 1.8-5.4) vs cancer-free stroke patients 	Qureshi et al ²⁴
	3 large cohorts (OSCP, Lothian Stroke Register, and IST; N = 7,710)	<ul style="list-style-type: none"> Primary finding: 38% of all deaths in these stroke cohorts were attributed to cancer 	Slot et al ²⁵
aCVD and MI	IBM MarketScan cohort Large database: >27 million individuals (≥36 mo follow-up) CVD, aCVD vs non-aCVD	<ul style="list-style-type: none"> HR (any CVD): 1.13 (95% CI: 1.12-1.13) HR (aCVD vs no CVD): 1.20 (95% CI: 1.19-1.21) HR (aCVD vs non-aCVD): 1.11 (95% CI: 1.11-1.12) 	Bell et al ²⁸
	SHIP cohort (32,095 participants with CVD)	<ul style="list-style-type: none"> Prevalence: 5% vs 2% (cancer), 6% vs 3% (mortality) in aCVD vs non-aCVD HR: 1.372 (95% CI: 1.199-1.569) for incident cancer Among aCVD patients, those with multiple atherosclerotic lesions had a 9% cancer incidence vs 5% with a single atherosclerotic site Risk of death rose incrementally with aCVD, cancer, or both (all $P = 0.0001$) 	Suzuki et al ²⁶
	Danish registry (2,871,168 adults; 122,275 had MI)	<ul style="list-style-type: none"> IR (MI group) 19.1 per 1,000 person-years for cancer vs 9.3 per 1,000 person-years in reference population IRR: 1.14 (95% CI: 1.10-1.19) age-sex adjusted; 1.08 (95% CI: 1.03-1.13) after additional comorbidity adjustment; dropped to 1.00 (95% CI: 0.96-1.05) excluding first 6 mo post-MI Peak incidence for both cancer and death occurred in the first year post-MI Younger MI patients (30-54 y) had particularly high rates of colorectal, lung, and urinary tract cancers; this risk was lower in older groups (55-69 y, 70-99 y) 	Malmborg et al ²⁷

This table highlights selected key studies illustrating associations between CVD subtypes and incident cancer risk or mortality.

aCVD = atherosclerotic cardiovascular disease; AF = atrial fibrillation; CV = cardiovascular; CVD = cardiovascular disease; HF = heart failure; IR = incidence rate; IRR = incidence rate ratio; IST = International Stroke Trial; MI = myocardial infarction; OSCP = Oxfordshire Community Stroke Project; RE-LY = Randomized Evaluation of Long-Term Anticoagulation Therapy; SHIP = Sakakibara Health Integrative Profile; SIR = standardized incidence ratio; VISP = Vitamin Intervention for Stroke Prevention.

Social determinants. Social determinants of health have an important impact on outcomes in both cancer and CVD. In a nationally representative cohort of U.S. cancer survivors, a higher cumulative social deprivation score was independently associated with increased cardiovascular (adjusted HR [aHR]: 1.31; 95% CI: 1.02-1.68), cancer (aHR: 1.20; 95% CI: 1.01-1.42), and all-cause mortality (aHR: 1.16; 95% CI: 1.02-1.31), even after adjusting for demographics, comorbidities, and traditional risk factors.⁴⁶ Similarly, the Social Vulnerability Index, which evaluates community-level social determinants of health, revealed that counties with high social vulnerability experienced worse outcomes, with a 34% higher mortality rate from combined cancer and CVD compared with counties with more favorable Social Vulnerability Index scores.⁴⁷

Emerging evidence highlights chronic stress, measured by allostatic load, as an important mediator linking social determinants of health with outcomes in cancer and CVD. In patients with breast, lung, colorectal, or prostate cancer, each 1-point increase in allostatic load corresponds to a 10% to 30% higher risk of major adverse cardiac events.^{48,49}

COMORBIDITIES AND THEIR THERAPIES AS SHARED RISK FACTORS. Hypertension. Hypertension significantly contributes to adverse cardiovascular outcomes such as myocardial infarction, stroke, and heart failure.⁵⁰ This risk is amplified in patients with cancer, who often exhibit higher rates of hypertension than the general population.⁷ Hypertension has also been associated with an increased risk of cancer incidence and mortality.^{51,52} In one meta-analysis that adjusted for multiple factors, hypertension was shown to be associated with increased risks of renal cell carcinoma (relative risk [RR]: 1.52; 95% CI 1.32-1.75), colorectal cancer (RR: 1.30; 95% CI: 1.03-1.66), and hormone-sensitive malignancies such as breast cancer (RR: 1.10; 95% CI: 1.02-1.18).⁵¹ Although the mechanism remains unclear, animal models suggest that elevated blood pressure may lead to dysregulated apoptosis.⁵³ Additionally, increased levels of angiotensin II in hypertension may promote vascular endothelial growth factor-mediated cancer angiogenesis.⁵³

Even modest reductions in systolic blood pressure reduce cardiovascular morbidity and mortality,⁵⁴ but whether specific antihypertensive medications or blood pressure reduction itself influences cancer risk remains uncertain. While meta-analyses of randomized trials show no overall increased cancer risk with angiotensin receptor blockers, some observational studies suggest reduced risks of keratinocyte cancer

and improved survival in pancreatic/non-small cell lung cancer.^{55,56} Similarly, large randomized trials have not demonstrated increased cancer risk with calcium channel blockers⁵⁷; however, observational studies report site-specific associations, including higher odds of basal cell carcinoma (OR: 1.15; 95% CI: 1.09-1.21), lung cancer (RR: 1.15; 95% CI: 1.01-1.32), and prostate cancer (RR: 1.08; 95% CI: 1.05-1.11).⁵⁵ Importantly, a recent meta-analysis of 324,168 participants from 31 randomized trials found that blood pressure lowering, regardless of drug class, was not associated with any change in overall cancer risk (RR per 5 mm Hg systolic blood pressure reduction: 1.00; 95% CI: 0.98-1.02).⁵⁸

Diabetes mellitus. Diabetes mellitus promotes endothelial dysfunction, oxidative stress, and chronic inflammation, accelerating atherosclerosis and increasing the risk of coronary artery disease (CAD), stroke, and heart failure.⁵⁹ Diabetes increases the risk of major adverse cardiovascular events and all-cause mortality, with these risks extending to prediabetic states.^{60,61}

The relationship between diabetes and cancer is also compelling. A meta-analysis of 151 cohort studies (>32 million individuals) found that diabetes was associated with increased risk of liver (RR: 2.23; 95% CI: 1.99-2.49), pancreatic (RR: 2.09; 95% CI: 1.88-2.33), endometrial (RR: 1.63; 95% CI: 1.41-1.88), gallbladder (RR: 1.61; 95% CI: 1.34-1.93), and colorectal (RR: 1.27; 95% CI: 1.21-1.34) cancers, along with an increase in cancer-related mortality (RR: 1.25; 95% CI: 1.18-1.33).⁸ This association is attributed to hyperinsulinemia, chronic hyperglycemia, and elevated insulin-like growth factors, which promote tumor growth and survival, as well as to oxidative stress and inflammation, which drive shared pathways in both CVD and cancer.⁶²

The varying effects of diabetes therapies on cancer incidence and outcomes further complicate the relationship between diabetes and cancer.⁵⁵ Metformin, for example, has been associated with reduced cancer incidence and improved survival in diabetes patients, likely due to its effects on insulin signaling and metabolic reprogramming.^{63,64} Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are being explored for their potential dual benefits of cardioprotection and anticancer effects.⁶⁵ Preclinical studies indicate potential anticancer effects across multiple cancer types (eg, breast, prostate, pancreas), likely mediated through metabolic modulation, anti-inflammatory activity, and inhibition of tumor proliferation pathways.⁶⁵ Evidence linking insulin therapy to cancer is inconclusive. A systematic review of

19 observational studies found no consistent association with cancer overall, though some suggested a possible increased breast cancer risk, limited by methodological shortcomings.⁶⁶

Obesity. Obesity is a well-established risk factor for both CVD and cancer, driven by metabolic, inflammatory, and hormonal pathways.^{5,67} Moreover, obesity contributes to increased cardiac output and left ventricular remodeling, exacerbating conditions like heart failure and atherosclerosis.⁶⁸ Adipose tissue expansion in obesity shifts from an anti-inflammatory to a proinflammatory state, with adipocyte hypertrophy, mechanical stress, and limited vascularization leading to chronic inflammation.⁶⁸ Elevated levels of leptin and interleukin (IL)-6 further contribute to angiogenesis, apoptosis inhibition, and tumor progression.⁵

Epidemiological studies have shown that every 5 kg/m² increase in body mass index (BMI) is associated with significantly higher risks of hypertension (RR: 1.49; 95% CI: 1.40-1.60), heart failure (RR: 1.41; 95% CI: 1.32-1.50), CAD (aHR: 1.15; 95% CI: 1.12-1.20), and cardiovascular mortality (aHR: 1.49; 95% CI: 1.44-1.53).⁶⁷

The relationship between obesity and cancer is similarly profound. It is estimated that up to 20% of malignancies may be attributed to obesity.⁶⁹ A comprehensive meta-analysis demonstrated a clear dose-response relationship between increasing BMI and elevated cancer risk.⁷⁰ Higher BMI was associated with greater incidence of brain, kidney, endometrial, ovarian, liver, and colorectal cancers.⁷⁰ Obesity is linked to worse cancer outcomes, including higher cancer mortality and recurrence rates in breast, colorectal, and pancreatic cancers.⁷¹

Glucagon-like peptide-1 (GLP-1) receptor agonists are effective agents for glycemic control and weight loss in patients with obesity and type 2 diabetes, with demonstrated cardiovascular benefits. However, early concerns about potential associations with pancreatic and thyroid neoplasms led to caution in their long-term use.^{72,73} Reassuringly, a recent large cohort study of over 1.6 million patients with type 2 diabetes found that GLP-1 receptor agonist use was associated with significantly lower risk of 10 out of 13 obesity-associated cancers compared with insulin.⁷⁴ This included reductions in pancreatic cancer (HR: 0.41; 95% CI: 0.33-0.50), colorectal cancer (HR: 0.54; 95% CI: 0.46-0.64), and hepatocellular carcinoma (HR: 0.47; 95% CI: 0.36-0.61).⁷⁴ These findings parallel cancer risk reductions seen with bariatric surgery,⁷⁵ suggesting that weight loss or metabolic

effects may drive the benefit, although a drug-specific effect cannot be excluded.

Hyperlipidemia. Hyperlipidemia is a well-established risk factor for CVD, with strong evidence linking elevated low-density lipoprotein (LDL) cholesterol and triglyceride levels to increased risks of CAD, stroke, and atherosclerotic CVD.⁷⁶ In the context of cancer, hyperlipidemia has been associated with increased risks of colorectal and breast cancers.^{77,78}

Intensive lipid-lowering therapies, such as statins, have decreased cardiovascular and all-cause mortality, with more significant benefits observed at higher baseline low-density lipoprotein (LDL) levels.⁷⁹ Although statins may modestly reduce cancer risk, evidence remains inconsistent despite their anti-inflammatory and potential antitumor effects in preclinical studies.⁸⁰

Protein convertase subtilisin/kexin type 9 (PCSK9) inhibitors may have anticancer effects by promoting tumor apoptosis and enhancing CD8⁺ T cell immunity. Preclinical models show reduced tumor growth and metastasis with PCSK9 deficiency, and Mendelian randomization links lower PCSK9 activity to reduced cancer risk.⁸¹ Overall, hyperlipidemia's link to cancer is complex, confounded by BMI, physical activity, and medications. Some tumors also deplete cholesterol to support growth, further complicating interpretation.^{82,83}

LIFESTYLE AND ENVIRONMENTAL SHARED RISK FACTORS. **Smoking.** Smoking is a significant modifiable risk factor for both CVD and cancer. The shared biology linking smoking to these diseases is complex and includes chronic inflammation, oxidative stress, and direct tissue damage from carcinogens and oxidizing agents.⁸⁴

Large epidemiological studies have demonstrated that current smoking increases the risk of CVD by approximately 63% and more than doubles the risk of CVD-related mortality.⁶ Even light smoking—just 1 cigarette per day—is associated with significant risks of CAD and stroke, with RRs exceeding 1.4 for men and 1.5 for women compared with never-smokers.⁸⁵

In addition to its cardiovascular impact, smoking is a leading cause of cancer, responsible for 30% of cancer-related deaths in the United States.⁸⁶ Smoking contributes to site-specific cancers such as breast, colorectal, bladder, and pancreatic cancer in a dose-dependent manner, and Mendelian randomization studies support its causal role in both cancer and CVD.⁸⁷⁻⁸⁹

Smoking cessation confers substantial reductions in both cardiovascular and cancer risk. In a cohort of

over 5.3 million individuals, ex-smokers with fewer than 8 pack-years had CVD risk comparable to never-smokers (HR: 1.02; 95% CI: 0.97-1.07), while those with ≥ 8 pack-years required more than 25 years of abstinence for their CVD risk to normalize (HR: 1.11; 95% CI: 1.00-1.23).⁹⁰ Similarly, a systematic review showed that lung cancer risk declined by up to 50% within 10 years of cessation.⁹¹

Diet. Dietary practices are a potential modifiable factor influencing the risk of both CVD and cancer. A network meta-analysis of 40 randomized controlled trials (35,548 participants) showed that Mediterranean diet programs cut all-cause mortality (OR: 0.72; 95% CI: 0.56-0.92) and nonfatal myocardial infarction (OR: 0.48; 95% CI: 0.36-0.65) vs minimal dietary advice, while low-fat programs also lowered all-cause mortality (OR: 0.84; 95% CI: 0.74-0.95).⁹² Similarly, plant-based diets also demonstrated a reduced incidence of CVD and mortality.⁹³

Diet also plays a crucial role in cancer prevention, with strong evidence linking a healthy diet to reduced risks of colorectal, breast, and other site-specific cancers. A meta-analysis of 117 studies encompassing 3.2 million participants, highest vs lowest Mediterranean-diet adherence was linked to 13% lower cancer mortality (RR: 0.87; 95% CI: 0.82-0.92) and reduced incidence of colorectal (RR: 0.83; 95% CI: 0.76-0.90), head-and-neck (RR: 0.56; 95% CI: 0.44-0.72), respiratory (RR: 0.84; 95% CI: 0.76-0.94), gastric (RR: 0.70; 95% CI: 0.61-0.80), liver (RR: 0.64; 95% CI: 0.54-0.75), and bladder (RR: 0.87; 95% CI: 0.76-0.98) cancers.⁹⁴ Similarly, a prospective cohort study demonstrated that a healthy plant-based diet was associated with decreased cancer risk.⁹³

Protective effects are primarily attributed to increased intake of fruits, vegetables, whole grains, and legumes, which provide antioxidants, fiber, and polyphenols that modulate inflammation, oxidative stress, microbiota, metabolic dysregulation, and cell proliferation.^{95,96} In contrast, processed and red meats and sugar-sweetened beverages may heighten the risk of CVD and colorectal cancer, likely through carcinogenic compounds such as nitrosamines and polycyclic aromatic hydrocarbons.^{96,97} Other dietary carcinogens, such as aflatoxins—produced by mold on staple foods like nuts and grains—have been strongly linked to liver cancer, while excessive salt intake is associated with gastric cancer.⁹⁸

Alcohol. Alcohol has a complex, dose-dependent link to CVD and cancer. Though low-to-moderate intake has been tied to reduced cardiovascular mortality in some studies, these benefits are inconsistent and often diminish after adjusting for confounders.⁹⁹

For instance, Mendelian randomization studies suggest a small increase in CVD risk even with light drinking, with an exponential rise in risk for heavy consumption.¹⁰⁰ Heavy alcohol intake (>30 g/day) is strongly linked to hypertension, CAD, stroke, and peripheral arterial disease, underscoring its detrimental effects on cardiovascular health.^{100,101}

Alcohol consumption is an established risk factor for cancer, with a clear dose-dependent association.¹⁰² Meta-analyses and population-based cohort studies reveal increased risks for oropharyngeal, esophageal, colorectal, laryngeal, liver, and breast cancers. For example, consuming ≥ 30 g/day of alcohol is associated with a 34% higher risk of cancer incidence, while even light drinking (15-29.9 g/day) increases cancer risk by 10%.¹⁰⁰ Mechanisms underlying these effects include the genotoxic impact of acetaldehyde (an alcohol metabolite), increased estrogen levels, impaired DNA repair, and the production of reactive oxygen species (ROS).¹⁰³

Physical activity. Physical activity is strongly associated with lower risk of CVD, cancer, and related mortality. Engaging in at least 150 minutes of moderate aerobic exercise per week has been linked to a 17% decrease in incident CVD and a 23% reduction in cardiovascular mortality.¹⁰⁴ Conversely, sedentary behavior, such as prolonged sitting, has been linked to an increased risk of CVD.¹⁰⁵ Similarly, in a cohort of nearly 270,000 cancer survivors, maintaining or initiating activity after diagnosis was associated with significantly lower risks of myocardial infarction (subdistribution HR: 0.80; 95% CI: 0.70-0.91) and heart failure (subdistribution HR: 0.84; 95% CI: 0.78-0.90), including among those who became active only after diagnosis.¹⁰⁶

Physical activity also reduces cancer risk and mortality, with a meta-analysis of 1.4 million participants showing lower incidence of cancers such as esophageal, lung, and kidney, independent of BMI.¹⁰⁷ In the UK Biobank cohort of 346,000 participants, higher moderate-to-vigorous physical activity was linked to lower all-cause mortality (HR: 0.87; 95% CI: 0.83-0.91), lower cardiovascular mortality (HR: 0.85; 95% CI: 0.76-0.95), and lower cancer-specific mortality (HR: 0.86; 95% CI: 0.79-0.93).¹⁰⁸ Recently, a phase 3 randomized trial demonstrated that a 3-year structured exercise program following adjuvant chemotherapy for colon cancer significantly improved disease-free survival (HR: 0.72; 95% CI: 0.55-0.94) and overall survival (HR: 0.63; 95% CI: 0.43-0.94) compared with usual care.¹⁰⁹

These protective effects are thought to be mediated by improvements in weight control, reduced adiposity, enhanced autophagy and mitochondrial

function, and reductions in inflammation and carcinogenic hormones.^{110,111}

Environmental shared risk factors. Air pollution is a significant environmental risk factor for CVD and cancer, contributing to 6.7 million global deaths in 2019, including 4.1 million from ambient air pollution and 2.3 million from indoor air pollution.^{112,113} Fine particulate matter <2.5 μm in diameter (PM2.5) is particularly harmful, penetrating deep into the lungs and bloodstream to trigger systemic inflammation, oxidative stress, and endothelial dysfunction.¹¹² These processes accelerate atherogenesis and create a protumorigenic environment through mechanisms such as ROS production and epigenetic modifications.^{114,115}

Epidemiological evidence highlights the link between PM2.5 and increased risks of both CVD and cancer.¹¹² For every 10 μg/m³ rise in PM2.5, cardiovascular mortality increases by up to 45%, while cancer risks, especially lung cancer, are markedly higher in populations exposed to elevated air pollution levels.^{112,116} Low- and middle-income countries and urban areas face disproportionately higher pollution, while minority groups in the United States have greater exposure to traffic-related air pollution, potentially raising their CVD and cancer risks.¹¹²

Beyond air pollution, water and soil contaminants such as agricultural runoff, industrial waste, and heavy metals like mercury and arsenic are also linked to cancer and CVD.¹¹⁷ Additionally, growing evidence links microplastics to cardiovascular and oncologic disease, through mechanisms involving oxidative stress and inflammation.¹¹⁸

SHARED BIOLOGICAL PATHWAYS

Multiple processes highlight the shared biology that links cancer and CVD (Figure 1).

CHRONIC INFLAMMATION AND IMMUNE DYSREGULATION. Chronic inflammation serves as a critical link between CVD and cancer, underpinning their shared pathogenesis through persistent low-grade systemic immune activation.^{34,119} Unlike acute inflammation, which resolves following injury or infection, chronic inflammation persists due to cellular damage, immune dysregulation, and environmental exposures, contributing to both atherosclerosis and carcinogenesis.¹²⁰

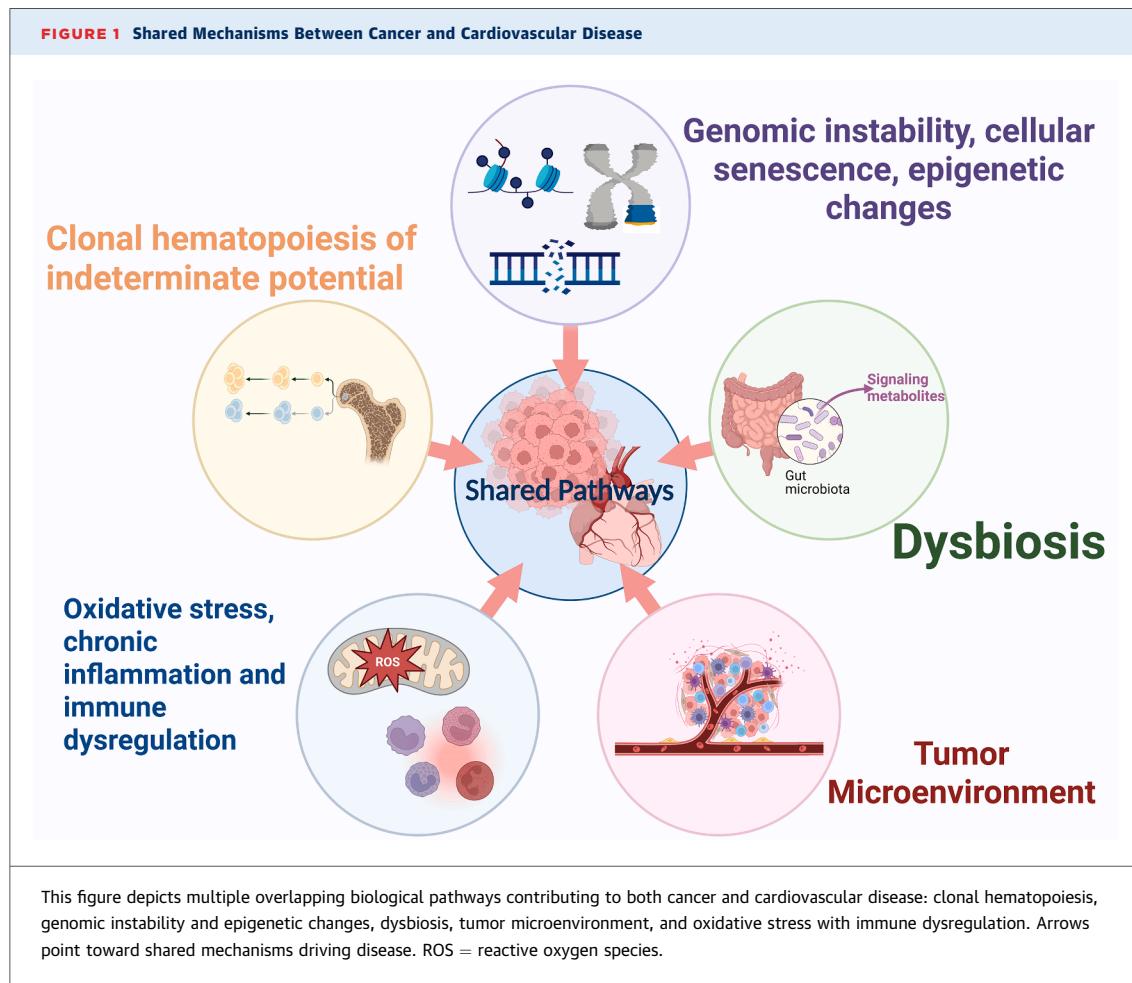
Chronic inflammation drives all stages of atherosclerosis, from initiation to plaque rupture. The NLRP3 inflammasome, a key innate immune sensor that regulates caspase-1 activation and inflammatory cytokine release, triggers the production of IL-1β, IL-6, and IL-18, promoting endothelial dysfunction,

leukocyte adhesion, and foam cell formation.^{121,122} Immune dysregulation, particularly involving macrophages and T cells, exacerbates vascular inflammation and destabilizes atherosclerotic plaques.¹²¹

In cancer, inflammation promotes tumorigenesis through immune suppression within the tumor microenvironment (TME), as well as activation of proinflammatory transcription factors such as nuclear factor κB (Nuclear Factor kappa-light-chain-enhancer of activated B cells) and STAT3 (Signal Transducer and Activator of Transcription 3).¹²³ These pathways have been linked with enhancing cancer cell survival, proliferation, and metastasis.¹²³ Chronic inflammatory conditions induced by infections, such as *Helicobacter pylori* in gastric cancer or human papillomavirus in cervical cancer, further highlight inflammation's role in promoting cancer risk.¹²⁴

Emerging therapies that target inflammation show promise. In COLCOT (Colchicine Cardiovascular Outcomes Trial), low-dose colchicine reduced the risk of major cardiovascular events following myocardial infarction (HR: 0.77; 95% CI, 0.61-0.96; $P = 0.02$).¹²⁵ Likewise, CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study) demonstrated a reduction in recurrent cardiovascular events with canakinumab compared with placebo (HR: 0.85; 95% CI, 0.74-0.98; $P = 0.021$).¹²⁶ The CANTOS trial incidentally showed reduced lung cancer incidence and mortality, prompting oncology-focused trials. In the CANOPY-1 (Study of Efficacy and Safety of Pembrolizumab Plus Platinum-based Doublet Chemotherapy With or Without Canakinumab in Previously Untreated Locally Advanced or Metastatic Non-squamous and Squamous NSCLC Subjects) and CANOPY-2 (Phase III Study Evaluating Efficacy and Safety of Canakinumab in Combination With Docetaxel in Adult Subjects With Non-small Cell Lung Cancers as a Second or Third Line Therapy) trials, there was no cancer survival benefit with canakinumab in patients with advanced non-small cell lung cancer who progressed after platinum-based chemotherapy and immunotherapy.^{127,128} Notably, the CANOPY trials and the earlier CANTOS trial differed substantially in both study populations and clinical endpoints. It remains possible that the antitumor effects of canakinumab, mediated through inflammation modulation, may be more effective if initiated during the asymptomatic or subclinical stages of cancer development.

OXIDATIVE STRESS. Oxidative stress occurs when the production of reactive oxygen species (ROS) overwhelms antioxidant defenses and leads to cellular damage and redox imbalance.¹²⁹ ROS are



generated both endogenously through metabolic reactions and exogenously via exposures like smoking and toxins.¹³⁰ Chronic conditions such as diabetes, hypertension, and obesity further exacerbate oxidative stress, bridging the pathogenesis of CVD and cancer through inflammation.^{12,129}

In CVD, oxidative stress damages macromolecules, shortens telomeres, and disrupts mitochondrial function, driving conditions such as atherosclerosis, cardiac hypertrophy, and ischemia-reperfusion injury.^{12,129} Lipid peroxidation, a consequence of oxidative stress, further exacerbates vascular injury and inflammation, perpetuating the cycle of cardiovascular damage.⁸⁶

Oxidative stress plays a dual role in cancer. While elevated ROS levels promote tumor growth, angiogenesis, and metastasis by driving genomic instability and proliferative signaling, excessive ROS can also trigger apoptosis, autophagy, and necrosis.^{11,131} To maintain this balance, cancer cells

upregulate antioxidant pathways, such as Nrf2, to sustain ROS at protumorigenic levels while avoiding cell death.^{11,131} This unique dependency of cancer cells on ROS has inspired therapeutic strategies to increase ROS to induce cancer cell death selectively.¹³¹

PIGENETIC MODIFICATIONS, GENOMIC INSTABILITY, AND CELLULAR SENESCENCE. Epigenetic changes, including DNA methylation, histone modifications, and noncoding RNA activity, further link cancer and CVD by altering gene expression without modifying the underlying DNA sequence.^{10,132} While broadly involved in aging and chronic disease, specific patterns like tumor suppressor gene silencing in cancer and histone deacetylation in vascular remodeling reflect disease-specific roles.

DNA methylation and histone modification. DNA methylation plays a key role in maintaining genomic integrity and regulates gene expression under normal

conditions. However, its dysregulation contributes unchecked proliferation in cancer and vascular and myocardial injury in CVD. In cancer, hypermethylation silences tumor suppressor genes, a mechanism associated with tumor initiation and oncogenic progression.^{9,10} Hypomethylation can promote tumorigenesis by inducing genomic instability, inflammation, and activation of oncogenes.^{9,10} These two epigenetic alterations may occur independently or simultaneously.

Methylation-dependent cancer germline genes are implicated in multiple oncogenic pathways. For instance, the CG gene Maelstrom (*MAEL*) is upregulated in various malignancies, including breast, lung, colorectal, hepatocellular, bladder, and stomach cancers.¹³³ Mutations in DNA methyltransferase 3 alpha (*DNMT3A*), a key enzyme in de novo methylation, are among the most common genetic alterations in hematologic malignancies such as acute myeloid leukemia, myelodysplastic syndromes, and T cell lymphomas.¹³⁴ *DNMT3A* has emerged as an important therapeutic target, with two hypomethylating agents—5-aza-2'-deoxycytidine (decitabine) and 5-azacitidine (azacitidine)—currently approved for the treatment of myelodysplastic syndrome.¹³⁵ While these agents have improved outcomes in hematologic cancers, they are associated with notable cardiovascular toxicities, including heart failure (3%–11%) and atrial fibrillation (3%–5%).¹³⁶ While the role of DNA methylation in CVD remains under investigation, reduced activity of DNA methyltransferases such as *DNMT3A* has been associated with heart failure, and aberrant methylation patterns have been linked to CAD and vascular calcification.¹⁰

Histone modification, including acetylation, methylation, and phosphorylation, critically shapes chromatin accessibility and gene transcription.¹⁰ Acetylation of histone lysine residues by histone acetyltransferases typically facilitates transcriptional activation by loosening chromatin structure, while histone deacetylases (HDACs) remove these acetyl groups, promoting chromatin compaction and gene repression.⁹ In cancer, overactive histone acetyltransferases can drive oncogene expression, while HDACs promote cell proliferation and survival by inhibiting apoptosis and differentiation, and supporting tumor angiogenesis.⁹ HDAC inhibitors have shown limited success in clinical practice to date, but they remain an active area of investigation.⁹

The balance between histone acetylation and methylation is crucial for vascular remodeling,

contributing to cardiomyocyte hypertrophy and fibrosis.^{10,137,138} HDACs, in particular, have been implicated in the pathogenesis of myocardial fibrosis and heart failure, and HDAC inhibitors are currently being explored for their potential anti-inflammatory and antifibrotic effects in CVD.¹⁰

Noncoding RNA. Noncoding RNAs (ncRNAs) are classified as housekeeping or regulatory, with regulatory ncRNAs further divided into small (eg, small interfering RNAs, microRNAs [miRNAs]) and long ncRNAs.⁹ Tumor-suppressive miRNAs like miR-34 and Let-7 inhibit oncogenes (MYC, MET, RAS) by reducing proliferation and promoting apoptosis but are frequently silenced in lung, colorectal, pancreatic, prostate, and hepatocellular cancers.^{9,139}

Multiple preclinical studies highlight the potential role of miRNAs in CVD, demonstrating their regulation of vascular remodeling, fibrosis, and cardiac function. Proinflammatory miRNAs (eg, miR-92a) may drive atherosclerosis, while others (eg, miR-125b, miR-21a-5p) demonstrate protection in myocardial infarction.¹⁰ Dysregulated miRNAs contribute to plaque formation (miR-33a/b) and cardiac fibrosis (miR-433).^{140,141} In arrhythmia, miR-1 and miR-133a control cardiac conduction, with miR-1 dysregulation linked to atrial and ventricular arrhythmia, and miR-133a downregulation contributing to atrial fibrosis.^{142,143}

Given their disease-specific expression profiles and regulatory functions, miRNAs are being explored as both biomarkers and therapeutic targets in cancer and CVD.¹⁴⁴ Therapeutically, restoration of miR-34a has been explored using MRX34, a liposomal miRNA mimic evaluated in early-phase cancer trials.¹⁴⁴

Cellular senescence and telomere shortening. Cellular senescence, a hallmark of aging and chronic disease, is characterized by irreversible cell-cycle arrest induced by DNA damage, telomere shortening, and oncogene activation.^{119,145} While senescence initially functions as a tumor-suppressive mechanism, it is paradoxically associated with chronic inflammation and tissue dysfunction through the senescence-associated secretory phenotype.^{146,147} The senescence-associated secretory phenotype releases proinflammatory cytokines (eg, IL-6, IL-8), proteases, and growth factors, creating a protumorigenic and proatherogenic environment.^{147,148}

Telomere shortening, commonly observed in aging and senescence, is linked with genomic instability, atherosclerosis, and cancer progression.¹⁴⁹ In CVD, telomere attrition is linked to endothelial dysfunction, increased vascular stiffness, and heart

failure.^{145,150} Conversely, cancer cells may reactivate telomerase to enable unlimited replication.¹⁵¹

CLONAL HEMATOPOIESIS. Somatic mutations accumulate over time in hematopoietic stem cells, leading to clonal expansion of mutated leukocytes in the blood, a process known as clonal hematopoiesis of indeterminate potential (CHIP).^{13,152} CHIP is particularly common in older adults and persons with cancer.^{153,154}

The most frequently mutated driver genes in CHIP are *DNMT3A*, *TET2*, and *ASXL1*, collectively known as “DTA mutations.” These account for approximately 80% of CHIP cases and are associated with a 1.7- to 2.0-fold increased risk of CAD.^{155,156} Additional mutations, such as *JAK2*, are linked to elevated thrombosis risk and a markedly higher risk of CAD (HR: 12.0; 95% CI: 3.8-38.4).¹⁵⁵ CHIP promotes atherosclerosis by enhancing inflammatory macrophage activity; for instance, *TET2* mutations drive overexpression of cytokines like IL-6, IL-1 β , and IL-8, which stimulate leukocyte recruitment and plaque formation.¹⁵⁷ CHIP is also associated with hematologic malignancies, conferring a 0.5% to 1.0% annual risk of progression compared with <0.1% in non-carriers.¹⁵⁸ Moreover, mutations in DNA repair genes such as *PPM1D*, *TP53*, and *ATM* may expand after chemotherapy exposure, amplifying cancer risk.¹⁵⁹

Notably, a recent retrospective cohort study of 1,036 patients with multiple myeloma undergoing hematopoietic cell transplantation found that those with CHIP had a significantly higher 5-year incidence of CVD (21.1% vs 8.4%; $P < 0.001$) and nearly triple the adjusted risk compared with individuals without CHIP.¹⁶⁰ While CHIP-associated inflammation and clonal expansion increase disease burden, targeted therapies are still under investigation.

MICROBIAL DYSBIOSIS. Microbial dysbiosis, or imbalance in gut microbiota, is increasingly linked to both CVD and cancer. In CVD, microbial dysbiosis is primarily associated with increased production of proatherogenic metabolites such as trimethylamine *N*-oxide (TMAO).^{14,161} TMAO is produced from dietary precursors like choline and L-carnitine through microbial metabolism, has been shown to promote atherosclerosis by enhancing platelet hyperreactivity, vascular inflammation, and endothelial dysfunction.^{14,162} Dysbiosis also leads to increased gut permeability, allowing translocation of microbes and their products into systemic circulation, further exacerbating inflammation and contributing to hypertension and heart failure.^{163,164} Reduction in beneficial short-chain fatty acid-producing bacteria,

such as *Faecalibacterium* and *Roseburia*, has been linked to reduced anti-inflammatory effects, worsening cardiovascular outcomes.^{14,164}

In cancer, microbial dysbiosis promotes tumorigenesis through multiple pathways, including chronic inflammation, genotoxic metabolite production, and suppression of immune surveillance.¹⁶⁵ For instance, *Fusobacterium nucleatum*, enriched in colorectal cancer tissues, can activate β -catenin signaling pathways, promoting tumor proliferation and metastasis.¹⁶⁶ Dysbiosis also impacts systemic antitumor immunity by modulating T cell populations, such as regulatory T cells and T helper 17 cells, and by altering the TME.^{167,168} Furthermore, specific microbiota metabolites, such as secondary bile acids and ammonia, have been implicated in DNA damage and cancer progression, especially in gastrointestinal malignancies.¹⁶⁹ Emerging therapies aim to restore microbial balance through probiotics, prebiotics, diet, and fecal microbiota transplantation.^{14,170}

TUMOR MICROENVIRONMENT. The TME, comprising tumor cells, stromal cells, immune cells, and extracellular matrix, plays an important role in the bidirectional relationship between cancer and CVD. Hypoxia within the TME stabilizes hypoxia-inducible factors (HIFs), driving angiogenesis, metabolic reprogramming, and tumor progression, while also contributing to endothelial dysfunction and cardiovascular remodeling.¹⁷¹ HIF activation recruits immunosuppressive cells (eg, regulatory T cells, M2 macrophages), exacerbating tumor growth and impairing vascular repair.¹⁷²

Immune dysregulation in the TME amplifies both cancer and cardiovascular pathology. Tumor-associated macrophages adopt a protumorigenic M2 phenotype, promoting tumor immune evasion and destabilizing atherosclerotic plaques through foam cell formation.¹⁷³⁻¹⁷⁵ Similarly, CD8+ T cells exhibit dysfunction in lipid-rich TMEs, impairing antitumor immunity while exacerbating atherosclerosis via inflammatory cytokine overproduction.^{172,176}

Metabolic reprogramming in the TME has systemic effects, with tumor cells upregulating lipid synthesis and scavenging exogenous lipids, leading to dyslipidemia and ectopic lipid deposition in cardiac tissue.¹⁷² This lipid overflow promotes atherosclerosis and impairs cardiomyocyte energy metabolism, increasing heart failure risk.¹⁷²

Therapeutic strategies targeting TME pathways vary in their stage of development: immune checkpoint modulators (eg, PD-1/PD-L1 blockade) are well

established, HIF-1 α inhibitors are under active investigation, and natural compounds show promise but remain investigational.^{172,177}

CIRCULATING FACTORS. After myocardial injury, cytokines, chemokines, and growth factors support repair but may also promote tumor progression. These circulating factors may link CVD to increased cancer risk. Preclinical models have shown that myocardial infarction, heart failure, and cardiac remodeling can accelerate tumor growth and metastasis, associated with elevated levels of protumorigenic mediators such as serpin A3 and periostin.^{178–182} For instance, Serpin A3 promotes tumor progression in melanoma, glioma, and endometrial cancer and enhances colorectal cancer cell proliferation via AKT pathway activation.^{181,182}

CONCLUSIONS

Cancer and CVD share overlapping epidemiology and mechanistic pathways that call for integrated strategies in prevention and management. This review outlines how common risk factors, including aging, metabolic disease, environmental exposures, and social determinants, converge through biological mechanisms such as chronic inflammation, oxidative stress, epigenetic dysregulation, and clonal hematopoiesis. Recognizing these connections presents opportunities to intervene in ways that may reduce the burden of both diseases simultaneously.

While lifestyle modification remains central to prevention, there is growing evidence that pharmacologic agents such as GLP-1 receptor agonists, SGLT2i, and statins may confer benefits across both

disease spectrums. In addition, emerging areas of investigation such as gut microbiome modulation, targeted therapies for clonal hematopoiesis, and interventions that influence the TME offer promising avenues for future research.

Actionable opportunities already exist in clinical practice. For example, coronary artery calcification incidentally identified on low-dose lung computed tomography scans for cancer screening can be leveraged to stratify cardiovascular risk and initiate preventive therapies.¹⁸³ Similarly, routine oncology encounters can serve as touchpoints for cardiovascular screening and risk management. Continued efforts should focus on developing shared biomarkers of risk, refining prediction models, and embedding cardio-oncology principles into broader public health strategies. Collaborative, multidisciplinary approaches will be essential to reducing the growing impact of cancer and CVD and improving outcomes for affected individuals.

ACKNOWLEDGMENTS All authors have approved this manuscript and this submission. BioRender.com was used in the creation of Figure 1.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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REFERENCES

- Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2024;74(3):229–263.
- Mensah GA, Fuster V, Murray CJL, et al. Global Burden of Cardiovascular Diseases and Risks, 1990–2022. *J Am Coll Cardiol.* 2023;82(25):2350–2473.
- Paterson DI, Wiebe N, Cheung WY, et al. Incident cardiovascular disease among adults with cancer: a population-based cohort study. *JACC CardioOncol.* 2022;4(1):85–94.
- Battisti NML, Welch CA, Sweeting M, et al. Prevalence of cardiovascular disease in patients with potentially curable malignancies: a national registry dataset analysis. *JACC CardioOncol.* 2022;4(2):238–253.
- Guha A, Wang X, Harris RA, et al. Obesity and the bidirectional risk of cancer and cardiovascular diseases in African Americans: disparity vs. ancestry. *Front Cardiovasc Med.* 2021;8:761488. <https://doi.org/10.3389/fcvm.2021.761488>.
- Banks E, Joshy G, Korda RJ, et al. Tobacco smoking and risk of 36 cardiovascular disease subtypes: fatal and nonfatal outcomes in a large prospective Australian study. *BMC Med.* 2019;17(1):128. <https://doi.org/10.1186/S12916-019-1351-4>
- Cohen JB, Geara AS, Hogan JJ, Townsend RR. Hypertension in cancer patients and survivors: epidemiology, diagnosis, and management. *JACC CardioOncol.* 2019;1(2):238–251.
- Ling S, Brown K, Miksza JK, et al. Association of type 2 diabetes with cancer: a meta-analysis with bias analysis for unmeasured confounding in 151 cohorts comprising 32 million people. *Diabetes Care.* 2020;43(9):2313–2322.
- Balamurli G, Liew AQX, Tee WW, Pervaiz S. Interplay between epigenetics, senescence and

- cellular redox metabolism in cancer and its therapeutic implications. *Redox Biol.* 2024;78:103441. <https://doi.org/10.1016/j.redox.2024.103441>
10. Shi Y, Zhang H, Huang S, et al. Epigenetic regulation in cardiovascular disease: mechanisms and advances in clinical trials. *Signal Transduct Target Ther.* 2022;7(1):200. <https://doi.org/10.1038/S41392-022-01055-2>
11. Hayes JD, Dinkova-Kostova AT, Tew KD. Oxidative stress in cancer. *Cancer Cell.* 2020;38(2):167–197.
12. Peoples JN, Saraf A, Ghazal N, Pham TT, Kwong JQ. Mitochondrial dysfunction and oxidative stress in heart disease. *Exp Mol Med.* 2019;51(12):1–13.
13. Calvillo-Argüelles O, Jaiswal S, Shlush LI, et al. Connections between clonal hematopoiesis, cardiovascular disease, and cancer: a review. *JAMA Cardiol.* 2019;4(4):380–387.
14. Witkowski M, Weeks TL, Hazen SL. Gut microbiota and cardiovascular disease. *Circ Res.* 2020;127(4):553–570.
15. Park EM, Chelvanambi M, Bhutiani N, Kroemer G, Zitvogel L, Wargo JA. Targeting the gut and tumor microbiota in cancer. *Nat Med.* 2022;28(4):690–703.
16. Miller KD, Nogueira L, Devasia T, et al. Cancer treatment and survivorship statistics, 2022. *CA Cancer J Clin.* 2022;72(5):409–436.
17. Gao S, Zhu H, Chang X, et al. Cardiovascular death risk in patients with solid tumors: a population-based study in the United States. *Eur J Cancer Prev.* 2025;34(1):11–23.
18. Ng HS, Meng R, Marin TS, et al. Cardiovascular mortality in people with cancer compared with the general population: a systematic review and meta-analysis. *Cancer Med.* 2024;13(15):e70057. <https://doi.org/10.1002/CAM4.70057>
19. Armenian SH, Xu L, Ky B, et al. Cardiovascular disease among survivors of adult-onset cancer: a community-based retrospective cohort study. *J Clin Oncol.* 2016;34(10):1122–1130.
20. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med.* 2006;355(15):1572–1582.
21. Armstrong GT, Liu Q, Yasui Y, et al. Late mortality among 5-year survivors of childhood cancer: a summary from the Childhood Cancer Survivor Study. *J Clin Oncol.* 2009;27(14):2328–2338.
22. Ostenfeld EB, Erichsen R, Pedersen L, Farkas DK, Weiss NS, Sørensen HT. Atrial fibrillation as a marker of occult cancer. *PLoS One.* 2014;9(8):e102861. <https://doi.org/10.1371/JOURNAL.PONE.0102861>
23. Conen D, Wong JA, Sandhu RK, et al. Risk of malignant cancer among women with new-onset atrial fibrillation. *JAMA Cardiol.* 2016;1(4):389–396.
24. Qureshi AI, Malik AA, Saeed O, Adil MM, Rodriguez GJ, Suri MFK. Incident cancer in a cohort of 3,247 cancer diagnosis free ischemic stroke patients. *Cerebrovasc Dis.* 2015;39(5–6):262–268.
25. Slot KB, Berge E, Sandercock P, Lewis SC, Dorman P, Dennis M. Causes of death by level of dependency at 6 months after ischemic stroke in 3 large cohorts. *Stroke.* 2009;40(5):1585–1589.
26. Suzuki M, Tomoike H, Sumiyoshi T, et al. Incidence of cancers in patients with atherosclerotic cardiovascular diseases. *Int J Cardiol Heart Vasc.* 2017;17:11–16.
27. Malmborg M, Christiansen CB, Schmiegelow MD, Torp-Pedersen C, Gislason G, Schou M. Incidence of new onset cancer in patients with a myocardial infarction – a nationwide cohort study. *BMC Cardiovasc Disord.* 2018;18(1):198. <https://doi.org/10.1186/S12872-018-0932-Z>
28. Bell CF, Lei X, Haas A, et al. Risk of cancer after diagnosis of cardiovascular disease. *JACC CardioOncol.* 2023;5(4):431–440.
29. Jaiswal V, Ang SP, Agrawal V, et al. Association between heart failure and the incidence of cancer: a systematic review and meta-analysis. *Eur Heart J Open.* 2023;3(5):399–414.
30. Marijon E, Le Heuzey JY, Connolly S, et al. Causes of death and influencing factors in patients with atrial fibrillation: a competing-risk analysis from the randomized evaluation of long-term anticoagulant therapy study. *Circulation.* 2013;128(20):2192–2201.
31. Vinter N, Christesen AMS, Fenger-Grøn M, Tjønneland A, Frost L. Atrial fibrillation and risk of cancer: a Danish population-based cohort study. *J Am Heart Assoc.* 2018;7(17):e009543. <https://doi.org/10.1161/JAHA.118.009543>
32. Lettino M, Mascherbauer J, Nordaby M, et al. Cardiovascular disease in the elderly: proceedings of the European Society of Cardiology—Cardiovascular Round Table. *Eur J Prev Cardiol.* 2022;29(10):1412–1424.
33. Siegel RL, Kratzer TB, Giaquinto AN, Sung H, Jemal A. Cancer statistics, 2025. *CA Cancer J Clin.* 2025;75(1):10–45.
34. Ioffe D, Bhatia-Patel SC, Gandhi S, Hamad EA, Dotan E. Cardiovascular concerns, cancer treatment, and biological and chronological aging in cancer: JACC Family Series. *JACC CardioOncol.* 2024;6(2):143–158.
35. Argentieri MA, Xiao S, Bennett D, et al. Proteomic aging clock predicts mortality and risk of common age-related diseases in diverse populations. *Nat Med.* 2024;30(9):2450–2460.
36. NOT-OD-15-102. Consideration of Sex as a Biological Variable in NIH-funded Research. Accessed March 21, 2025. <https://grants.nih.gov/grants/guide/notice-files/not-od-15-102.html>
37. Wilcox NS, Rotz SJ, Mullen M, et al. Sex-specific cardiovascular risks of cancer and its therapies. *Circ Res.* 2022;130(4):632–651.
38. Bale TL, Epperson CN. Sex as a biological variable: who, what, when, why, and how. *Neuropsychopharmacology.* 2016;42:386–396.
39. Gauci S, Cartledge S, Redfern J, et al. Biology, bias, or both? The contribution of sex and gender to the disparity in cardiovascular outcomes between women and men. *Curr Atheroscler Rep.* 2022;24(9):701–708.
40. Son H, Zhang D, Shen Y, et al. Social determinants of cardiovascular health: a longitudinal analysis of cardiovascular disease mortality in U.S. counties from 2009 to 2018. *J Am Heart Assoc.* 2023;12(2):e026940. <https://doi.org/10.1161/JAHA.122.026940>
41. Eberly LA, Shultz K, Merino M, et al. Cardiovascular disease burden and outcomes among American Indian and Alaska Native Medicare beneficiaries. *JAMA Netw Open.* 2023;6(9):e2334923. <https://doi.org/10.1001/jamanetworkopen.2023.34923>
42. Coughlin SS, Datta B, Guha A, Wang X, Weintraub NL. Cardiovascular health among cancer survivors. From the 2019 Behavioral Risk Factor Surveillance System Survey. *Am J Cardiol.* 2022;178:142–148.
43. Grines CL, Klein AJ, Bauser-Heaton H, et al. Racial and ethnic disparities in coronary, vascular, structural, and congenital heart disease. *Catheter Cardiovasc Interv.* 2021;98(2):277–294.
44. Vince RA, Jiang R, Merrick B, et al. Evaluation of social determinants of health and prostate cancer outcomes among black and white patients: a systematic review and meta-analysis. *JAMA Netw Open.* 2023;6(1):e2250416. <https://doi.org/10.1001/jamanetworkopen.2022.50416>
45. Tan MC, Stabellini N, Tan JY, et al. Reducing racial and ethnic disparities in cardiovascular outcomes among cancer survivors. *Curr Oncol Rep.* 2024;26(10):1205–1212.
46. Chan JSK, Satti DI, Ching YLA, et al. Associations between social determinants of health and cardiovascular and cancer mortality in cancer survivors: a prospective cohort study. *Eur J Prev Cardiol.* 2025;32(4):336–347.
47. Ganatra S, Dani SS, Kumar A, et al. Impact of social vulnerability on comorbid cancer and cardiovascular disease mortality in the United States. *JACC CardioOncol.* 2022;4(3):326–337.
48. Stabellini N, Cullen J, Bittencourt MS, et al. Allostatic load/chronic stress and cardiovascular outcomes in patients diagnosed with breast, lung, or colorectal cancer. *J Am Heart Assoc.* 2024;13(14):e033295. <https://doi.org/10.1161/JAHA.123.033295>
49. Stabellini N, Cullen J, Bittencourt MS, et al. Allostatic load and cardiovascular outcomes in males with prostate cancer. *JNCI Cancer Spectr.* 2023;7(2):pkad005. <https://doi.org/10.1093/JNCICS/PKAD005>
50. Fuchs FD, Whelton PK. High blood pressure and cardiovascular disease. *Hypertension.* 2020;75(2):285–292.
51. Seretis A, Cividini S, Markozannes G, et al. Association between blood pressure and risk of cancer development: a systematic review and meta-analysis of observational studies. *Sci Rep.* 2019;9(1):8565. <https://doi.org/10.1038/S41598-019-45014-4>
52. Harding JL, Sooriyakumaran M, Anstey KJ, et al. Hypertension, antihypertensive treatment and cancer incidence and mortality: a pooled collaborative analysis of 12 Australian and New Zealand cohorts. *J Hypertens.* 2016;34(1):149–155.
53. Mohammed T, Singh M, Tiu JG, Kim AS. Etiology and management of hypertension in patients

- with cancer. *Cardiooncology*. 2021;7(1):14. <https://doi.org/10.1186/S40959-021-00101-2>
- 54.** Adler A, Agodoa L, Algra A, et al. Pharmacological blood pressure lowering for primary and secondary prevention of cardiovascular disease across different levels of blood pressure: an individual participant-level data meta-analysis. *Lancet*. 2021;397(10285):1625–1636.
- 55.** Kidoguchi S, Sugano N, Yokoo T, et al. Antihypertensive drugs and cancer risk. *Am J Hypertens*. 2022;35(9):767–783.
- 56.** Nakai Y, Isayama H, Ijichi H, et al. Inhibition of renin-angiotensin system affects prognosis of advanced pancreatic cancer receiving gemcitabine. *Br J Cancer*. 2010;103(11):1644–1648.
- 57.** Copland E, Canoy D, Nazarzadeh M, et al. Antihypertensive treatment and risk of cancer: an individual participant data meta-analysis. *Lancet Oncol*. 2021;22(4):558–570.
- 58.** Nazarzadeh M, Copland E, Smith Byrne K, et al. Blood pressure lowering and risk of cancer: individual participant-level data meta-analysis and Mendelian randomization studies. *JACC CardioOncol*. 2025;7(5):609–623.
- 59.** Ritchie RH, Abel ED. Basic mechanisms of diabetic heart disease. *Circ Res*. 2020;126(11):1501–1525.
- 60.** Cai X, Zhang Y, Li M, et al. Association between prediabetes and risk of all cause mortality and cardiovascular disease: updated meta-analysis. *BMJ*. 2020;370:848–849.
- 61.** Wong ND, Sattar N. Cardiovascular risk in diabetes mellitus: epidemiology, assessment and prevention. *Nat Rev Cardiol*. 2023;20(10):685–695.
- 62.** Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. *Diabetes Care*. 2010;33(7):1674–1685.
- 63.** O'Connor L, Bailey-Whyte M, Bhattacharya M, et al. Association of metformin use and cancer incidence: a systematic review and meta-Analysis. *J Natl Cancer Inst*. 2024;116(4):518–529.
- 64.** Hua Y, Zheng Y, Yao Y, Jia R, Ge S, Zhuang A. Metformin and cancer hallmarks: shedding new lights on therapeutic repurposing. *J Transl Med*. 2023;21(1):403. <https://doi.org/10.1186/S12967-023-04263-8>
- 65.** Dabour MS, George MY, Daniel MR, Blaes AH, Zordoky BN. The cardioprotective and anticancer effects of SGLT2 inhibitors: *JACC: CardioOncology State-of-the-Art Review*. *JACC CardioOncol*. 2024;6(2):159–182.
- 66.** Wu JW, Filion KB, Azoulay L, Doll MK, Suissa S. Effect of long-acting insulin analogs on the risk of cancer: a systematic review of observational studies. *Diabetes Care*. 2016;39(3):486–494.
- 67.** Kim MS, Kim WJ, Khera AV, et al. Association between adiposity and cardiovascular outcomes: an umbrella review and meta-analysis of observational and Mendelian randomization studies. *Eur Heart J*. 2021;42(34):3388–3403.
- 68.** Litwin SE. Cardiac remodeling in obesity: time for a new paradigm. *JACC Cardiovasc Imaging*. 2010;3(3):275–277.
- 69.** Wolin KY, Carson K, Colditz GA. Obesity and cancer. *Oncologist*. 2010;15(6):556–565.
- 70.** Chen J, Ke K, Liu Z, et al. Body mass index and cancer risk: an umbrella review of meta-analyses of observational studies. *Nutr Cancer*. 2023;75(4):1051–1064.
- 71.** Petrelli F, Cortellini A, Indini A, et al. Association of obesity with survival outcomes in patients with cancer: a systematic review and meta-analysis. *JAMA Netw Open*. 2021;4(3):e213520. <https://doi.org/10.1001/jamanetworkopen.2021.3520>
- 72.** Yang Z, Lv Y, Yu M, et al. GLP-1 receptor agonist-associated tumor adverse events: a real-world study from 2004 to 2021 based on FAERS. *Front Pharmacol*. 2022;13:925377. <https://doi.org/10.3389/FPHAR.2022.925377/FULL>
- 73.** Cao C, Yang S, Zhou Z. GLP-1 receptor agonists and risk of cancer in type 2 diabetes: an updated meta-analysis of randomized controlled trials. *Endocrine*. 2019;66(2):157–165.
- 74.** Wang L, Xu R, Kaelber DC, Berger NA. Glucagon-like peptide 1 receptor agonists and 13 obesity-associated cancers in patients with type 2 diabetes. *JAMA Netw Open*. 2024;7(7):e2421305. <https://doi.org/10.1001/jamanetworkopen.2024.21305>
- 75.** Lim PW, Stucky CCH, Wasif N, et al. Bariatric surgery and longitudinal cancer risk a review. *JAMA Surg*. 2024;159(3):331–338.
- 76.** Alloubani A, Nimer R, Samara R. Relationship between hyperlipidemia, cardiovascular disease and stroke: a systematic review. *Curr Cardiol Rev*. 2021;17(6):e051121189015. <https://doi.org/10.2174/1573403X1699920120200342>
- 77.** Yuan F, Wen W, Jia G, Long J, Shu XO, Zheng W. Serum lipid profiles and cholesterol-lowering medication use in relation to subsequent risk of colorectal cancer in the UK Biobank cohort. *Cancer Epidemiol Biomarkers Prev*. 2023;32(4):524–530.
- 78.** Nouri M, Mohsenpour MA, Katsiki N, et al. Effect of serum lipid profile on the risk of breast cancer: systematic review and meta-analysis of 1,628,871 women. *J Clin Med*. 2022;11(15):4503. <https://doi.org/10.3390/JCM11154503>
- 79.** Navarese EP, Robinson JG, Kowalewski M, et al. Association between baseline LDL-C level and total and cardiovascular mortality after LDL-C lowering: a systematic review and meta-analysis. *JAMA*. 2018;319(15):1566–1579.
- 80.** Jeong GH, Lee KH, Kim JY, et al. Effect of statin on cancer incidence: an umbrella systematic review and meta-analysis. *J Clin Med*. 2019;8(6):819. <https://doi.org/10.3390/JCM8060819>
- 81.** Oza PP, Kashfi K. The evolving landscape of PCSK9 inhibition in cancer. *Eur J Pharmacol*. 2023;949:175721. <https://doi.org/10.1016/J.EJP.2023.175721>
- 82.** Nowak C, Ärnlöv J. A Mendelian randomization study of the effects of blood lipids on breast cancer risk. *Nat Commun*. 2018;9(1):3957. <https://doi.org/10.1038/S41467-018-06467-9>
- 83.** Ganjali S, Banach M, Pirro M, Fras Z, Sahebkar A. HDL and cancer - causality still needs to be confirmed? Update 2020. *Semin Cancer Biol*. 2021;73:169–177.
- 84.** Caliri AW, Tommasi S, Besaratinia A. Relationships among smoking, oxidative stress, inflammation, macromolecular damage, and cancer. *Mutat Res*. 2021;787:108365. <https://doi.org/10.1016/J.MRREV.2021.108365>
- 85.** Hackshaw A, Morris JK, Boniface S, Tang JL, Milenkov D. Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports. *BMJ*. 2018;360. <https://doi.org/10.1136/BMJ.J5855>
- 86.** Koen RJ, Prizment AE, Blaes A, Konety SH. Shared risk factors in cardiovascular disease and cancer. *Circulation*. 2016;133(11):1104–1114.
- 87.** Islami F, Moreira DM, Boffetta P, Freedland SJ. A systematic review and meta-analysis of tobacco use and prostate cancer mortality and incidence in prospective cohort studies. *Eur Urol*. 2014;66(6):1054–1064.
- 88.** Macacu A, Autier P, Boniol M, Boyle P. Active and passive smoking and risk of breast cancer: a meta-analysis. *Breast Cancer Res Treat*. 2015;154(2):213–224.
- 89.** Larsson SC, Burgess S. Appraising the causal role of smoking in multiple diseases: a systematic review and meta-analysis of Mendelian randomization studies. *EBioMedicine*. 2022;82. <https://doi.org/10.1016/J.EBIO.2022.104154>
- 90.** Cho JH, Shin SY, Kim H, et al. Smoking cessation and incident cardiovascular disease. *JAMA Netw Open*. 2024;7(11):e2442639. <https://doi.org/10.1001/jamanetworkopen.2024.42639>
- 91.** Allaighar M, Althwayee M, Sabah A, et al. Smoking cessation as a preventative measure of cancer: a systematic review. *Int J Med Dev Countries*. 2024;8(1):354–360.
- 92.** Karam G, Agarwal A, Sadeghirad B, et al. Comparison of seven popular structured dietary programmes and risk of mortality and major cardiovascular events in patients at increased cardiovascular risk: systematic review and network meta-analysis. *BMJ*. 2023;380:e072003. <https://doi.org/10.1136/BMJ-2022-072003>
- 93.** Thompson AS, Tresserra-Rimbau A, Karavasiloglou N, et al. Association of healthy plant-based diet adherence with risk of mortality and major chronic diseases among adults in the UK. *JAMA Netw Open*. 2023;6(3):e2344714. <https://doi.org/10.1001/jamanetworkopen.2023.4714>
- 94.** Morze J, Danielewicz A, Przybyłowicz K, Zeng H, Hoffmann G, Schwingschackl L. An updated systematic review and meta-analysis on adherence to mediterranean diet and risk of cancer. *Eur J Nutr*. 2021;60(3):1561–1586.
- 95.** Steck SE, Murphy EA. Dietary patterns and cancer risk. *Nat Rev Cancer*. 2019;20(2):125–138.
- 96.** Miller V, Micha R, Choi E, Karageorgou D, Webb P, Mozaffarian D. Evaluation of the quality of evidence of the association of foods and nutrients with cardiovascular disease and diabetes: a systematic review. *JAMA Netw Open*. 2022;5(2):e46705. <https://doi.org/10.1001/jamanetworkopen.2021.46705>
- 97.** Mansour ST, Ibrahim H, Zhang J, Farag MA. Extraction and analytical approaches for the determination of post-food processing major

- carcinogens: a comprehensive review towards healthier processed food. *Food Chem.* 2025;464:141736. <https://doi.org/10.1016/j.foodchem.2024.141736>
- 98.** Key TJ, Bradbury KE, Perez-Cornago A, Sinha R, Tsilidis KK, Tsugane S. Diet, nutrition, and cancer risk: what do we know and what is the way forward? *BMJ.* 2020;368:m511. <https://doi.org/10.1136/BMJ.M511>
- 99.** Zhao J, Stockwell T, Roemer A, Naimi T, Chikritzhs T. Alcohol consumption and mortality from coronary heart disease: an updated meta-analysis of cohort studies. *J Stud Alcohol Drugs.* 2017;78(3):375–386.
- 100.** Biddinger KJ, Emdin CA, Haas ME, et al. Association of habitual alcohol intake with risk of cardiovascular disease. *JAMA Netw Open.* 2022;5(3):e223849. <https://doi.org/10.1001/jamanetworkopen.2022.3849>
- 101.** Wood AM, Kaptoge S, Butterworth A, et al. Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies. *Lancet.* 2018;391(10129):1513–1523.
- 102.** Yoo JE, Han K, Shin DW, et al. Association between changes in alcohol consumption and cancer risk. *JAMA Netw Open.* 2022;5(8):e2228544. <https://doi.org/10.1001/jamanetworkopen.2022.28544>
- 103.** Bagnardi V, Rota M, Botteri E, et al. Light alcohol drinking and cancer: a meta-analysis. *Ann Oncol.* 2013;24(2):301–308.
- 104.** Wahid A, Manek N, Nichols M, et al. Quantifying the association between physical activity and cardiovascular disease and diabetes: a systematic review and meta-analysis. *J Am Heart Assoc.* 2016;5(9):e002495. <https://doi.org/10.1161/JAHA.115.002495>
- 105.** Bailey DP, Hewson DJ, Champion RB, Sayegh SM. Sitting time and risk of cardiovascular disease and diabetes: a systematic review and meta-analysis. *Am J Prev Med.* 2019;57(3):408–416.
- 106.** Jung W, Cho IY, Jung J, et al. Changes in physical activity and cardiovascular disease risk in cancer survivors: a nationwide cohort study. *JACC CardioOncol.* 2024;6(6):879–889.
- 107.** Moore RA, Adel N, Riedel E, et al. High incidence of thromboembolic events in patients treated with cisplatin-based chemotherapy: a large retrospective analysis. *J Clin Oncol.* 2011;29(25):3466–3473.
- 108.** Ding D, Van Buskirk J, Nguyen B, et al. Physical activity, diet quality and all-cause cardiovascular disease and cancer mortality: a prospective study of 346 627 UK Biobank participants. *Br J Sports Med.* 2022;56(20):1148–1156.
- 109.** Courneya KS, Vardy JL, O'Callaghan CJ, et al. Structured exercise after adjuvant chemotherapy for colon cancer. *N Engl J Med.* 2025;393:13–25.
- 110.** Friedenreich CM, Stone CR, Cheung WY, Hayes SC. Physical activity and mortality in cancer survivors: a systematic review and meta-analysis. *JNCI Cancer Spectr.* 2019;4(1):pkz080. <https://doi.org/10.1093/JNCICS/PKZ080>
- 111.** Wernhart S, Rassaf T. Exercise, cancer, and the cardiovascular system: clinical effects and mechanistic insights. *Basic Res Cardiol.* 2024;120(1):35–55.
- 112.** Zhu W, Al-Kindi SG, Rajagopalan S, Rao X. Air pollution in cardio-oncology and unraveling the environmental nexus: JACC: CardioOncology State-of-the-Art Review. *JACC CardioOncol.* 2024;6(3):347–362.
- 113.** Moloney JN, Cotter TG. ROS signalling in the biology of cancer. *Semin Cell Dev Biol.* 2018;80:50–64.
- 114.** Chen R, Li H, Cai J, et al. Fine particulate air pollution and the expression of microRNAs and circulating cytokines relevant to inflammation, coagulation, and vasoconstriction. *Environ Health Perspect.* 2018;126(1):017007. <https://doi.org/10.1289/EHP1447>
- 115.** Sima M, Rossnerova A, Simova Z, Rossner P. The impact of air pollution exposure on the microRNA machinery and lung cancer development. *J Pers Med.* 2021;11(1):60. <https://doi.org/10.3390/JPM11010060>
- 116.** Cheng I, Yang J, Tseng C, et al. Outdoor ambient air pollution and breast cancer survival among California participants of the Multiethnic Cohort Study. *Environ Int.* 2022;161:107088. <https://doi.org/10.1016/j.envint.2022.107088>
- 117.** Shetty SS, Sonkusare S, Naik PB, Kumari SN, Madhyastha H. Environmental pollutants and their effects on human health. *Helijon.* 2023;9:e19496. <https://doi.org/10.1016/j.heliyon.2023.e19496>
- 118.** Winiarska E, Jutel M, Zemelka-Wiaczek M. The potential impact of nano- and microplastics on human health: understanding human health risks. *Environ Res.* 2024;251(Pt 2):118535. <https://doi.org/10.1016/j.envres.2024.118535>
- 119.** Li X, Li C, Zhang W, Wang Y, Qian P, Huang H. Inflammation and aging: signaling pathways and intervention therapies. *Signal Transduct Target Ther.* 2023;8(1):239. <https://doi.org/10.1038/s41392-023-01502-8>
- 120.** Furman D, Campisi J, Verdin E, et al. Chronic inflammation in the etiology of disease across the life span. *Nat Med.* 2019;25(12):1822–1832.
- 121.** Kong P, Cui ZY, Huang XF, Zhang DD, Guo RJ, Han M. Inflammation and atherosclerosis: signaling pathways and therapeutic intervention. *Signal Transduct Target Ther.* 2022;7(1):131. <https://doi.org/10.1038/S41392-022-00955-7>
- 122.** Soehnlein O, Libby P. Targeting inflammation in atherosclerosis - from experimental insights to the clinic. *Nat Rev Drug Discov.* 2021;20(8):589–610.
- 123.** Zhao H, Wu L, Yan G, et al. Inflammation and tumor progression: signaling pathways and targeted intervention. *Signal Transduct Target Ther.* 2021;6(1):263. <https://doi.org/10.1038/S41392-021-00658-5>
- 124.** Kamp DW, Shacter E, Weitzman SA. Chronic inflammation and cancer: the role of the mitochondria. *Oncology (Williston Park).* 2011;25(5):400–410, 413.
- 125.** Tardif JC, Kouz S, Waters DD, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. *N Engl J Med.* 2019;381(26):2497–2505.
- 126.** Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med.* 2017;377(12):1119–1131. <https://doi.org/10.1056/NEJMoa1707914>
- 127.** Tan DSW, Felip E, de Castro G, et al. Canakinumab versus placebo in combination with first-line pembrolizumab plus chemotherapy for advanced non-small-cell lung cancer: results from the CANOPY-1 trial. *J Clin Oncol.* 2024;42(2):192–204.
- 128.** Paz-Ares L, Goto Y, Wan-Teck Lim D, et al. Canakinumab in combination with docetaxel compared with docetaxel alone for the treatment of advanced non-small cell lung cancer following platinum-based doublet chemotherapy and immunotherapy (CANOPY-2): a multicenter, randomized, double-blind, phase 3 trial. *Lung Cancer.* 2024;189:107451. <https://doi.org/10.1016/j.lungcan.2023.107451>
- 129.** Forman HJ, Zhang H. Targeting oxidative stress in disease: promise and limitations of antioxidant therapy. *Nat Rev Drug Discov.* 2021;20(9):689–709.
- 130.** Thanan R, Oikawa S, Hiraku Y, et al. Oxidative stress and its significant roles in neurodegenerative diseases and cancer. *Int J Mol Sci.* 2014;16(1):193–217.
- 131.** Perillo B, Di Donato M, Pezone A, et al. ROS in cancer therapy: the bright side of the moon. *Exp Mol Med.* 2020;52(2):192–203.
- 132.** Yen CY, Huang HW, Shu CW, et al. DNA methylation, histone acetylation and methylation of epigenetic modifications as a therapeutic approach for cancers. *Cancer Lett.* 2016;373(2):185–192.
- 133.** Tao J, Cui J, Xu Y, et al. MAEL in human cancers and implications in prognosis and predicting benefit from immunotherapy over VEGFR/mTOR inhibitors in clear cell renal cell carcinoma: a bioinformatic analysis. *Aging (Albany NY).* 2024;16(3):2090–2122.
- 134.** Chen BF, Chan WY. The de novo DNA methyltransferase DNMT3A in development and cancer. *Epigenetics.* 2014;9(5):669. <https://doi.org/10.4161/EPI.28324>
- 135.** Stomper J, Rotondo JC, Greve G, Lübbert M. Hypomethylating agents (HMA) for the treatment of acute myeloid leukemia and myelodysplastic syndromes: mechanisms of resistance and novel HMA-based therapies. *Leukemia.* 2021;35(7):1873–1889.
- 136.** Johnson IM, Bezerra ED, Farrukh F, et al. Cardiac events in patients with acute myeloid leukemia treated with venetoclax combined with

- hypomethylating agents. *Blood Adv.* 2022;6(17):5227-5231.
- 137.** Yoon S, Kook T, Min HK, et al. PP2A negatively regulates the hypertrophic response by dephosphorylating HDAC2 S394 in the heart. *Exp Mol Med.* 2018;50(7):1-14.
- 138.** Leng Y, Wu Y, Lei S, et al. Inhibition of HDAC6 activity alleviates myocardial ischemia/reperfusion injury in diabetic rats: potential role of peroxiredoxin 1 acetylation and redox regulation. *Oxid Med Cell Longev.* 2018;2018:9494052. <https://doi.org/10.1155/2018/9494052>
- 139.** Zhang L, Liao Y, Tang L. MicroRNA-34 family: a potential tumor suppressor and therapeutic candidate in cancer. *J Exp Clin Cancer Res.* 2019;38(1):53. <https://doi.org/10.1186/S13046-019-1059-5>
- 140.** Rayner KJ, Esau CC, Hussain FN, et al. Inhibition of miR-33a/b in non-human primates raises plasma HDL and lowers VLDL triglycerides. *Nature.* 2011;478(7369):404-407.
- 141.** Ni H, Li W, Zhuge Y, et al. Inhibition of circHIPK3 prevents angiotensin II-induced cardiac fibrosis by sponging miR-29b-3p. *Int J Cardiol.* 2019;292:188-196.
- 142.** Zhu Y, Pan W, Yang T, et al. Upregulation of circular RNA CircNFIB attenuates cardiac fibrosis by sponging miR-433. *Front Genet.* 2019;10:564. <https://doi.org/10.3389/FGENE.2019.00564>
- 143.** Li M, Ding W, Tariq MA, et al. A circular transcript of ncx1 gene mediates ischemic myocardial injury by targeting miR-133a-3p. *Theranostics.* 2018;8(21):5855-5869.
- 144.** Kim T, Croce CM. MicroRNA: trends in clinical trials of cancer diagnosis and therapy strategies. *Exp Mol Med.* 2023;55(7):1314-1321.
- 145.** Abdellatif M, Rainer PP, Sedej S, Kroemer G. Hallmarks of cardiovascular ageing. *Nat Rev Cardiol.* 2023;20(11):754-777.
- 146.** Coppé JP, Patil CK, Rodier F, et al. Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. *PLoS Biol.* 2008;6(12):2853-2868.
- 147.** Coussens LM, Werb Z. Inflammation and cancer. *Nature.* 2002;420(6917):860-867.
- 148.** Aird KM, Iwasaki O, Kossenkov AV, et al. HMGB2 orchestrates the chromatin landscape of senescence-associated secretory phenotype gene loci. *J Cell Biol.* 2016;215(3):325-334.
- 149.** Anun JR, Cho WC, Søreide K. The biology of aging and cancer: a brief overview of shared and divergent molecular hallmarks. *Aging Dis.* 2017;8(5):628-642.
- 150.** Luo Y, Ma J, Lu W. The significance of mitochondrial dysfunction in cancer. *Int J Mol Sci.* 2020;21(16):1-24.
- 151.** Saretzki G. Telomeres, telomerase and ageing. *Subcell Biochem.* 2018;90:221-308.
- 152.** Yura Y, Cochran JD, Walsh K. Therapy-related clonal hematopoiesis: a new link between cancer and cardiovascular disease. *Heart Fail Clin.* 2022;18(3):349-359.
- 153.** Fuster JJ. Clonal hematopoiesis and cardiovascular disease in cancer patients and survivors. *Thromb Res.* 2022;213(Suppl 1):S107-S112.
- 154.** Karlstaedt A, Moslehi J, de Boer RA. Cardio-onco-metabolism: metabolic remodelling in cardiovascular disease and cancer. *Nat Rev Cardiol.* 2022;19(6):414-425.
- 155.** Jaiswal S, Natarajan P, Silver AJ, et al. Clonal hematopoiesis and risk of atherosclerotic cardiovascular disease. *N Engl J Med.* 2017;377(2):111-121.
- 156.** Marnell CS, Bick A, Natarajan P. Clonal hematopoiesis of indeterminate potential (CHIP): Linking somatic mutations, hematopoiesis, chronic inflammation and cardiovascular disease. *J Mol Cell Cardiol.* 2021;161:98-105.
- 157.** Jaiswal S, Ebert BL. Clonal hematopoiesis in human aging and disease. *Science.* 2019;366(6465):eaan4673. <https://doi.org/10.1126/science.aan4673>
- 158.** Jaiswal S, Fontanillas P, Flannick J, et al. Age-related clonal hematopoiesis associated with adverse outcomes. *N Engl J Med.* 2014;371(26):2488-2498.
- 159.** Coombs CC, Zehir A, Devlin SM, et al. Therapy-related clonal hematopoiesis in patients with non-hematologic cancers is common and associated with adverse clinical outcomes. *Cell Stem Cell.* 2017;21(3):374-382.e4.
- 160.** Rhee JW, Pillai R, He T, et al. Clonal hematopoiesis and cardiovascular disease in patients with multiple myeloma undergoing hematopoietic cell transplant. *JAMA Cardiol.* 2024;9(1):16-24.
- 161.** Chakroun RM, Olsson LM, Bäckhed F. The potential of tailoring the gut microbiome to prevent and treat cardiometabolic disease. *Nat Rev Cardiol.* 2023;20(4):217-235.
- 162.** Zhu Y, Li Q, Jiang H. Gut microbiota in atherosclerosis: focus on trimethylamine N-oxide. *APMIS.* 2020;128(5):353-366.
- 163.** Jain A, Li XH, Chen WN. An untargeted fecal and urine metabolomics analysis of the interplay between the gut microbiome, diet and human metabolism in Indian and Chinese adults. *Sci Rep.* 2019;9(1):9191. <https://doi.org/10.1038/S41598-019-45640-Y>
- 164.** Toubal A, Kifayat B, Beaudoin L, et al. Mucosal-associated invariant T cells promote inflammation and intestinal dysbiosis leading to metabolic dysfunction during obesity. *Nat Commun.* 2020;11(1):3755. <https://doi.org/10.1038/S41467-020-17307-0>
- 165.** Rahman MM, Islam MR, Shohag S, et al. Microbiome in cancer: Role in carcinogenesis and impact in therapeutic strategies. *Biomed Pharmacother.* 2022;149:112898. <https://doi.org/10.1016/J.BIOPHA.2022.112898>
- 166.** Wong CC, Yu J. Gut microbiota in colorectal cancer development and therapy. *Nat Rev Clin Oncol.* 2023;20(7):429-452.
- 167.** Mima K, Sukawa Y, Nishihara R, et al. Fusobacterium nucleatum and T cells in colorectal carcinoma. *JAMA Oncol.* 2015;1(5):653-661.
- 168.** Seely KD, Morgan AD, Hagenstein LD, Florey GM, Small JM. Bacterial involvement in progression and metastasis of colorectal neoplasia. *Cancers (Basel).* 2022;14(4):1019. <https://doi.org/10.3390/CANCERS14041019>
- 169.** Sadrekarimi H, Gardanova ZR, Bakhshis M, et al. Emerging role of human microbiome in cancer development and response to therapy: special focus on intestinal microflora. *J Transl Med.* 2022;20(1):301. <https://doi.org/10.1186/S12967-022-03492-7>
- 170.** Zhao LY, Mei JX, Yu G, et al. Role of the gut microbiota in anticancer therapy: from molecular mechanisms to clinical applications. *Signal Transduct Target Ther.* 2023;8(1):201. <https://doi.org/10.1038/S41392-023-01406-7>
- 171.** Chen Z, Han F, Du Y, Shi H, Zhou W. Hypoxic microenvironment in cancer: molecular mechanisms and therapeutic interventions. *Signal Transduct Target Ther.* 2023;8(1):70. <https://doi.org/10.1038/S41392-023-01332-8>
- 172.** Zhu G, Cao L, Wu J, et al. Co-morbid intersections of cancer and cardiovascular disease and targets for natural drug action: reprogramming of lipid metabolism. *Biomed Pharmacother.* 2024;176:116875. <https://doi.org/10.1016/J.BIOPHA.2024.116875>
- 173.** Wang J, Mi S, Ding M, Li X, Yuan S. Metabolism and polarization regulation of macrophages in the tumor microenvironment. *Cancer Lett.* 2022;543:215766. <https://doi.org/10.1016/J.CANLET.2022.215766>
- 174.** Shi SZ, Lee EJ, Lin YJ, et al. Recruitment of monocytes and epigenetic silencing of intratumoral CYP7B1 primarily contribute to the accumulation of 27-hydroxycholesterol in breast cancer. *Am J Cancer Res.* 2019;9(10):2194.
- 175.** Goossens P, Rodriguez-Vita J, Etzerodt A, et al. Membrane cholesterol efflux drives tumor-associated macrophage reprogramming and tumor progression. *Cell Metab.* 2019;29(6):1376-1389.e4.
- 176.** Ma X, Xiao L, Liu L, et al. CD36-mediated ferroptosis dampens intratumoral CD8+ T cell effector function and impairs their antitumor ability. *Cell Metab.* 2021;33(5):1001-1012.e5.
- 177.** Babar Q, Saeed A, Tabish TA, Sarwar M, Thorat ND. Targeting the tumor microenvironment: potential strategy for cancer therapeutics. *Biochim Biophys Acta Mol Basis Dis.* 2023;1869(6):166746. <https://doi.org/10.1016/J.BBADIS.2023.166746>
- 178.** Abraham S, Abu-Sharki S, Shofti R, et al. Early cardiac remodeling promotes tumor growth and metastasis. *Circulation.* 2020;142(7):670-683.
- 179.** Awwad L, Aronheim A. Cardiac dysfunction promotes cancer progression via multiple secreted factors. *Cancer Res.* 2022;82(9):1753-1761.

- 180.** Dorafshan S, Razmi M, Safaei S, Gentilin E, Madjd Z, Ghods R. Periostin: biology and function in cancer. *Cancer Cell Int*. 2022;22(1):315. <https://doi.org/10.1186/S12935-022-02714-8>
- 181.** Meijers WC, Maglione M, Bakker SJL, et al. Heart failure stimulates tumor growth by circulating factors. *Circulation*. 2018;138(7):678-691.
- 182.** Delrue L, Vanderheyden M, Beles M, et al. Circulating SERPINA3 improves prognostic stratification in patients with a de novo or worsened heart failure. *ESC Heart Fail*. 2021;8(6):4780-4790.
- 183.** Al-Antary N, Hirko KA, Cassidy-Bushrow AE, et al. Coronary artery calcification identified on lung cancer screening CT scans: a scoping review. *Chest*. Published online April 18, 2025. <https://doi.org/10.1016/J.CHEST.2025.03.031>

KEY WORDS bidirectional, cancer, cardiovascular disease, epigenetics, pathways, reverse cardio-oncology, risk factors, mechanisms

APPENDIX For an expanded Methods section, please see the online version of this paper.