

REVIEW

Heart of the matter: Neutrophils, cancer, and cardiovascular disease

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Cancer and cardiovascular disease together are leading causes of death worldwide, and cancer patients display an abnormally elevated burden of cardiovascular disease. Neutrophils—key immune cells known primarily by their roles in inflammation and infection—can link these two pathological conditions. Neutrophils contribute to cancer progression and cardiovascular complications through various mechanisms, including their ability to promote inflammation, thrombosis, and vascular damage by interacting with vascular endothelial cells, platelets, and other immune cells, or by forming NETs. In cancer, neutrophils contribute to a hypercoagulability state, which promotes tumor growth and metastasis, and can also lead to thrombotic events, myocardial infarction, and stroke. Cancer affects neutrophil numbers and functional properties, induces the appearance of several neutrophil subtypes, and can alter hematopoiesis. Here we summarize the links between cancer and cardiovascular disease, focusing on the role of neutrophils and cancer-elicited changes to their function in connecting these two disease states and highlighting the neutrophils' dynamic interaction with both diseases.

Introduction

Cancer and cardiovascular disease (CVD) are the second and first causes of death, respectively (Heron, 2021). Many risk factors are shared between the two, including smoking, obesity, low physical activity, high-fat diet, chronic inflammation, hypertension, or clonal hematopoiesis (CH) (Handy et al., 2018), and numerous clinical reports show a correlation between cancer and CVD. For instance, lung cancer patients have a 90% increase in the risk of coronary artery disease and over a 66% increased risk of overall CVD compared with the general population (Kravchenko et al., 2015; Yuan and Li, 2018). Acute cardiovascular events are, thus, common drivers of cancer patient mortality (Boire et al., 2024).

Cancer treatment is a prime suspect for the disproportionate burden of CVD in cancer patients. Stemming from seminal studies on the cardiotoxic effect of anthracyclines (Von Hoff et al., 1979), many different approaches used for cancer therapy have now been shown to be detrimental for the cardiovascular system (Chung et al., 2018; De Keulenaer et al., 2010; Jaworski et al., 2013; Cheng and Force, 2010), leading to the establishment of a new cardio-oncology discipline and practice (Cubbon and Lyon, 2016; Pareek et al., 2018). Importantly, however, treatment-naïve cancer patients are also at higher risk of CVD compared with the general population (Bradshaw et al., 2016; Cramer et al., 2014; Pavo et al., 2015), suggesting that treatment-independent effects are also at play. These treatment-

independent effects are related to cancer-imposed changes to its host macroenvironment. Of those, changes to the immune compartment are well documented (Hiam-Galvez et al., 2021) and likely to contribute to cancer-driven CVD.

Neutrophils are the first line of defense of the organism, can rapidly migrate to inflamed sites, and exert several effector functions to deal with tissue injury. These effector functions include phagocytosis, production of high amounts of ROS, release of the cytotoxic content of their granules (Borregaard et al., 2007), or neutrophil extracellular trap (NETs) formation (Brinkmann et al., 2004; Papayannopoulos, 2018; Hidalgo et al., 2022). Neutrophils are prominently involved in CVD (Haumer et al., 2005; Shah et al., 2017; Silvestre-Roig et al., 2020; Luo et al., 2023; Morrissey et al., 2025). Their transcriptional profile and function can be modulated in the steady state by cell-intrinsic, systemic, or tissue-specific cues (Adrover et al., 2019; Casanova-Acebes et al., 2018; Ballesteros et al., 2020; Adrover et al., 2020), as well as by disease states. Cancer, in particular, significantly influences neutrophil properties, with both pro-tumorigenic and anti-tumorigenic neutrophil subpopulations described in different cancer contexts (Ng et al., 2025).

Traditionally, cancer research has focused on genetic alterations of the cancerous cells themselves, only to later acknowledge the critical role of the microenvironment where these cells reside (Koliarakis et al., 2020). Current research, however, has begun to pay more attention to the whole-body

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“macroenvironment” (Swanton et al., 2024; Rabas et al., 2024), as cancer cells induce not only local but also distant changes to their host.

The realization that cancer elicits global changes to the host is not new; in the 19th century, Armand Trousseau established that cancer patients are at heightened risk of thrombosis and that thromboembolic disease in an otherwise healthy individual was, with a substantial likelihood, secondary to an occult malignancy (Silverstein and Nachman, 1992). Since then, many observations suggest that cancer is a systemic disease and that the tumor macroenvironment is a key driver of cancer progression.

Although tumor immunologists have classically focused on the local immune response at the tumor site, the immune system is deeply coordinated across whole-body physiology. Inflammation is a hallmark of cancer, and the immune system is the system that is most directly and profoundly affected by it (Coussens and Werb, 2002). Many immune system compartments, both adaptive and innate, are affected by growing tumors (Allen et al., 2020): immature monocytes are released early into the circulation and can become immunosuppressive, while dendritic cells, which are key orchestrators of adaptive immunity (Cabeza-Cabrerizo et al., 2021), are reduced in number and defective in many human cancers and mouse models (Almand et al., 2001; Bella et al., 2003; Tabarkiewicz et al., 2008; Lin et al., 2020). Macrophages acquire anti-inflammatory programs, and many of their functions are co-opted by growing tumors (Kloosterman and Akkari, 2023), and natural killer cells are progressively dysfunctional during cancer progression (Mamessier et al., 2011). A reduced number of T cells is a common phenomenon in several types of cancer (Ray-Coquard et al., 2009), and the remaining cells can show a reduced TCR repertoire, which is associated with reduced anti-tumor activity (Manuel et al., 2012; Liu et al., 2019b). Interestingly, the number of regulatory T cells (Liyanage et al., 2002; Wolf et al., 2003) and regulatory B cells (Murakami et al., 2019) is increased in cancer patients. Thus, while the rest of this review will focus on neutrophils, cancer affects the immune system profoundly and systemically beyond the local microenvironment.

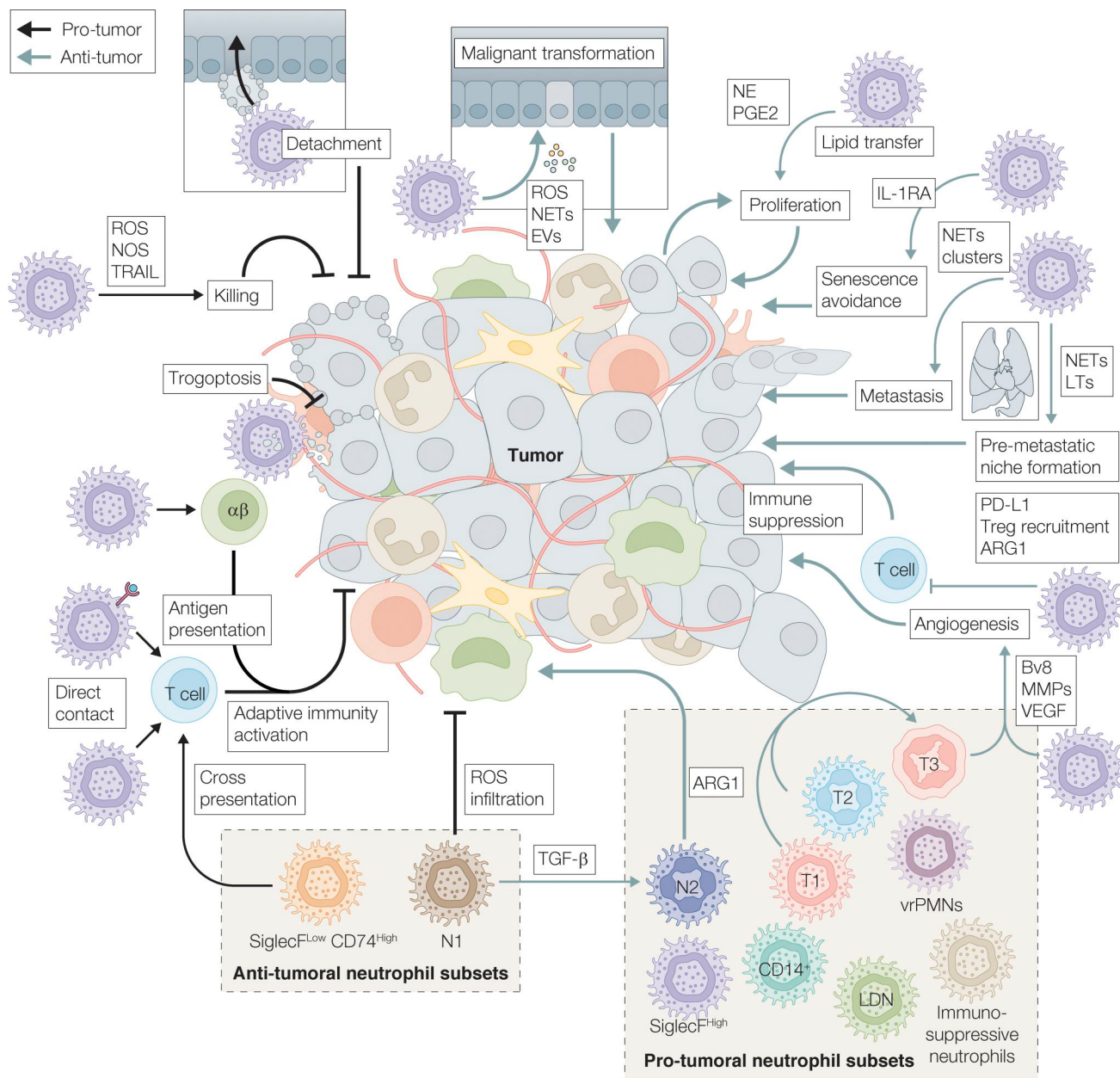
Neutrophils in cancer

Neutrophils are vastly affected by cancer (Quail et al., 2022; Maas et al., 2023; Adrover et al., 2023; Ng et al., 2025) and represent the most adverse prognostic cell type in pan-cancer studies (Gentles et al., 2015; Templeton et al., 2014). Neutrophils originate from hematopoietic stem cells in the bone marrow, through common myeloid progenitors, granulocyte-monocyte progenitors, and recently described unipotent neutrophil progenitors (Zhu et al., 2018; Kwok et al., 2020; Evrard et al., 2018). Neutrophil production is controlled by an array of transcription factors (Lawrence et al., 2018), including purine-rich box 1 (PU.1), CCAAT/enhancer-binding protein alpha, beta, and epsilon (C/EBP α , C/EBP β , and C/EBP ϵ), growth factor independent 1 (Gfi-1), and GATA-binding factor 1 (GATA-1). Before exiting to the bloodstream, neutrophils spend up to 6 days in the bone marrow (Dancey et al., 1976) under control of antagonistic chemokine signaling between the pro-mobilizing CXC motif chemokine receptor 2 (CXCR2) and the pro-retention CXC motif

chemokine receptor 4 (CXCR4) (Eash et al., 2010; Martin et al., 2003).

Neutrophils are short-lived (Dancey et al., 1976; Hidalgo et al., 2019; Adrover et al., 2019, 2020), but at the same time, they are the most abundant immune cell in the human circulation. Not surprisingly, the hematopoietic system devotes two-thirds of its resources just to replenish neutrophils (Borregaard, 2010), and this has been estimated to involve the production of $\sim 2 \times 10^{11}$ neutrophils each day (Kolaczowska and Kubes, 2013; Scheiermann et al., 2015). Many factors that regulate neutrophil life cycle are highly expressed by tumors, causing a dysregulation of neutrophil maturation, lifespan, and effector functions in cancer (Adrover et al., 2023). One such process altered in cancer is the rate of neutrophil production in the bone marrow compartment. Cancer patients display a myeloid skew of hematopoiesis and harbor an increased number of granulocyte-monocyte progenitors (Wu et al., 2014). The same is true for preclinical breast, skin, and pancreatic cancer models (Casbon et al., 2015; Khaled et al., 2014; Kamran et al., 2018). This drives a systemic alteration of neutrophil function, contributing to tumor progression and cancer-associated thrombosis (Demers et al., 2012). Hematopoietic progenitor cells can sense and respond to peripheral inflammation cues (Chavakis et al., 2019), and, in cancer, factors produced by a variety of cells have been proposed to drive hematopoietic adaptation, including granulocyte CSF (G-CSF) (Casbon et al., 2015), GM-CSF (Almand et al., 2001; Morales et al., 2010), IL-17 (Coffelt et al., 2015), IL-8 (Dominguez et al., 2017), TNF α (Al Sayed et al., 2019), IL-1 β (Aggen et al., 2021), Receptor for advanced glycation endproducts (Engblom et al., 2017), and cancer cell-derived exosomes (Peinado et al., 2012). How all these pieces coordinate is still unclear but, nonetheless, the altered hematopoietic output leads to changes in the lymphoid/myeloid ratio, and together with the effect of various other cancer cell- or tumor stromal cell-produced mediators (a prime example of which is TGF- β [Fridlender et al., 2009]), ultimately lead to the appearance of distinct neutrophil subpopulations either systemically or within the tumor microenvironment (TME).

Cancer-associated neutrophils exhibit a dual nature, capable of both inhibiting and promoting tumor growth and metastasis. This duality stems from their plasticity and responsiveness to environmental cues systemically and within the TME (Baghban et al., 2020). The TME is a local inflammatory microenvironment comprising tumor cells, immune cells, endothelial and stromal cells, as well as extracellular matrix components that support tumor initiation, development, and metastasis (De Visser and Joyce, 2023). Neutrophils are now considered to be one of the major participants of the TME and have been shown to make up a substantial proportion of the immune infiltrate in a wide variety of cancer types, including non-small cell lung cancer (Rakaee et al., 2016), renal cell carcinoma (Jensen et al., 2009), colorectal cancer (Rao et al., 2012), breast cancer (Lotfinejad et al., 2020), melanoma (Jensen et al., 2012), and hepatocellular carcinoma (Li et al., 2011). These tumor-associated neutrophils are typically associated with poor prognosis (Shen et al., 2014; Gentles et al., 2015), but subpopulations



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Figure 1. Neutrophils in cancer. Neutrophils show both anti-tumoral (green lines) and pro-tumoral (red lines) properties that affect tumor progression in opposite ways. Identified pro-tumoral and anti-tumoral neutrophil subsets are highlighted in the respective colored boxes. TRAIL, TNF-related apoptosis-inducing ligand; VEGF, vascular endothelial growth factor; NE, neutrophil elastase.

with both pro- and anti-tumor functions have been described and are outlined below.

The apparent conundrum of pro- and anti-tumoral neutrophil states (Fig. 1) may stem from the different ways in which various cancer types affect neutrophil biology and respond to neutrophil-driven signals. Indeed, neutrophils are not a homogeneous population, as once assumed, and many studies have highlighted that neutrophils, despite their short lifespan, can differentiate into different subpopulations that exert diverse functions (Hedrick and Malanchi, 2022; Yu et al., 2024; Ballesteros et al., 2020; Adrover et al., 2019; Casanova-Acebes

et al., 2018; Nicolás-Ávila et al., 2017). A recent example is that neutrophils gain a matrix-producing phenotype upon TGF- β stimulation and are able to actively deposit collagen fibers (Vicanolo et al., 2025). Studies in the last decade have started to unravel this neutrophil heterogeneity and have led to new frameworks for neutrophil adaptation (Ng et al., 2019, 2025).

Early reports showed that neutrophils can adapt and change in the TME and proposed a skew from an anti-tumorigenic “N1” to a pro-tumorigenic “N2” phenotype of neutrophils driven by TGF- β signaling in cancer (Fridlender et al., 2009). N1 neutrophils enhance cytotoxic T cell recruitment and activation by

secreting chemokines (e.g., CXCL9 and CXCL10) and cytokines (e.g., IL-12, TNF α , and GM-CSF) (Fridlender et al., 2009). Conversely, N2 neutrophils suppress cytotoxic T cells and recruit regulatory T cells, leading to immune tolerance and tumor progression (Mishalian et al., 2014).

Other reports indicated that neutrophils change systemically as well as within the TME with cancer progression, with a systemic accumulation of immunosuppressive neutrophils (Sagiv et al., 2015). Cytokines like G-CSF and IL-6 modulate neutrophil phenotypes in the bone marrow, driving pro-tumoral neutrophil behaviors (Yan et al., 2013). Furthermore, we have recently shown that cancer can remotely affect the bone marrow to induce a myeloid skew of hematopoiesis and induce the appearance of a subpopulation of vascular-restricted neutrophils (vrPMNs). vrPMNs do not extravasate toward inflammatory insults but are highly reactive inside the vasculature, form NETs more efficiently, and interact more with platelets. We show that neutrophils block the blood flow in the tumor vasculature in a NET-dependent manner, causing tumor necrosis, which in turn enhances metastatic spread (Adrover et al., 2025).

Neutrophil phenotypes also seem to change in the TME, where a population of CD14⁺-immunosuppressive neutrophils was identified (Veglia et al., 2021). A population of Siglec^F^{High} neutrophils stemming from tumor-induced changes to the marrow stromal compartment was also found to show pro-tumorigenic properties (Engblom et al., 2017). Conversely, a population of Siglec^F^{Low} CD74^{High} neutrophils has recently been proposed to be able to cross-present antigen (Tang et al., 2024) and have anti-tumorigenic functions. Neutrophils have been proposed to gain APC capability through several mechanisms: cytokines, such as GM-CSF (Matsushima et al., 2013) can induce the expression of MHC-II, CD80, and CD86 by neutrophils and stimulate lymphocyte proliferation (Hampton et al., 2015), and upon direct contact with T cells (Abi Abdallah et al., 2011). Nonetheless, the precise mechanisms of antigen processing by neutrophils and their functional relevance in cancer or CVD are still poorly understood.

Another recent study found three distinct intratumoral neutrophil states: T1 (immature), T2 (mature), and T3 (dcTRAIL-R1⁺), which were different from blood, bone marrow or splenic neutrophils and showed a deterministic path of differentiation from T1/T2 to T3 state in several tumor models (Ng et al., 2024). This work suggested that neutrophils, regardless of their maturation state, can reach a definite state in the TME (T3), which was associated with an increased lifespan and with hypoxic and glycolytic niches within the context of pancreatic ductal adenocarcinoma tumors, where they were pro-angiogenic.

Most of the reports of neutrophil function in cancer show them promoting tumor initiation, progression, and metastatic spread. For instance, neutrophils can elicit malignant transformation by inducing DNA damage through ROS (Weitzman and Stossel, 1981; Weitberg et al., 1983; Weitzman et al., 1985; Canli et al., 2017; Wculek et al., 2020) or by producing pro-inflammatory microRNA-bearing microparticles (Butin-Israeli et al., 2019). They also promote tumor progression by releasing different mediators, including prostaglandin E2 (PGE2) to promote cancer cell proliferation (Antonio et al., 2015), IL-1 receptor

antagonist (IL-1RA) that protects prostate cancer cells from senescence (Di Mitri et al., 2014), matrix metalloproteinase-9 (MMP-9) to activate vascular endothelial growth factor (Nozawa et al., 2006; Deryugina et al., 2014), prokineticin-2 (Bv8) to promote angiogenesis (Shojaei et al., 2007), or neutrophil elastase, which degrades insulin receptor substrate 1 (IRS-1) and induces cancer cell proliferation (Houghton et al., 2010). Neutrophils can also directly provide lipids to cancer cells to fuel cancer cell proliferation (Li et al., 2020).

Neutrophils contribute to immune suppression by several mechanisms, including suppressing T cell function through expression of programmed cell death ligand 1 (PD-L1) (He et al., 2015; Wang et al., 2017), direct physical contact (Thewissen et al., 2011), suppressing IL-17⁺ $\gamma\delta$ T cells (Mensurado et al., 2018), and recruiting regulatory T cells or macrophages (Zhou et al., 2016; Wang et al., 2021a). Neutrophils also promote metastatic spread, for instance, by producing leukotrienes to aid cancer cell proliferation (Wculek and Malanchi, 2015), forming clusters with circulating cancer cells that expand their metastatic potential (Szczerba et al., 2019), or helping establish a pro-metastatic niche (Bald et al., 2014; Casbon et al., 2015; Coffelt et al., 2015; Wculek and Malanchi, 2015; Spiegel et al., 2016; He et al., 2024). Neutrophils also produce NETs in the context of cancer, and NETs have been implicated in virtually all stages of tumorigenesis, progression, and metastasis (Adrover et al., 2023).

NETs are web-like, filamentous extracellular structures released by neutrophils in response to supernumerary (Brinkmann et al., 2004) or oversized (Branzk et al., 2014) pathogens, but are also released in sterile injuries (Jorch and Kubes, 2017). NETs trap pathogens in a meshwork of DNA, histones, proteases, and cytolytic and pro-inflammatory compounds (Brinkmann et al., 2004; Pham, 2006; Jaillon et al., 2007; Lauth et al., 2009; Urban et al., 2009; Kessenbrock et al., 2009; Papayannopoulos, 2018) and are, therefore, highly cytotoxic and pro-thrombotic structures.

NETs expose more than 500 proteins (Rayes et al., 2020), many of which can affect cancer directly. For instance, MMP9 is a key neutrophil protease associated with NETs (Egeblad and Werb, 2002), and it can induce vascular dysfunction by causing endothelial cell damage (Carmona-Rivera et al., 2015), while also inducing angiogenesis (Ardi et al., 2007). NET-bound cathepsin G can activate metalloproteases and proteolyze many extracellular matrix components to enable cancer cell invasion (Guan et al., 2021). Histones within NETs can damage endothelial cells directly, as they are inherently cytotoxic (Parseghian and Luhrs 2006; Silvestre-Roig et al., 2019), while NET-associated DNA physically traps circulating cancer cells to allow metastatic colonization (Cools-Lartigue et al., 2013; Najmeh et al., 2017) and acts as a scaffold to concentrate protease activity on ECM substrates (Albregues et al., 2018).

NETs play important roles in tumor establishment, progression, aggressiveness, and dissemination. Several cancer cell lines induce NET formation, and NETs, in turn, stimulate cancer cell invasion (Park et al., 2016; Jung et al., 2019; Nie et al., 2019; Jin et al., 2021), metastatic dissemination (Cools-Lartigue et al., 2013; Ren et al., 2021), and tumor growth, leading to reduced survival (Miller-Ocuin et al., 2019). NETs can also affect tumor

metabolism, as NET-derived neutrophil elastase stimulates TLR4 signaling on tumor cells to enhance mitochondrial production of ATP, thereby increasing primary tumor growth (Yazdani et al., 2019). Furthermore, NETs seem to be present in premetastatic tissues before overt metastasis takes place (Lee et al., 2019; Rayes et al., 2019; Yang et al., 2020) and can awaken dormant disseminated cancer cells (Albrengues et al., 2018). NETs also impair adaptive immune responses, for instance, by acting as a physical barrier that limits cancer cells and cytotoxic natural killer or T cell interaction (Teijeira et al., 2020; Xia et al., 2020) or by exposing PD-L1 (Kaltenmeier et al., 2021). In consequence, NET inhibition can improve response to immunotherapy (Teijeira et al., 2020).

While most reports show that neutrophils and NETs are pro-tumoral, they can also show anti-tumor behaviors. For instance, NETs can limit the migration and proliferation of melanoma cells *in vitro* (Schedel et al., 2020) and promote the activation of CD4⁺ T cells in co-culture (Tillack et al., 2012). Neutrophils can kill cancer cells by producing ROS or reactive nitrogen species (Fridlender et al., 2009; Granot et al., 2011; Finisguerra et al., 2015; Mahiddine et al., 2019), by expressing TNF-related apoptosis-inducing ligand (Koga et al., 2004), by inducing cancer cell detachment from the basement membrane (Blaisdell et al., 2015), or by mechanically disrupting the cancer cell's plasma membrane, in a process termed trogoptosis (Matlung et al., 2018). Neutrophils can also stimulate adaptive immune responses against tumors. For instance, neutrophils can directly activate T cells (Radsak et al., 2000; Eruslanov et al., 2014), present antigens (Beauvillain et al., 2007; Singhal et al., 2016; Tang et al., 2024), and promote the anti-tumoral polarization of unconventional $\alpha\beta$ T cells (Ponzetta et al., 2019).

Cancers can communicate with neutrophils or their progenitors through various mediators produced by cancer cells themselves or by the TME (Fig. 2), including G-CSF to control granulopoiesis (Nishizawa et al., 1990; Manz and Boettcher, 2014; Casbon et al., 2015) and mobilization from the marrow (Semerad et al., 2005; Christopher et al., 2009). Other cancer-produced growth factors and cytokines such as GM-CSF, IL-6, IL-1 β , and IL-17 also affect hematopoiesis (Forlow et al., 2001; Morales et al., 2010; Manz and Boettcher, 2014; Aggen et al., 2021). Several chemokines, such as CXCL1, CXCL2, CXCL5, CXCL6, and IL-8, act to recruit circulating neutrophils to the tumor (Jamieson et al., 2012; Park et al., 2016; Mollica Poeta et al., 2019). While signaling through CXCR2 is a prime chemo-attracting signal for neutrophils, it also has other roles in neutrophil biology, such as accelerating the acquisition of an aged phenotype (Adrover et al., 2019), but whether tumor-released CXCR2 ligands (such as CXCL1 or CXCL2) affect this phenomenon remains to be understood. Pro-angiogenic factors like vascular endothelial growth factor A (VEGFA) can also attract neutrophils to the TME, likely toward hypoxic regions (Zittermann and Issekutz, 2006). Furthermore, apoptosis of cancer cells leads to the release of IL-8 to attract neutrophils in colorectal cancer (Schimek et al., 2022). IL-8 and other signals induce the formation of NETs (Adrover et al., 2023; Teijeira et al., 2021), including the loss of histidine-rich glycoprotein (Yin et al., 2023), or the expression of cathepsin C (Xiao et al.,

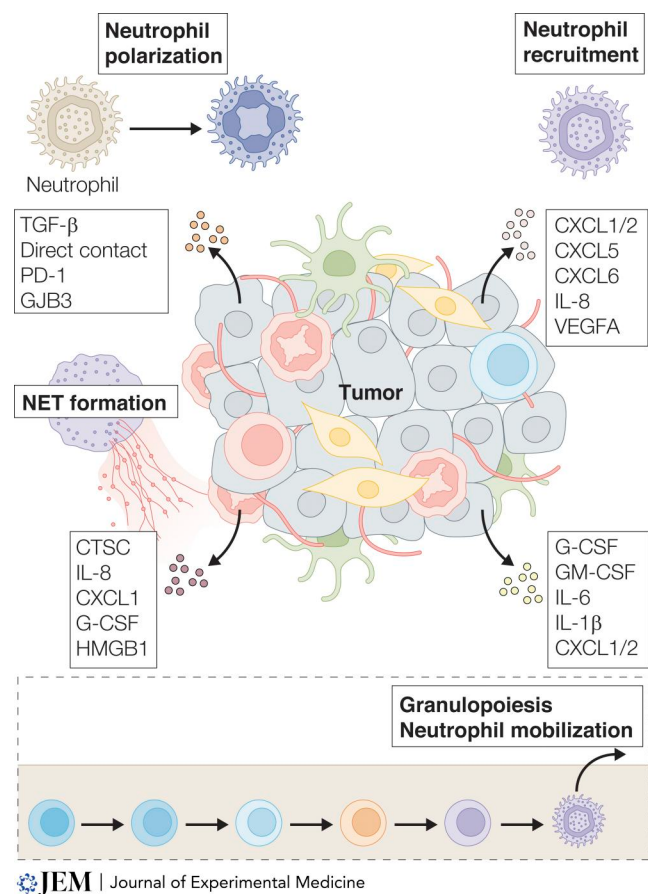


Figure 2. **Cancer-derived signals affect neutrophil properties.** Cancer can affect neutrophils by producing a variety of signals that alter neutrophil properties or their production at the bone marrow level. CTSC, cathepsin C.

2021). Cancer cells can also suppress neutrophil functions through direct interaction (Yajuk et al., 2021; Huo et al., 2022). Finally, cancer treatments can affect neutrophil function, for instance, by modifying their migration ability (Mendonça et al., 2006) or their release from the bone marrow (Yu et al., 2022).

Neutrophils are also affected in premalignant conditions, such as CH. CH refers to the acquisition of somatic mutations in hematopoietic stem cells that confer a self-renewal, proliferative, or survival competitive advantage over neighboring cells (Weeks and Ebert, 2023). Most common mutations take place in epigenetic regulators, such as TET2, DNMT3A, or ASXL1, but also in signal transduction genes like JAK2 or DNA damage response, such as TP53 (Genovese et al., 2014). While somatic mutations are common with age (Martincorena, 2019), the hematopoietic system is among the most affected systems because of its high turnover rate. CH is seldom detected in individuals under 40 years of age, but it may be an inevitable phenomenon in the elderly (Zink et al., 2017). While CH is a premalignant state, the relative progression risk is low (Jaiswal et al., 2014), but it can lead to hematological malignancies, particularly myeloid neoplasms (Genovese et al., 2014; Jaiswal et al., 2014; Desai et al., 2018). CH is common as well in patients with solid tumors, especially in ovarian, thyroid, lung, and kidney cancers (Bolton et al., 2020; Kar et al., 2022), and it leads to increased

inflammatory and neutrophil-related gene signatures in several cancer types (Fairchild et al., 2023). But treatment regimens in cancer patients make interpretation of these data difficult, as genotoxic stress (i.e., radiation or chemotherapy) can drive therapy-related CH or enhance preexisting CH (Coombs et al., 2017; Gillis et al., 2017) in cancer patients.

Beyond cancer, CH is associated with a variety of disease manifestations, most notably CVD. CH associates (an association as strong as that of smoking, hyperlipidemia, and diabetes) with increased risk of coronary heart disease, myocardial infarction (MI), ischemic stroke, atherosclerosis (Jaiswal et al., 2017; Fuster et al., 2017), and nonischemic heart failure (Yura et al., 2021). DNMT3A or TET2 mutations accelerate disease progression and increase all-cause mortality risk in ischemic heart failure patients (Dorsheimer et al., 2019; Li et al., 2025). Beyond CVD, individuals with CH are at higher risk for a variety of other conditions, including chronic lung disease (Miller et al., 2022), chronic liver disease (Wong et al., 2023), diabetes (Jaiswal et al., 2014), gout (Agrawal et al., 2022), autoimmune disease (Tanaka et al., 2020), and infection (Quin et al., 2024; Zekavat et al., 2021). In most cases, the effect of CH in these diseases revolves around increased inflammation.

Clonally expanded, mutated stem cells produce progeny carrying the same mutations, leading to altered downstream immune cell number or function. CH is associated with increased amounts of circulating neutrophils and platelets (Kar et al., 2022; Zekavat et al., 2021). Most notably, TET2 mutation causes a myeloid bias of hematopoiesis, a myeloid-rich TME (Pich et al., 2025), and endows myeloid cells with increased pro-inflammatory ability (Fairchild et al., 2023). TET2 deficiency alters neutrophil function, promotes the production of immature neutrophils, and enhances neutrophil expression of pro-inflammatory mediators (such as IL-6 or IL-1 β), while reducing neutrophil phagocytosis, motility, and extravasation. TET2-mutant neutrophils also produce NETs that are more resistant to degradation (Huerga Encabo et al., 2023; Quin et al., 2024; Fuster et al., 2017; Agrawal et al., 2022).

Neutrophils, thus, are greatly affected by growing tumors, as well as by premalignant states such as CH. Importantly, their behavior is affected systemically. It is, thus, conceivable that these reprogrammed neutrophils then show altered behaviors in sites other than the tumor itself and, as such, could be involved in the heightened CVD that cancer patients endure.

Cancer and CVD

CVD and cancer together account for nearly 70% of disease-related deaths in developed countries (Von Itter and Moore, 2024; Sturgeon et al., 2019). Recent research has increasingly shown that cancer patients face a substantially higher risk of developing CVD (Florido et al., 2022; Paterson et al., 2022) and that CVD is not only highly prevalent but also remains a leading cause of death among cancer survivors (Miller et al., 2019; Sturgeon et al., 2019). Furthermore, cancer diagnosis is linked to an elevated risk for CVD across disease manifestations, including heart failure (Marenzi et al., 2025), stroke (Zaorsky et al., 2019), MI (Guo et al., 2021), and venous thromboembolism (VTE) (van Es et al., 2014).

So far, research has been mostly focused on the contribution of cancer therapy, but treatment-naïve cancer patients also

display abnormally elevated levels of CVD (Bradshaw et al., 2016), suggesting that treatment is not the only factor at play. One additional, non-mutually exclusive explanation lies in the broad effects that cancer elicits in the host and, particularly, in the changes that it elicits on the hematopoietic compartment and on neutrophils. In fact, in patients with cancer and CVD, an elevated neutrophil-to-lymphocyte ratio (NLR) is linked to higher mortality rates (Cassidy et al., 2017). Higher NLR values are also associated with deleterious outcomes in cancer treatment-related cardiotoxicity (Akinci Ozyurek et al., 2017; Drobni et al., 2020b). This suggests that NLR or other inflammation markers could be a useful tool for risk stratification in patients (Ridker et al., 2000; Zhan et al., 2021; Higaki et al., 2022).

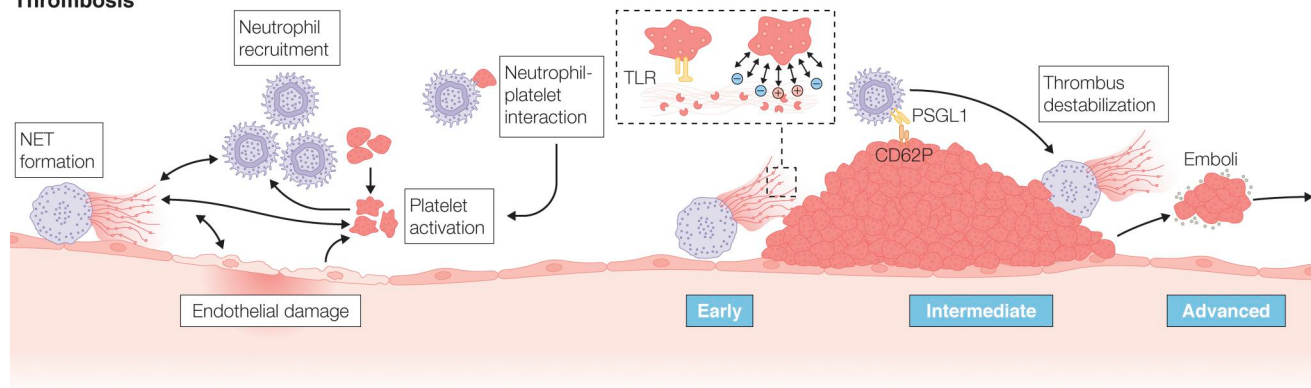
Interestingly, many of the risk factors shared between cancer and CVD affect neutrophils directly. Obesity (McDowell et al., 2021), high-fat diet (D'Abbondanza et al., 2019), hypercholesterolemia (Warnatsch et al., 2002), smoking (Albregues et al., 2018), CH (Wolach et al., 2018; Huerga Encabo et al., 2023), or hypertension (McCarthy et al., 2021) all increase the likelihood of neutrophils forming NETs. On the other hand, NETs are critically involved in cancer, as outlined above (Adrover et al., 2023), but also in CVD (Bonaventura et al., 2020), including in atherosclerosis (Knight et al., 2014; Warnatsch et al., 2002), MI (Mangold et al., 2015), and stroke (Peña-Martínez et al., 2019; Peña-Martínez et al., 2022). Importantly, NETs are also known drivers of intravascular inflammation and thrombosis (Gómez-Moreno et al., 2018), which are highly prevalent complications in both cancer (Pantazi et al., 2024; Demers et al., 2012; Rosell et al., 2022) and CVD (Stark and Massberg, 2021).

Thrombosis

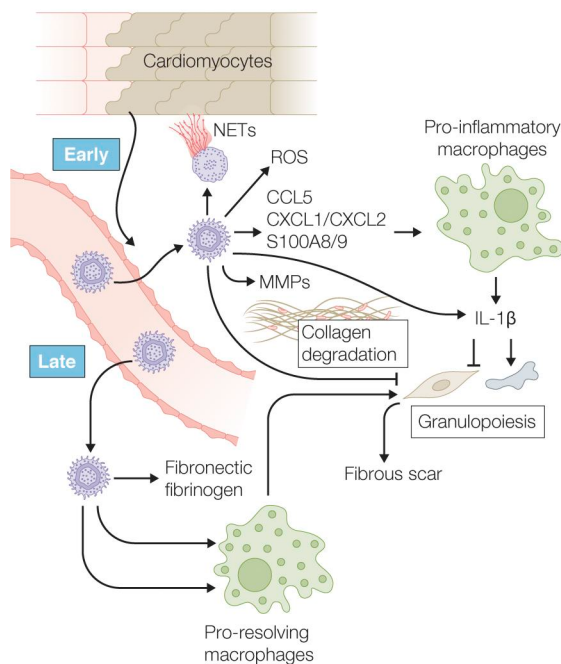
Thrombosis refers to the formation of blood clots within the vasculature, which impair blood flow and can result in tissue infarction of areas downstream of the affected vessel, with significant clinical consequences (Mackman, 2008). Neutrophils play prominent roles in thrombosis (Fig. 3) through their interaction with platelets (von Brühl et al., 2012; Hidalgo et al., 2009; Sreeramkumar et al., 2014) and through NET formation (Fuchs et al., 2010; Maugeri et al., 2014). Interestingly, neutrophils can be recruited to the damaged endothelium even before platelets (Darbousset et al., 2014), and although platelets are the prime players in thrombosis, NETs can also induce platelet-independent clots (Jiménez-Alcázar et al., 2017).

VTE, which includes both deep vein thrombosis (DVT) and pulmonary embolism, can act as an early warning of cancer (Fernandes et al., 2019), as it is often the first presenting symptom in individuals with undiagnosed malignancy (Otten and Prins, 2001). VTE is the second most common preventable cause of death in cancer (Lyman et al., 2021), and cancer patients have a higher incidence and recurrence rate of VTE than other patient groups (Grilz et al., 2021; Timp et al., 2013). In a study examining risk factors for VTE, individuals with cancer had a fourfold higher risk of developing thrombosis compared with those without cancer (Mulder et al., 2021). Additionally, cancer patients with VTE experienced a twofold or greater increase in mortality compared with cancer patients without VTE (Lee and Levine, 2003).

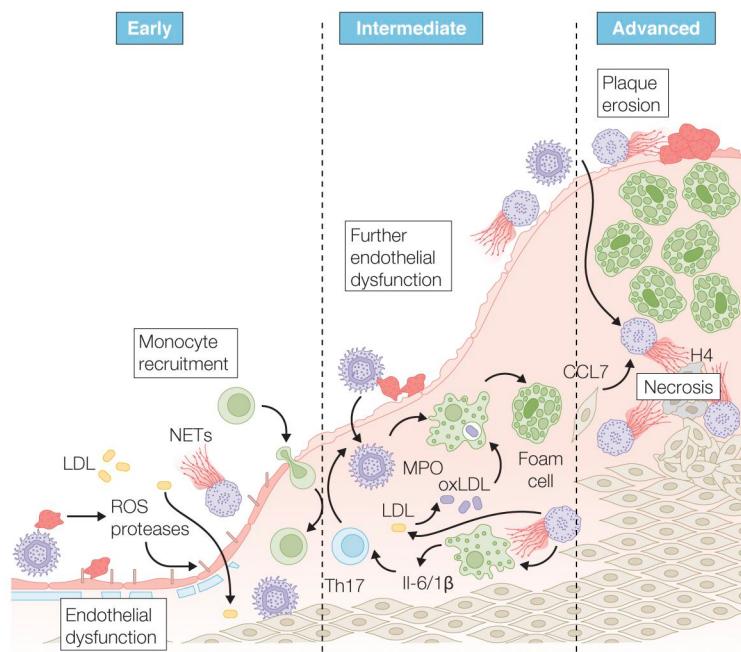
Thrombosis



Myocardial infarction



Atherosclerosis



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Figure 3. Neutrophils in CVD. Neutrophils are key players in CVD. In thrombosis, neutrophils and platelets enter a feed-forward loop of activation that drives further endothelial damage and platelet deposition. Neutrophils, through NET formation, can also destabilize thrombi, leading to emboli formation. In MI, neutrophils play dual roles. In the early phase, they are pro-inflammatory, help polarize macrophages to a pro-inflammatory state, degrade ECM, and block fibroblast function. In late stages, they assume anti-inflammatory functions, activate fibroblasts, and, through efferocytosis, polarize macrophages to a pro-resolving phenotype. In atherosclerosis, neutrophils induce endothelial damage, helping LDL deposition and monocyte recruitment. In intermediate phases, neutrophils release NETs and degranulate, releasing MPO that oxidizes LDL particles and fuels foam cell formation. In advanced stages, neutrophils drive plaque erosion and aid in forming a necrotic core through NET formation and the release of membrane-damaging histones. LDL, low-density lipoprotein.

These findings highlight the importance of understanding how the hypercoagulable state of cancer is established. VTE is triggered by a combination of plasma hypercoagulability, blood flow vortices, stasis, and endothelial activation (Mackman, 2012). Risk factors for VTE, including thrombocytosis (Sylvan et al., 2017), tissue factor (Zwicker et al., 2009), cytokines, soluble P-selectin (Ay et al., 2008), and elevated coagulation factors in cancer, can contribute to the prothrombotic state (Connolly and Khorana, 2010; Demers et al., 2012; Hisada and Mackman, 2017). Furthermore, several studies have shown that leukocytosis (high levels of white blood cells in circulation) is linked to an increased risk of VTE in lung (Kasuga et al., 2001) and

colorectal cancer patients (Hajebi et al., 2021), suggesting that leukocytosis may be common in cancer-associated thrombosis (Hisada and Mackman, 2017; Khorana et al., 2008). Leukocytosis is, however, a vague term, and further research is needed to understand which specific immune populations are at play. Interestingly, neutrophils are often increased in cancer patients (Schmidt et al., 2005; Antoine et al., 1998; Lechner et al., 2010; Templeton et al., 2014) and are critically involved in VTE (Stewart, 1993; von Brühl et al., 2012; Kushnir et al., 2016). Beyond numbers, activation of neutrophils and NET formation have also been associated with the pathogenesis of VTE (Dhanesha et al., 2023). NETs are particularly relevant

(Martinod et al., 2013), to the point that the circulating levels of citrullinated histone H3 (a marker for NETs) predict the risk of VTE in cancer patients (Mauracher et al., 2018). NETs bind active coagulation factor XII, which stimulates further adhesion and NET formation (Schmaier and Stavrou, 2019), and contain tissue factor (Kambas et al., 2012), both of which trigger the coagulation cascade (Kambas et al., 2012).

As discussed above, cancer can promote NET formation in multiple ways, and NETs interact with the endothelium, platelets, erythrocytes, and coagulation factors to stimulate thrombus formation (Thålin et al., 2019) and coagulation in DVT (Fuchs et al., 2012), ultimately driving fibrin deposition in venous thrombosis (Fuchs et al., 2010). The signaling pathways underlying the induction of NETs in DVT are not yet fully understood, but ROS (Gutmann et al., 2020) and IL-8 (Van Aken et al., 2002) have been proposed to play an important role. Of note, IL-8 is often elevated in cancer patients (Waugh and Wilson, 2008; Todorović-Raković and Milovanović, 2013) and can directly trigger NET formation (An et al., 2019).

MI and stroke

Arterial thromboembolism (ATE) refers to the obstruction of an artery by a clot (thrombus) or an embolus, which can be a traveling clot or other materials, such as ruptured atherosclerotic plaques. This blockage obstructs blood flow, resulting in ischemia and damage to the tissues perfused by the affected artery (May and Moll, 2021). This can occur in different vascular areas, such as the brain (resulting in a stroke [Chen et al., 2011]), the heart (causing a MI [Rinde et al., 2017]), the kidneys, or the legs (leading to acute limb ischemia [Wang et al., 2021b]). ATE represents a significant challenge, contributing to increased mortality and morbidity rates among cancer patients (Balomenakis et al., 2023). Patients with a newly diagnosed cancer experience a substantially elevated short-term risk of ATE (Navi et al., 2017), and ATE risk increases by 70% in elderly patients (Navi et al., 2019). The risk of ATE seems to be highest in lung and colorectal cancer (Navi et al., 2019; Guo et al., 2021).

Ischemic stroke is one of the leading causes of death globally (Bogiatzi et al., 2014), and it is widely acknowledged as a complication of cancer (Herrmann, 2020; Lindvig et al., 1990). A stroke can occur at any point during the course of the disease in 5% of cancer patients (Salazar-Camelo et al., 2021) and may be the first symptom in up to 3% of patients with an occult malignancy (Cocho et al., 2015; Taccone et al., 2008; Xie et al., 2024). MI is another leading cause of death and disability globally (Thygesen et al., 2007). The relative risks for MI and ischemic stroke in cancer patients are similar (Navi et al., 2019). Beyond increased incidence, individuals with a prior cancer diagnosis and MI had lower lipid profiles (LDL, triglycerides and cholesterol) than non cancer patients (Koo et al., 2021), and experience higher postMI mortality than those without cancer (Pothineni et al., 2017), potentially due to a sustained pro-inflammatory state and vascular toxicity from cancer treatments (Libby and Kobold, 2019). Chemotherapy is known to cause cardiotoxicity (Economopoulou et al., 2015), while immunotherapy (Matzen et al., 2021) and radiotherapy can accelerate atherosclerosis and coronary artery disease (Kwok et al., 2021). Furthermore,

immune checkpoint inhibitors (ICIs) have been associated with a threefold higher risk for atherosclerotic cardiovascular events, including MI (Drobni et al., 2020a). This link between ICIs and cardiovascular complications (Green et al., 2023) is currently under active investigation. Retrospective studies have reported an increased incidence of VTE following ICI therapy (Allouchery et al., 2022). Furthermore, a commonly reported complication of ICI is myocarditis (Berg et al., 2017; Johnson et al., 2016), which causes immune cell infiltration into the cardiac sinus, cardiac tissue, and atrioventricular nodes (Mahmood et al., 2018). Interestingly, patients under ICI who develop myocarditis have been shown to have changes in the proportion of circulating neutrophils (Drobni et al., 2020b).

Neutrophils are considered detrimental in the acute phase of MI (Zhang et al., 2022) and are among the first immune cells to infiltrate the infarcted myocardium to propagate inflammation (Fig. 3), with their numbers peaking around 24–48 h after the acute event (Ma et al., 2016). During this initial phase, their influx contributes to acute myocardial injury, for example, through the release of proteolytic enzymes that weaken the structural integrity of the myocardium (Romson et al., 1983) or through ROS production (El Kazzi et al., 2020; Carbone et al., 2020), especially during reperfusion (Jolly et al., 1986). Neutrophil-derived serine proteases can also activate the coagulation cascade and cause the occlusion of large vessels, leading to arterial thrombosis (Massberg et al., 2010). NETs also play a detrimental role in acute MI (Liu et al., 2019a; Langseth et al., 2020; Ge et al., 2015; Savchenko et al., 2014). As discussed above, cancer can promote NET formation, ROS production, and the release of neutrophil proteases, which could potentially lead to worsened MI outcomes. Neutrophils also release many pro-inflammatory factors, including MIP-1 α , CCL5, CXCL1, CXCL2, S100A8, S100A9, and IL-1 β that, collectively, drive further immune cell influx (Daseke et al., 2021) and polarize macrophages to a pro-inflammatory phenotype. Through inflammasome activation, this leads to further IL-1 β production (Kawaguchi et al., 2011), which inhibits fibroblast function and, together with neutrophil-derived proteases like MMP8, leads to collagen degradation (Saxena et al., 2013). IL-1 β and neutrophil-released alarmins further drive granulopoiesis to enhance systemic neutrophil availability (Sreejit et al., 2020). At later stages, neutrophils start to show anti-inflammatory functions (Ma et al., 2016) and release fibronectin or fibrinogen (Daseke et al., 2019), which in turn promote fibroblast activity (Gray et al., 1993). Neutrophils then die by apoptosis and are phagocytosed by macrophages to induce pro-repair macrophage polarization (Peet et al., 2020). The conversion from pro-inflammatory to pro-resolving neutrophils over time in AMI is critical, as evidenced by studies blocking this conversion that show worsened remodeling and outcome (Iyer et al., 2015).

The circadian status of neutrophils and the acquisition of an “aged” phenotype are important in MI, as the presence of aged neutrophils in circulation worsens the outcome of acute MI (Adrover et al., 2019). Neutrophil ageing refers to the phenotypic changes experienced by neutrophils from the time they are released into blood to their disappearance from the circulation. Aged neutrophils show a hyper-segmented nucleus, low extravasation

ability toward inflammatory stimuli, and are identified as CD62L^{Low}, CXCR2^{Low}, and CXCR4^{High} neutrophils (Aroca-Crevillén et al., 2020). In this line, it is intriguing to note that cancer can promote the ageing of circulating neutrophils (Mittmann et al., 2021; Yang et al., 2021), and aged neutrophils have been shown to promote intravascular coagulation (Adrover et al., 2019).

Interestingly, neutrophil subsets similar to some found in the context of cancer have been found in MI: SiglecF^{High} neutrophils with increased phagocytosis and ROS production ability increase over time in the cardiac tissue after MI (Vafadarnejad et al., 2020). The acquisition of SiglecF has been proposed to drive neutrophil apoptosis to promote the resolution of inflammation. Studies also found the presence of N1 pro-inflammatory neutrophils (expressing *Ccl3*, *Il1b*, *Il12a*, and *Trfa*) in the heart upon MI, which shifted over time toward an N2 (expressing *Cd206* and *Il10*) anti-inflammatory phenotype (Ma et al., 2016). What the different subsets of neutrophils present in the cardiac tissue do in the context of cancer, and what other cancer-associated neutrophil subtypes do in MI remains, however, to be explored.

Atherosclerosis

Atherosclerosis is a progressive inflammatory disease of large arteries, characterized by an accumulation of lipids, inflammatory cells, and fibrous tissue in arterial walls, thickened intimal layers, altered endothelium, and overall compromised arterial function. It leads to reduced and turbulent luminal blood flow and, when the lesions become unstable, to embolic clinical complications such as MI and stroke (Björkegren and Lusis, 2022). Cancer is linked to heightened inflammation, which can significantly contribute to the development of atherosclerosis (Crusz and Balkwill, 2015). In breast and colorectal cancer, patients show a high burden of atherosclerosis and related CVDs at the time of cancer diagnosis (Melson et al., 2024; Wang et al., 2018). Interestingly, the prevalence of risk factors for atherosclerosis is high in patients with a history of breast cancer, and differential associations between these risk factors suggest potential differences in the pathogenesis of atherosclerosis between breast cancer patients and controls (Šrámek et al., 2013).

While cancer can contribute to atherosclerosis through various mechanisms, including those discussed in the previous section on thrombosis, the most commonly studied are the side effects of radiotherapy and anti-tumor drugs. Radiotherapy can induce vascular damage, which increases vascular permeability and triggers inflammation, leading to intimal proliferation, collagen deposition, and fibrosis, all of which promote the formation of atherosclerosis plaques (Morganti et al., 2002). Several chemotherapeutic agents have also been linked to an increased incidence of atherosclerosis (Jiang et al., 2024), most notably antimetabolites (Raposeiras Roubín and Cordero, 2019), anti-microtubule agents (Hassan et al., 2018), and tyrosine kinase inhibitors (Albini et al., 2010). Checkpoint blockade inhibitors have reignited interest in the development of immunotherapeutic drugs for cancer, but an increased incidence of atherosclerosis in treated patients has been reported and should be carefully studied (Chan et al., 2023; Drobni et al., 2020a; Poels et al., 2021). NLR is an independent predictor of atherosclerotic cardiovascular risk and is useful in monitoring ICI-induced atherosclerosis (Zhang et al.,

2021), suggesting that neutrophils could be playing a role in this phenomenon, especially given that neutrophils and NETs are known to play prominent roles in atherosclerosis (Pérez-Olivares and Soehnlein, 2021; Warnatsch et al., 2002; Drechsler et al., 2010; Knight et al., 2014; Döring et al., 2014).

Hypercholesterolemia is a critical driver of atherosclerosis. Atherogenic lipoproteins interact with vascular wall cells and induce monocyte recruitment, leading to macrophage differentiation, lipid uptake, and necrotic core formation in the sub-intima layer (Fan and Watanabe, 2022). In early phases of atherosclerosis (Fig. 3), neutrophils drive vascular dysfunction by producing ROS and NETs and releasing proteases in the arterial luminal space (Soehnlein, 2012; Silvestre-Roig et al., 2020), promote the accumulation of low-density lipoprotein in the arteries (Higazi et al., 1997), and help recruit monocytes to the lesion area (Drechsler et al., 2010). Additionally, neutrophils release CCL2, which increases monocyte adhesion (Winter et al., 2018) and endothelial activation, stimulating neutrophils to produce NETs, leading to further monocyte recruitment (Gupta et al., 2010). Hypercholesterolemia also leads to the release of chemokines that drive neutrophil infiltration into the lesion (Drechsler et al., 2010). At intermediate stages, neutrophils degranulate and release ROS and proteases like myeloperoxidase (MPO) that oxidize lipoproteins, enhancing the formation of foam cells (Carr et al., 2000), lipid-laden macrophages, which are a hallmark of atherosclerotic lesions (Gallo et al., 2025). Neutrophils also promote macrophage polarization to a pro-inflammatory state, increasing their production of IL-6 and IL-1 β , which in turn promote the differentiation of Th17 cells, that further increase neutrophil infiltration to the lesion (Warnatsch et al., 2002). At later stages, neutrophils destabilize the plaque, inducing endothelial denudation and plaque erosion (Quillard et al., 2015). Hypercholesterolemia also promotes NET formation (Warnatsch et al., 2002; Rada, 2017), and NETs cause plaque destabilization by inducing death or damage of smooth muscle cells or endothelial cells, resulting in superficial plaque erosion (Quillard et al., 2015) and plaque rupture (Mawhin et al., 2018; Silvestre-Roig et al., 2019). Besides their role in plaque destabilization, NET-associated histone H2a also mediates monocyte adhesion to endothelial cells and accelerates atherosclerosis (Schumski et al., 2021). Neutrophils also play an important role in clearing cell debris and recruiting other immune cells, including monocytes and lymphocytes, to the injury site, which is critical for scar formation (Soehnlein et al., 2009; Chalise et al., 2021). Finally, NET-platelet interaction and thrombus formation accelerate atherosclerosis progression by causing endothelial dysfunction in humans and mice (Megens et al., 2012). Therefore, the ways in which cancer affects neutrophil biology, including by promoting their NET-formation ability, likely affect atherosclerosis in cancer patients.

Concluding remarks: Neutrophils as drivers of cancer-related CVD

Cancer patients experience an increased risk of CVD, which is usually attributed to the effects of treatment and shared risk factors. We propose that neutrophils provide a mechanistic link between cancer and CVD (Fig. 4). As discussed above, neutrophils

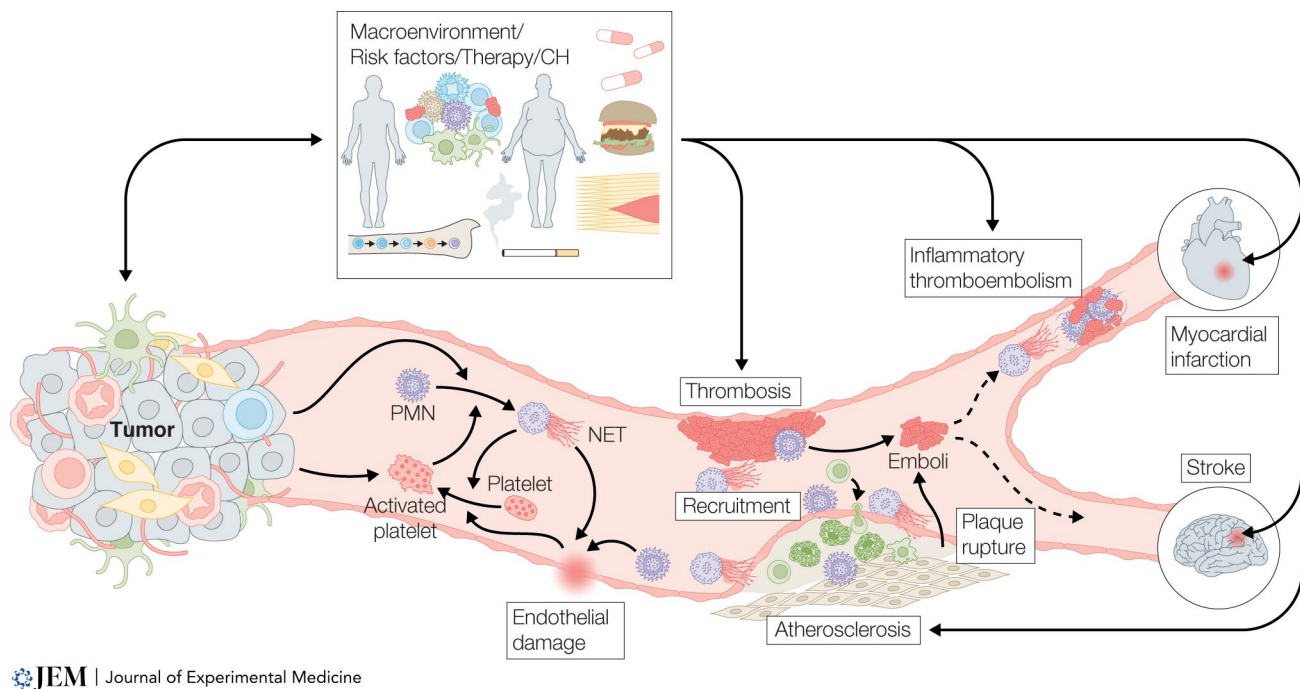


Figure 4. Neutrophils in cancer-driven CVD. Neutrophils are key players in CVD and are heavily affected by the TME and tumor macroenvironment and premalignant states, such as CH and cancer treatment. The interplay between cancer and vascular health is likely to be influenced by cancer-elicited changes to neutrophil behavior.

are drivers of CVD and are affected by cancer at multiple levels. A central mechanism through which neutrophils promote these effects appears to be NET formation, and these structures are commonly found in cancer patients, not only in the tumors but also systemically (Demers et al., 2012; Leal et al., 2017; Zhang et al., 2019). NETs, as discussed above, are highly pro-thrombotic structures, and thrombosis greatly affects CVD onset and outcome.

Additionally, central to the association between cancer and CVD is the capacity of tumors to alter hematopoiesis, leading to altered production of neutrophils, as well as to recruit them by releasing growth factors and inflammatory cytokines that can directly mobilize these cells out of the marrow to contribute to systemic inflammation and thrombosis. Cancer treatments, including targeted therapies and chemotherapy, can amplify these effects.

All this leads to the appearance of cancer-induced neutrophil subpopulations, as discussed above, whose potential involvement in systemic damage and CVD is still largely unknown. We have recently shown (Adrover et al., 2025) that cancer can elicit the appearance of vrPMNs with increased NET formation ability, increased ability to interact with platelets, and decreased extravasation capacity. We believe that these neutrophils, which are highly reactive inside the vasculature, are in an ideal position to link cancer and CVD. In addition, this could help explain why treatment-naïve cancer patients also show increased CVD burden. Unfortunately, the field has paid little attention so far to vascular events and the intravascular role of cancer-associated neutrophils. We believe that further research should be devoted to understanding the systemic effects of cancer at the systemic vascular level and the roles of cancer-elicited neutrophil subtypes in CVD. This research has the potential to open new

therapeutic avenues to relieve the CVD burden that cancer patients and survivors currently endure.

Acknowledgments

This work was supported by funding provided to J.M. Adrover by the British Heart Foundation (SP/F/24/150081) and by the Francis Crick Institute, which receives its core funding from Cancer Research UK (FC001003), the UK Medical Research Council (FC001003), and the Wellcome Trust (FC001003).

Author contributions: S. Ambreen: visualization and writing—original draft, review, and editing. A. McCarthy: writing—original draft. A. Hidalgo: writing—review and editing. J.M. Adrover: conceptualization, funding acquisition, supervision, visualization, and writing—original draft, review, and editing.

Disclosures: The authors declare no competing interests exist.

Submitted: 17 March 2025

Revised: 16 May 2025

Accepted: 22 July 2025

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