Aging and Disease
www.aginganddisease.org
Early access date: October 11, 2025
http://dx.doi.org/10.14336/AD.2025.0861

Review

Aging-Related Mechanisms Underlying Carcinogenesis: Therapeutic Opportunities.

Ana Guijarro[1], Giulia Allavena[2], Livia Pisciotta[1,3], Alessio Nencioni[1,3], Irene Caffa[1,3*]

[1]Department of Internal Medicine and Medical Specialties, University of Genoa, 16132 Genoa, Italy.
[2]Institute for Research on Cancer and Aging of Nice (IRCAN), CNRS UMR7284, INSERM U1081, Université Côte d'Azur, 06107 Nice, France.
[3]IRCCS Ospedale Policlinico San Martino, 16132 Genoa, Italy.

[Received July 21, 2025; Revised September 26, 2025; Accepted September 27, 2025]

ABSTRACT: Aging is a gradual loss of tissue homeostasis that leads to impaired physiological organ functions and constitutes a major risk factor for cancer initiation and progression. Despite advances in anti-tumor therapies, cancer remains the second leading cause of death worldwide. The rising incidence of cancer is intimately associated with increased lifespan and the growing proportion of older adults, with 64% of cancers diagnosed in people aged 60 and above. Mechanisms underlying aging include accumulation of somatic mutations, deficient DNA damage repair machinery, telomere shortening, enhanced genomic instability, epigenetic alterations, loss of heterochromatin, chronic low-grade inflammation, mitochondrial dysfunction, cellular senescence and its associated secretory phenotype, stem cell exhaustion, aberrant intercellular communications, remodeling of extracellular matrix and microenvironment, impaired nutrient sensing and alterations in the proteome. Additionally, dysregulation of the circadian clock, the endocannabinoid system and the microbiota may also play important roles. Given that many of these processes are also crucial for cancer development, it is widely admitted that aging and cancer are tightly interconnected. Consequently, many therapies aimed at delaying or mitigating aging, such as physical exercise, specific dietary regimens, chronotherapy, epigenetic drugs and senotherapeutics, might also prevent or retard cancer development and progression and reduce the side effects of cancer therapies. However, special caution must be taken in older cancer patients due to their comorbidities and possible frailty, selecting specific patients' treatments and balancing the extended survival with the preservation of independence and quality of life.

Key words: Aging, aging-delaying therapies, clinical trials, inflammation, senescence, somatic mutations, tumorigenesis.

1. Introduction

Aging can be defined as a progressive series of physiological alterations that lead to the loss of tissue homeostasis and subsequent decline of biological functions, ultimately predisposing to multiple pathologies, including emphysema, osteoarthritis, cardiovascular diseases, cognitive decline, dementias and malignancies, collectively referred to as age-related diseases (ARDs) [1]. Traditionally, the accumulation of nuclear and mitochondrial DNA damage, genomic instability, loss of heterochromatin [1] and somatic mutations [2] has been considered as a primary cause of aging [3, 4]. However, this view has evolved in light of evidence showing that certain features of aging can be reversed by anti-aging interventions and that lifespan can be extended [5-10].

Chronological age, defined as the time elapsed since birth, does not always correspond to biological age, which reflects the physiological state of tissues and organs as

***Correspondence should be addressed to:** Dr. Irene Caffa, Department of Internal Medicine and Medical Specialties, University of Genoa, 16132 Genoa, Italy. Email: irene.caffa@unige.it

they accumulate molecular and cellular damage. Biological age is influenced by a variety of different biological and physiological factors, including lifestyle, nutrition and genetics [11]. The discrepancy between biological and chronological age is defined as "age acceleration", and subjects displaying a positive age acceleration are more prone to earlier onset of functional decline [12, 13]. This distinction between chronological and biological age is particularly relevant in oncology, where therapeutic decisions for elderly cancer patients should be based on both chronological and biological age [14, 15]. Furthermore, it is also important to distinguish healthy aging [14, 16] from unhealthy aging [17], which is characterized by premature senescence, senescence-associated secretory phenotype (SASP), chronic low-grade inflammation ("inflammaging") and ARDs.

Cancers comprise a heterogeneous group of diseases in which normal cells acquire specific somatic "driver" mutations in tumor-suppressor genes and/or proto-oncogenes, leading to their transformation into malignant cells capable of uncontrolled proliferation, tumor formation, and metastatic spread. Despite notable therapeutic progress, cancer remains the second leading cause of death worldwide, after cardiovascular diseases [18], and the fourth most common cause of death among the very old [19]. In 2020, 64% of newly diagnosed cancer cases occurred in people aged 60 and above, while those aged 85 years or older accounted for more than 6% of all cancer cases [18, 20], highlighting aging as a main, well-recognized, risk factor for cancer occurrence [18, 21]. According to the World Health Organization, the global population aged 60 years and older will reach 2.1 billion by 2050, with the number of subjects aged 80 years or above expected to triple to 426 million [22]. Therefore, given the ongoing increase in life expectancy [23-26], global cancer incidence is expected to rise to 20.7 million new cases and 12.7 million deaths by 2040 [18, 27], accounting for a major burden on healthcare systems. Furthermore, aging influences both cancer incidence [28-31] and prognosis [32-36], with older patients generally experiencing shorter progression-free survival (PFS) and lower overall survival (OS), underscoring the biological interconnection between aging and tumorigenesis.

At cellular level, aging is driven by mechanisms such as impaired DNA damage repair, telomere shortening, enhanced genomic instability [37], cellular senescence [38], reduced basal autophagy [39], epigenetic alterations, mitochondrial dysfunction, stem cell decline, aberrant intercellular communications, changes in the extracellular matrix (ECM) and microenvironment composition, impaired nutrient sensing and alterations in proteome composition [1, 40, 41]. Remarkably, many of these mechanisms also underpin cancer development [42-45], despite the apparent contrast between the "loss of function and fitness" seen in aging cells [46] and the "gain of function and fitness" observed in cancer cells [1]. As highlighted by Trastus *et al.* in their recent comprehensive review, the relative contribution of different aging mechanisms and pathways in tumorigenesis is complex and context-dependent [47].

2. Biological systems and mechanisms altered by aging with potential impact on carcinogenesis

2.1. Somatic mutations and genome instability

2.1.1. Progressive acquisition of somatic mutations

Somatic mutations arise due to error-prone DNA repair, replicating damaged DNA, stochastic errors by DNA polymerases or telomere shortening [48-52]. Additional mechanisms include the accumulation of oxidative DNA damage due to mitochondrial dysfunction [53], defective cell cycle checkpoints [54] and exogenous environmental factors, such as radiation and chemicals [55]. While such mutations are the driving force of genetic diversity and evolution, they also represent the key form of genome instability, a hallmark of both aging [1, 56] and diseases, particularly cancer [46, 57] (Fig. 1A).

In somatic cells, genome instability typically alters regulatory sequences, impacting cell proteome and homeostasis, which eventually leads to functional decline in tissues and organs. However, mutations can also affect protein-coding genes [58] or key regulatory elements, enabling cells to acquire oncogenic properties such as growth factor independence and enhanced metastatic potential [46]. According to the somatic mutation theory of aging, the cumulative burden of such mutations results in cell senescence, cell death or loss of function, thereby promoting aging [59, 60]. When these mutations occur in stem cells, they can lead to their depletion or dysfunction, contributing to both aging and malignant transformation [56, 58] (Fig. 1C).

Somatic mutations are broadly acknowledged as drivers of tumorigenesis [45, 61], with some "neutral/passenger mutations", which do not directly contribute to the tumor phenotype, and others "driver mutations", which confer a selective growth advantage that promotes clonal expansion [55, 62-66]. Somatic mutations can occur in cell cycle genes, resulting in the activation of oncogenes (e.g., *ERBB2*, *EGFR*, *MCL1*, *MYC, KRAS, BRAF, CCNC, CCND1*) [67-74], or the inactivation of tumor-suppressor genes (e.g., *RB1*, *PTEN*, *CDKN2A/B, p16*) [62, 64] (Fig. 1A). To add another layer of complexity, a third class of mutations known as "latent drivers" [75] may become drivers at a specific stage of cancer progression or when combined with other mutations [66]. The mutational heterogeneity within

tumors further enables them to evade immune system surveillance and resist therapeutic intervention.

Notably, cancer-associated mutations accumulate with age, and in elderly adults, the prevalence of cancer-associated mutations in normal tissue can approach 100% [45]. For instance, clonal patches of somatic mutations in normal skin often involve well-known skin cancer drivers, such as *NOTCH* family, *TP53*, *FAT1* and *RBM10* [76]. Likewise, many mutations found in normal cells are additionally found in cancers from the same tissues. For example, in the esophagus, up to 80% of cells in older individuals harbor *NOTCH1* mutations, also common in esophageal cancer [77]. A systematic study of somatic mutations, carried out in thousands of cancer patients, demonstrated that the mutations frequency increases exponentially with age [78], with distinct mutation spectra associated with aging [79]. These findings were supported by studies on adult stem cells of the small intestine, colon and liver, which exhibited age-related mutation burdens reflective of tissue-specific cancer mutation profiles [80]. Similar overlap in the somatic mutation pattern of normal aging tissue and its associated cancer has been reported by Hoang *et al*., reinforcing the view that age-related mutational processes are central to both aging and oncogenesis [81].

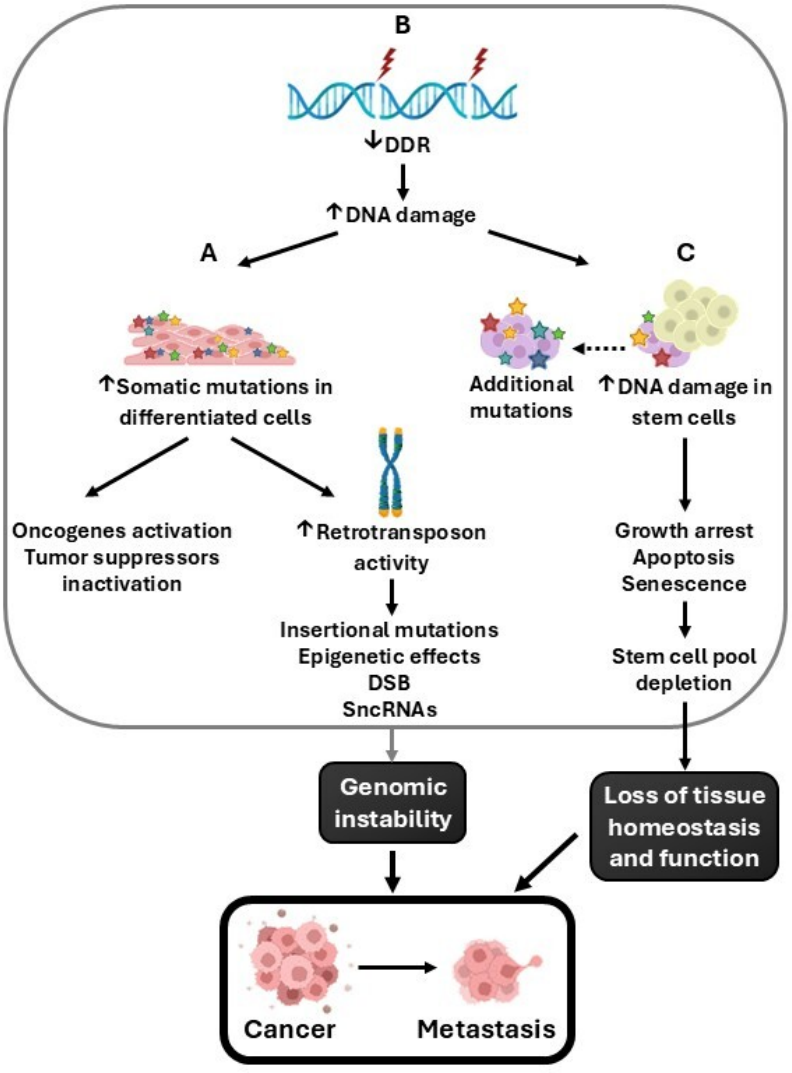

Figure 1. Processes that occur during aging that promote cancer initiation and progression: somatic mutations. (A) Somatic mutations can result in the silencing of tumor-suppressors or the activation of oncogenes driving tumorigenesis. The increased activation of retrotransposons leads to insertional mutations, genomic instability, epigenetic alterations, double strand breaks (DSB) and expression of small noncoding RNAs (SncRNAs), promoting carcinogenesis. **(B)** Aging is associated with a defective DNA damage repair response (DDR), which results in accumulation of DNA damage. **C.** With aging, stem cells accumulate DNA damage and mutations that lead to growth arrest, apoptosis or senescence, resulting in a reduction of the stem cells pool. Some of these damaged cells can evade control pathways by acquiring additional mutations, they continue to proliferate and provide a favorable environment for the development of new malignancies.

Despite this, determining the causative effect of aging-related mutations on cancer initiation remains challenging, since mutations can also arise after neoplastic transformation and during tumor progression. As mentioned above, driver mutations may result from random errors made during normal DNA replication, and this has been proposed as a major determinant of tissue-specific cancer risk [82]. Approximately three mutations are estimated to occur during each human stem cell division [83, 84]. Tomasetti *et al.* reported that the number

of these random mutations increases with age, and that lifetime cancer risks among 25 different tissues strongly correlate with the total number of stem cell divisions in those tissues [82]. Mouse studies corroborate this hypothesis, showing that both stem cell proliferation and DNA damage increase cancer risk [85].

Thus, cancer development likely results from a synergistic interaction between intrinsic factors (e.g., stem cell divisions, replication errors), genetic predisposition and extrinsic factors (e.g., environmental mutagens) [85]. The relative contribution of these three factors to cancer development is difficult to determine. After accounting for environmental and hereditary influences, a comprehensive genomic study attributed two-thirds of the mutations in human cancers to replication-associated errors [65]. Despite this, many cancers can still be preventable, as tumor formation generally requires more than one mutation [65, 86], and others are still amenable to secondary prevention through early detection and intervention [65].

Furthermore, tumor sequencing studies revealed hundreds to thousands of shared somatic mutations in tumor cells, with mutation burden correlating with patient age [78, 80, 87-89]. Remarkably, over half of these mutations appear to precede tumor initiation, emphasizing the impact of age-related mutation accumulation [84]. Across all tested cells and tissues, aging leads to the accrual of single-base substitutions (SBSs), single-nucleotide variants (SNVs) and small insertions/deletions (indels or IDs) [90]. The rate and spectrum of these mutations vary by cell types, genomic region and tissue [91-95], resulting in genomic mosaicism, where tissues are composed of cells with slightly different genomes [96], a dynamic phenomenon in both aging and disease [45]. It has been proposed that accumulated mutations act as a "genomic burden" that gradually impairs cellular functions [97]. High mutational load can trigger cell cycle arrest, senescence, or apoptosis, serving as a defense mechanism against malignant transformation [98]. However, in some contexts, these mutations contribute to tumor heterogeneity, treatment resistance, and poor prognosis. Furthermore, a role of copy number variations (CNVs) in tumor onset, progression, heterogeneity, treatment response and prognosis has been proposed [99-102].

2.1.2. Chromosomal rearrangements: Structural variations and chromothripsis

Historically, the extensive genomic alterations observed in tumors have been attributed to a stepwise process in which driver mutations progressively accumulate over time [64]. Nevertheless, the work by Stephens *et al.* demonstrated that certain chromosomal rearrangements in cancer genomes could not be fully explained by this "progressive" model. Instead, they might be the result of a single "catastrophic event" occurring within a single cell cycle, leading to multiple chromosomal breaks followed by random reassembly [103]. The emergence of such catastrophic mechanisms is closely linked to genomic instability [104].

A particularly important class of somatic mutations in carcinogenesis is structural variations (SVs), defined as genomic alterations (e.g., deletion, amplification or rearrangements of genomic segments) ranging from a few base pairs to kilobase and megabase-sized fragments [103, 105-112]. Somatic SVs, which are present only in a subset of cells, arise *de novo* in individual somatic cells and accumulate over successive cell divisions across the lifespan [111, 113]. Importantly, SVs frequently mediate gain- or loss-of-function of cancer-related genes and therapeutic targets [114].

Recent studies analyzing SVs patterns and signatures across the Pan-Cancer Analysis of Whole Genomes (PCAWG, 2,559 whole cancer genomes across 38 tumor types) revealed that 2,429 tumors harbored at least one somatic SV [109]. These studies highlighted marked variability in the SVs overall frequency and distribution across both tumor types and patients within a given tumor type [110, 115-118].

Another single "catastrophic event" is chromothripsis [103], in which one or more chromosomes shatter into multiple fragments and are then massively rearranged in a single event. Chromothripsis is a major driver of cancer initiation [119, 120] contributing to oncogenes overexpression [103, 120-122], loss of tumor-suppressor functions [103, 116, 123] and formation of fusion genes [123-125], and is also involved in the development of resistance to several anti-tumor drugs, including immunotherapy, platinum genotoxins and anti-angiogenesis drugs [126, 127]. Moreover, the transcriptional profile of tumors displaying chromothripsis has been associated with an immune evasion phenotype [127].

Whole genome sequencing has documented chromothripsis frequency exceeding 50% in certain tumors [128] and an average prevalence higher than 30% across cancer types [129], though the occurrence varies widely depending on tumor types [120]. The association between age and chromothripsis seems also to be tumor-specific: in acute myeloid leukemia (AML) [130, 131] and in a large multi-tumor screen [131], incidence increases with advanced age, whereas no correlation with age has been observed in prostate cancer (PC) [132]. In osteosarcomas, chromothripsis was detected throughout all ages, with incidence being highest at adolescence and old age [133].

2.1.3. Mini- and microsatellite copy number alterations

A distinct category of SVs comprises mini- and microsatellite copy number alterations. Given the positive correlation between lifespan and DNA repair capacity [134], it has been proposed that age-related deficiency in the cellular mechanisms of DNA repair [i.e., nucleotide excision repair pathway (NER), nonhomologous end-joining pathway and mismatch repair (MMR) system] [42, 135-138] could contribute to the progressive accumulation of genetic damage [135] (Fig. 1B).

In particular, impairment of the MMR system with age [139] is evidenced by the acquisition of microsatellite instability (MSI) [138], which may predispose individuals to cancer. Indeed, excessive MSI has been strongly linked to colorectal cancer (CRC), often due to loss of the DNA MMR system [140]. The biology of MSI-high (MSI-H) in elderly CRC patients is attributed to hypermethylation of the MMR gene promoters (e.g., MLH1). Age-related MLH1 promoter methylation in normal colonic mucosa is closely linked to age and to the development of sporadic CRCs [141].

Approximately 15% of spontaneous CRCs display MSI, being the vast majority of these caused by epigenetic silencing of MLH1 [142]. A similar age-related increase in MSI and the microsatellite variability have been documented in gastric lymphoma [143]. Microsatellite mutations in human blood also increase with age [137, 138], with the highest rates seen in tumors with MMR deficiency, such as endometrial, rectal and stomach cancer, but microsatellite mutations were also detected in cervical and breast tumors [144].

Defects in DNA MMR machinery correlated with specific driver mutations in *PIK3CA* and *FBXW7* in CRC and stomach cancer, and with mutations in *KRAS* in uterine carcinoma and stomach cancer [145]. Moreover, deficiency in the DNA-proofreading system has also been reported in uterine carcinoma and CRC and was associated with mutations in *PTEN* and in *APC* genes, indicating that *POLE* defects may cause characteristic driver lesions in these cancer types [87].

Given that (i) there is an association between cancer and MSI, (ii) most malignancies occur in old people, and (iii) DNA repair capacity decreases with age, it has been postulated that defects in MMR mechanisms may contribute to the high cancer incidence in the elderly and may affect the efficiency of cellular functions.

2.1.4. Transposable elements

Transposable elements (transposons, TEs), particularly retrotransposons that mobilize via an RNA intermediate [146], are mobile genetic elements capable of copying and inserting themselves into new genomic locations. This "copy-and-paste" mechanism, which leads to the generation of repetitive sequences, not only contributes to intra- and inter-individual variation, but also acts as a potent insertional mutagen [147]. Beyond this mutagen role, retrotransposons can also impact gene regulation, epigenetic landscapes, genomic stability, and the expression of small non-coding RNAs (sncRNAs) [147] (Fig. 1A), conditions also involved in cancer development and progression [148].

Among retrotransposons, long interspersed nuclear element (LINE-1, L1) is particularly significant as it is the only protein-coding mobile genetic element in the human genome [149]. L1 expression drives chromosomal rearrangements, copy-number alterations and subclonal copy-number heterogeneity, contributing to chromosomal instability [150]. L1 activation has been detected in approximately 50% of human tumors [151, 152] and is considered a potent mutagenic force [153]. Retrotranspositions of L1 has significantly higher frequencies in certain cancers: 97% of invasive breast carcinomas, 93.5% of high-grade ovarian carcinomas, 89% of pancreatic ductal adenocarcinomas and 61% of carcinomas originating in the endometrium, biliary tract, esophagus, bladder, head and neck, lung and colon. Conversely, lower levels are seen in kidney, liver, cervix and prostate tumors (~24%) [154]. Particularly, high L1 retrotransposition rates are found in tumors with *TP53* mutations, underscoring a link between loss of tumor-suppressor function and increased transpositional activity [152, 154, 155].

Somatic L1 retrotranspositions can impact carcinogenesis by promoting amplification of oncogenes, such as *CCND1* [152], activating proto-oncogenes like *HDAC9* and *RUNX1T1*, or by disrupting tumor-suppressors as *CYLD, APC, MCC, PTPRM, PCM1, CDH11* and *ROBO2* [156-160].

A noteworthy finding is the positive correlation between patient age and the number of L1 insertions in sporadic colon cancers, suggesting that aging and genomic instability may have cumulative effects on retrotransposition. Hypomethylation, commonly observed in aged and tumor tissues, may create a permissive environment for L1 activation [159].

Furthermore, a big body of evidence indicates that retrotransposons are not only a marker of aging but also active contributors to the aging process and ARDs [161-163], since they are reactivated in cell senescence and with age [163, 164]. The deleterious effects of retrotransposons linked to aging are primarily due to: (i) DNA damage and associated genome instability, (ii) genetic and epigenetic effects and (iii) triggering of immune pathways associated with detection of retrotransposon nucleic acids [161].

The expression and activity of L1 are tightly regulated by various cellular processes, including repressive epigenetic modifiers [165], DNA repair [166], innate immune response [167] and autophagy [168]. Aging disrupts these pathways, leading to L1 de-repression [169-171], often in a cell-type-specific manner [172, 173]. Additionally, aging promotes an environment that enhances L1 expression, particularly through oxidative stress [174, 175] and downregulation of TE repressive factors [176]. These changes are accompanied by epigenomic remodeling and global DNA hypomethylation [1, 177-179], closely resembling patterns found in cancer genomes [180].

Senescent cells, which accumulate with age [181], further increase L1 activity [182]. De Cecco *et al.* showed that in senescent mouse and human cells, L1 elements become transcriptionally de-repressed and trigger a type-I interferon (IFN-I) response that contributes significantly to the SASP. This response is antagonized by nucleoside reverse transcriptase inhibitors (NRTIs), suggesting a link between L1 activity and inflammaging [183]. Importantly, enhancing heterochromatin formation or silencing retrotransposons can reduce age-related L1 activation and even extend lifespan [184].

However, senescence is not the only contributor to the increased retrotransposon activity observed in aging, given that a robust retrotransposon activation with aging is observed in several species devoid of cell senescence [182, 185] and in mouse tissues with a low burden of senescent cells [183, 186]. Collectively, these studies indicate that retrotransposons causally contribute to the aging process and highlight them as potential targets to promote healthy longevity.

2.1.5. Mutational signatures

It has been estimated that human tissues generally accumulate approximately 40 mutations/genome/year, regardless of tissue type [80, 87]. Three landmark studies by Alexandrov *et al.* identified distinct "mutational signatures", each representing the footprint of a distinct mutagenic process that generates distinct combinations of mutation types, and provided further support for an underlying mutational process that gives rise to age-associated mutations [79, 187, 188]. The authors initially identified 21 mutational signatures operating over 30 cancer types [79], later, using a redefining approach, they identified 33 distinct mutational signatures, of which 29 were validated [87]. Among these signatures, signatures 1 and 5 displayed a correlation between mutation burden and age at diagnosis across many different cancer types [79, 87]. For both signatures, the mutation rate showed substantial variation among different cancer types and, in the case of signature 1, it seems to be determined by the cell proliferation rate [87]. Importantly, the mutation rates of both signatures do not correlate, indicating that they could have different origins.

A posterior study, which comprises 2,780 PCAWG whole genomes, also revealed a positive correlation between age and the number of mutations for several signatures [109]. Similarly, Temko *et al.* [145] showed that 6 associations between mutational processes and driver mutations involved signatures that are known to correlate with age at diagnosis [87], highlighting the important role of aging-related processes in cancer initiation.

2.2. DNA damage and DNA damage repair

The correction of DNA alterations induced by exogenous and endogenous environmental insults involves several complex DNA repair mechanisms, which trigger cell cycle checkpoints and allow DNA damage repair, hence reducing the probability of tumor development [189, 190]. Upon severe DNA damage, temporary/permanent cell cycle arrest or apoptosis may occur. While protecting against cancer, these responses can also have adverse long-term effects, such as the depletion of stem-cell reservoirs, contributing to aging (Fig. 1B).

Extensive evidence links DNA damage accumulation, defective DNA repair machinery and aging [3, 42, 134-136, 166, 191], and has pointed out the age-dependent accumulation of DNA damage as a contributor to the impairment of cellular and organ functions and the higher rate of diseases, such as cancer, in the elderly (Fig. 1B). Similarly, aberrations in DNA damage signaling and repair are closely associated with cancer [190, 192, 193]. Defective DNA damage repair pathways may arise from genetic inactivation (e.g., mutations in MMR genes or homologous recombination repair genes) or from epigenetics (e.g., silencing by promoter hyper-methylation, histone post-translational modifications) [190]. Genes encoding components of the DNA damage response (DDR) are among the most frequently mutated genes in cancer [194, 195] and their inactivation promotes a "mutator phenotype", leading to the accumulation of additional cancer-driving genomic aberrations [196-198]. Experimental work carried out in a zebrafish *MYCN* transgenic model shows that mutations in the DDR genes, including *Brca2*, *Atm* and *Palb2,* enhance neuroblastoma formation and metastasis and upregulates cell cycle checkpoint and DNA damage repair signatures [199].

In addition, DNA repair deficiencies have been proposed to accelerate the onset of a wide variety of ARDs [200]. Accordingly, mutations in DNA repair pathways (e.g., *POLH,* XPA/B/C/G, DDB2, *WRN, BLM, BRCA2, FANCA*, *ATM, RECQL4, ERCC4/6*) can also result in several premature aging (progeroid) syndromes

(which mimic many of the characteristics of human aging), including Werner syndrome (WS), Bloom syndrome (BS), Rothmund-Thomson syndrome, Cockayne syndrome, xeroderma pigmentosum (XP), trichothiodystrophy, Fanconi anaemia (FA), Seckel syndrome, ataxia telangiectasia (AT), ataxia telangiectasia-like disorder, cerebroretinal microangiopathy with calcifications and cysts and Nijmegen breakage syndrome [201]. Many of these syndromes not only display accelerated aging phenotypes, but also predispose to cancer, as seen in XP [202], WS [203], BS [204], FA [205], AT [206]. It has been suggested that the presence of DNA lesions can induce significant rearrangements of intracellular signaling pathways, metabolism and autophagy [207], changes that are observed in physiological aging, underscoring the central role of genome maintenance in cellular responses and, ultimately, aging.

Stem cells, with their long lifespan, are particularly vulnerable to replication-induced mutations and, although equipped with mechanisms to safeguard genomic integrity, they accumulate DNA damage with age [208]. Aged mesenchymal stem cells display enhanced DNA damage and a downregulation of genes associated with base excision repair (BER) and NER, MMR, and double-strand break repair (DSBR). In addition, hematopoietic stem and progenitor cells show an age-related decline in DSBR efficiency, fostering genomic instability and mutagenic burden, which can lead to bone marrow malignancies [41].

Similar to other tissue-specific stem cells, hematopoietic stem cells (HSCs) are susceptible to aging-related stress, losing self-renewal and regenerative capacities [209, 210], leading to a reduced blood cell production and immune dysfunction [211]. Aging also fosters clonal hematopoiesis, whereby genetically mutant HSCs expand selectively [209-211], conferring a modest but significant risk of leukemia [45]. DNA damage is a primary driver of HSC aging [212, 213], with aged HSCs exhibiting a 2- to 3-fold increase in accumulated DNA damage [213, 214]. In addition, mutations in epigenetic modifiers are often observed in healthy elderly individuals, altering the epigenetic landscape of HSCs and influencing both aging and hematological cancer susceptibility [212, 215]. Of note, changes in epigenetic methylation landscapes are a hallmark of hematological cancers and promote their initiation and progression.

Damaged stem cells undergo growth arrest, apoptosis or senescence leading to decreased overall number and/or functionality of the stem cells, with the subsequent reduction of regenerative capacity and loss of tissue homeostasis, contributing to cancer development (Fig. 1C). Furthermore, some of these damaged cells can evade control pathways acquiring additional mutations (e.g., reactivation of telomerase, loss of $p16^{INK4a}$) enabling unchecked proliferation and creating a permissive environment for new malignancies (Fig. 1C) [208].

Accretion of DNA damage contributes to aging not only by impairing tissue maintenance but also by promoting inflammation [191], a hallmark of aging and a driver of many ARDs, which will be discussed later. Notably, many progeroid syndromes exhibit chronic inflammation states [201]. Age-related DNA damage accumulation can activate the inflammation pathway via the cGAS-STING axis or NF-κB activation by ATM, two mechanisms also triggered by cellular senescence, transposon activation and the accumulation of persistent R-loops [191]. In turn, chronic inflammation perpetuates itself through cytokine secretion, which promotes redox stress, activates DDR, and leads to senescence and SASP production, thus establishing a vicious cycle of DNA damage and DDR-mediated senescence and inflammation, accompanied by the constitutive activation of the immune system [216].

2.3. Telomere attrition

Telomere shortening is a well-established feature of normal human aging, providing a barrier to tumor growth and contributing to cell senescence [217]. Indeed, age-dependent telomere attrition has been reported in 21 out of 24 human tissues examined [218]. Furthermore, two progeroid syndromes, Hoyeraal-Hreidarsson syndrome and dyskeratosis congenita (DKC), are linked to mutations in components of the telomerase complex (i.e., *ACD* [219] and *RTEL1* [220], respectively), that cause accelerated telomere attrition [216-219]. Notably, DKC, which involves mutations also in other telomerase-associated genes, including *WRAP53*, *TERC*, *CTC1* and *TERT*, exhibits increased cancer predisposition [221].

In non-proliferating, post-mitotic tissues, telomere dysfunction may arise from DNA damage within telomeres. Such lesions, which appear to be irreparable, lead to persistent DDR signaling [222]. This unrelenting telomeric DDR (tDDR) activation enforces a chronic senescent phenotype [223]. The tDDR activation is also triggered by age-related telomere shortening, and therefore is often causally linked to many aging hallmarks, including aberrant nutrient sensing, proteostasis loss, mitochondrial dysfunction, defective autophagy and epigenetic deregulation (Fig. 2A). This has led to the suggestion of a “telomere-centric” mechanistic rationale for explaining diverse aging-associated processes [218].

Evidence supporting tDDR as a driver of aging and ARDs comes from observations that conditions known to accelerate aging, including mitochondrial dysfunction, impaired autophagy, chronic inflammation and obesity,

promote tDDR. Conversely, interventions known to extend healthspan, including exercise, dietary restriction, 17β-estradiol and rapamycin administration, have been shown to blunt tDDR [223]. It has been proposed that it is not telomere deregulation *per se* that drives aging and ARDs, but rather is tDDR, activated by telomere dysfunction, that causes cellular senescence, which, through SASP induction, contributes to the age-related loss of tissue functions [224] (Fig. 2A).

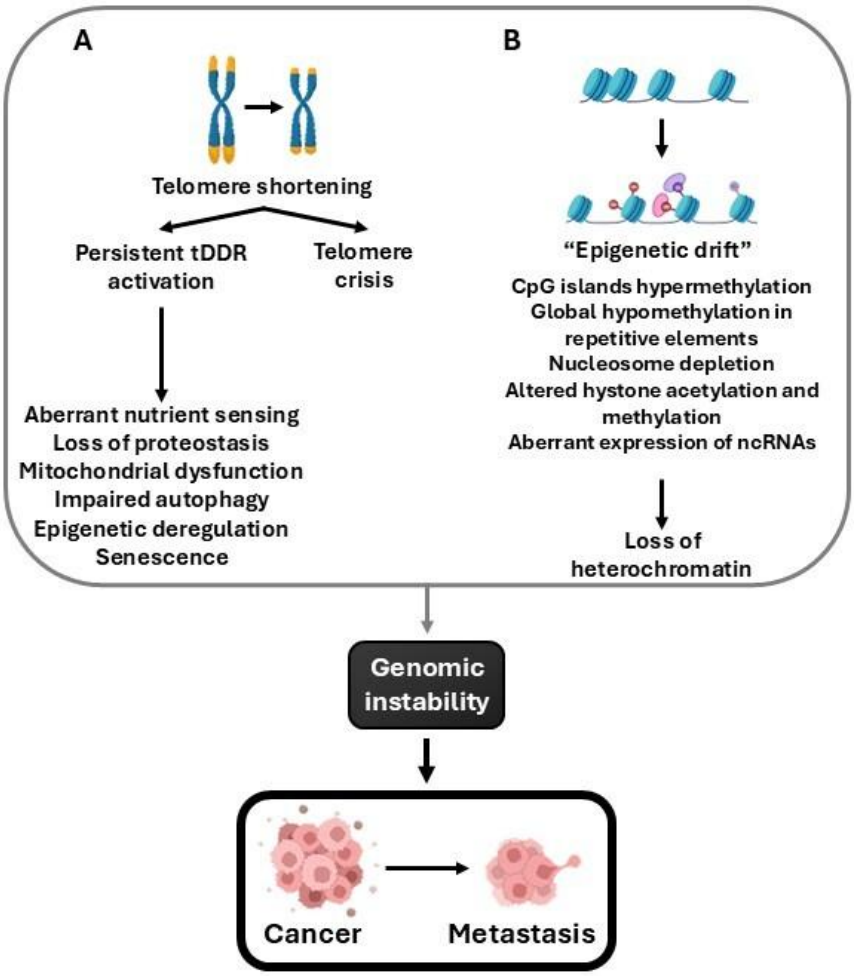

Figure 2. Processes that occur during aging that promote cancer initiation and progression: telomere shortening and "epigenetic drift". (A) Telomere shortening induces persistent activation of the telomeric DNA damage response (tDDR) that is causally linked to many aging hallmarks that promote cancer development. In addition, loss of telomere protection of the ends of chromosomes can result in telomere crisis, which is a state of extensive genome instability that can favor cancer initiation and progression. **(B)** Aging phenotype is associated with epigenetic drift, that can result in a higher risk of cancer development.

Telomere shortening exerts a paradoxical effect on cancer development. On one hand, critically short telomeres can suppress tumorigenesis by activating ATR and ATM kinases at unprotected chromosome ends, leading to senescence or apoptosis. On the other hand, loss of telomere protection can result in telomere crisis [225], a state of extensive genome instability that facilitates cancer progression by inducing chromothripsis, kataegis and tetraploidization [226] (Fig. 2A). Escape from telomere crisis typically requires telomerase activation, which restores telomere integrity and replicative potential. This results in a telomerase-positive, transformed cell with a massively rearranged, but stabilized, genome enriched with new and potentially tumorigenic genetic alterations [227].

Using a zebrafish model, Carneiro *et al.* demonstrated that, as age progresses, telomeres shorten to critical lengths only in specific tissues (gut and muscle), independently of their proliferative rates. This telomere-associated DNA damage not only impairs local tissue function, but also facilitates the onset of cancer, cachexia and infection in other tissues. The onset of such conditions correlated with the age at which most tissues started to exhibit short telomeres, and telomerase mutants ($tert^{-/-}$) zebrafish recapitulated these diseases prematurely [228].

Similarly, Lopes-Bastos *et al.* investigated melanoma progression and found that tumors display similar incidence and invasiveness in $tert^{-/-}$ and telomerase wild-type zebrafish. However, at later stages, $tert^{-/-}$ tumors show reduced cell proliferation, enhanced apoptosis,

melanocyte differentiation and immune cell infiltration. These results suggest that telomerase deficiency constrains melanoma progression through both tumor-autonomous and non-tumor-autonomous mechanisms [229].

2.4. Epigenetic changes

Aging profoundly remodels the epigenome, defined as the ensemble of heritable DNA and histone modifications that regulate chromatin spatial organization, modulating gene expression. The cumulative modifications occurring during aging are termed "epigenetic drift" [76] (Fig. 2B). The foremost age-associated epigenetic modifications encompass CpG islands hypermethylation at specific loci (e.g., Polycomb gene) alongside global hypomethylation in repetitive elements [172]. In addition, a general nucleosome depletion, altered histone acetylation and methylation, telomere shortening and an aberrant expression of ncRNAs are observed with aging [230, 231]. Collectively, these modifications reduce heterochromatin integrity and increase genomic instability (Fig. 2B). Notably, epigenetic age, as measured by CpG methylation profiles, has been proven distinct from cellular senescence, telomere attrition and genomic instability, yet it correlated with mitochondrial activity, nutrient sensing and stem cell composition [232].

Epigenetic reprogramming is also recognized to be one of the earliest and most comprehensive genomic aberrations happening during carcinogenesis [233], being associated with a broad spectrum of cancers [234]. Hypermethylation of the promoters of tumor-suppressor genes (e.g., *Rb*, *RUNX3*, *p14*, *p15*, *p16*, *p21*, *TIGI*), regulatory genes (e.g., RAS association domain family 1A), retinoic acid receptor β, and DNA repair system genes (e.g., *BRCA1*, *MGMT*) can result in their inactivation, genetic instability and subsequent cancer development [235]. Conversely, DNA hypomethylation contributes to carcinogenesis by activating oncogenes, inducing microsatellite instability, reactivating TEs within the genome, and altering therapy responses [236]. Interestingly, aging stem cells, which acquire an abnormal methylation pattern that stabilizes stemness, are similarly predisposed to malignant transformation [237]. Of note, parallel genetic mutations, often observed in leukemia, further support the clonal selection of altered stem cells during aging, thereby linking epigenetic drift to age-associated carcinogenesis [89].

Notably, the epigenetic drift reported in aged tissues mirrors alterations observed in tumorigenesis [238-241], with aging and cancer sharing overlapping epigenetic signatures [242]. For instance, histone acetylation changes are associated to aberrant metabolism in aging animals, potentially impacting global gene expression [243]. Moreover, the age-driven accumulation of epigenetic modifications has been associated with BRAF-driven tumorigenesis [244, 245], while mammary tissue harboring BRCA1/2 mutations, which predispose to BC, showed an accumulation of epigenetic modifications [246]. Specific epigenetic mutations, such as hotspots of CpG methylation in *TP53,* account for ~37% of somatic *TP53* mutations, underscoring that these mutations are strongly involved in cancer development [247]. Similarly, L1 hypomethylation in colorectal adenomas correlates with a higher CRC risk [248].

The strong relationship between epigenetic changes and biological aging has led to the development of the so-called "epigenetic clock", tens of different algorithms that use methylation levels at selected CpGs to estimate biological age in different tissues and organisms [249-252]. The discrepancies between chronological and epigenetic age is called "epigenetic age acceleration". A positive epigenetic age acceleration indicates that a tissue is aging faster than expected by the chronological age and it has been hypothesized to be associated with the risk of ARDs, including cancer [250, 253, 254].

Several studies have recently explored the association between the accelerated epigenetic clock and tumorigenesis [246, 253, 255-258]. Among these, the epiTOC (Epigenetic Timer Of Cancer) is particularly notable. Based on the methylation status of Polycomb genes' promoters, epiTOC predicts cancer risk and is accelerated not only in cancer, but also in preinvasive lesions, in normal epithelial cells at risk of neoplastic transformation and normal epithelial cells exposed to carcinogens [259]. Lung cancer susceptibility has been associated with intrinsic epigenetic age acceleration, with smokers showing a higher oncogenic risk [260]. Moreover, methylomic-drift of CpG island in premalignant esophageal lesions has been used by Curtius *et al.* to predict progression to esophageal adenocarcinoma [261].

However, findings across different epigenetic clocks and cancer types are not always consistent [255, 262]. For example, metagenomic studies reveal that the GrimAge acceleration may be the best indicator of CRC risk, while other clocks show less consistent association [262]. As suggested by Liu *et al.*, such discrepancies likely reflect the fact that distinct clocks capture different aspects of biological aging, influenced by tissue and population variability [255]. Therefore, more accurate clocks are being developed to improve the prediction of cancer associated risks [263-266].

A recent work studied the functionally enriched modules of age-related and cell type-specific DNA methylation sites associated with senescence, proliferation and stem cell fate, and their association with current and future cancer risk. It identified consistent age-

related patterns, exacerbated in cancer, that can be modified by carcinogenic exposures and are mitigated by risk-reducing interventions. Intriguingly, within the same individual, cancer may elicit an acceleration of aging in a tissue at risk but a deceleration of aging in other tissues [267].

2.5. Microenvironment and senescence

Apart from the gradual accretion of oncogenic mutations, malignant tumorigenesis also necessitates a permissive and supportive tissue environment in which mutant cells can fully express their neoplastic phenotype [268, 269]. Indeed, while genetic alterations in tumor cells are crucial for the initiation of malignancy, a dynamically evolving tumor-associated ECM is critical for tumor progression because it influences virtually every behavioral facet of stromal and tumor cells. These facets include uncontrolled proliferation, evasion of growth suppression, death resistance, replicative immortality, initiation of invasion, avoidance of immune destruction, chronic inflammation, enhanced angiogenesis and deregulation of cellular energetics, all of them well-established hallmarks of cancer [46, 270, 271].

During aging, components of the ECM become damaged through crosslinking, fragmentation, glycation and enhanced protein aggregation. These cumulative changes impair organ function, contributing to the subsequent development and progression of ARDs [272, 273]. Also, neoplastic progression could be promoted by cellular and molecular alterations of components of the tumor microenvironment (TME) induced by stromal aging and senescence. Experimental evidence shows that neoplastic transformed rat liver epithelial cells, which displayed low tumorigenic potential when transplanted into the livers of young adult rats, exhibit increasing tumorigenicity in the livers of older rats [274]. Likewise, placing tumor cells into an embryonic ECM reprograms them to lose their tumorigenicity and metastatic potential [275]. Inversely, placing aged stem cells or senescent cells in a “younger” ECM rejuvenates these old cells [272]. In the same line, a recent study carried out in syngeneic estrogen receptor (ER)+ breast cancer (BC) mouse models shows that dormant disseminated tumor cells (DTCs) maintain a dormant phenotype in young mice but accelerate metastatic outgrowth in an aged or fibrotic microenvironment [276]. Similarly, aged lung microenvironment constitutes a permissive niche for efficient outgrowth of DTCs, while aged skin inhibits melanoma growth but promotes dissemination [277].

WNT5A has been reported as an activator of dormancy in melanoma disseminated cancer cells within the lung [278]. Age-induced reprogramming of lung fibroblasts enhances their secretion of the soluble WNT antagonist sFRP1, which suppresses WNT5A expression in melanoma cells, enabling efficient metastatic outgrowth. Taken together, these findings indicate that progressive changes in the microenvironment, associated with increasing age, allow tumor formation by providing a less suppressive, and in many cases overtly supportive, microenvironment for expression of the tumorigenic phenotype. This supports the widely discussed notion that the high incidence of cancer linked to aging may result from a dual mechanism: both the accretion of somatic mutations in tumor cells [279] and age-related pro-oncogenic changes in the surrounding tissue milieu [280, 281].

The effects of this aged milieu on cancer can be attributed mostly to three interrelated factors: (i) biomechanical changes in the stromal microenvironment, (ii) senescent stromal cells and (iii) alterations in the secretome and the immune microenvironment [282, 283]. The TME that surrounds cells in solid tumors consists of ECM, composed primarily of structural proteins such as elastin, laminin, collagen and fibronectin, as well as diverse cell types (e.g., endothelial cells, smooth muscle cells, fibroblasts, myofibroblasts, mesenchymal stem cells, pericytes, nerves and tumor-associated immune cells) [284]. The relative proportions of these cells are impacted by several factors, including inflammation and aging itself, and can determine the establishment of a pro-oncogenic or a tumor-suppressing microenvironment.

2.5.1. ECM remodeling

One of the most well-documented changes is tissue stiffening, which is associated with aging and cancer, among other pathologies [285, 286] (Fig. 3A). ECM stiffness regulates proliferation, migration and invasion of cancer cells, stemness, angiogenesis and the ability of tumor cells to evade immune system surveillance, and therefore governs cancer initiation and progression, metastasis and drug resistance [287]. Breast ECM stiffness increases with aging, and it is associated with enhanced invasiveness and aggressiveness of BC cells [282]. Moreover, matrix stiffness can promote epithelial-to-mesenchymal transition (EMT) in hepatocellular carcinoma, and patients with stiffer livers display a higher incidence of cancer recurrence [230].

Multiple transcription factors have been implicated in the regulation of cancer progression in response to matrix stiffness, including NF-κB, SOX2, β-catenin, YAP/TAZ, Snail and HIF1A [287]. Aging also affects ECM remodeling enzymes: the activity of the matrix metalloproteinases (MMP), which degrade ECM components, increases with age [288], while the production of ECM components and ECM-modifiers by aged fibroblasts decreases [289], thereby facilitating the

invasion and metastasis of tumor cells [286]. For example, in a BC aging model, MMP-1 expression increased in the TME, and it is associated with enhanced local tumor growth and formation of brain metastases [290]. Similarly, in the skin, the increased age-related degradation of the ECM is a main determinant of melanoma progression [289].

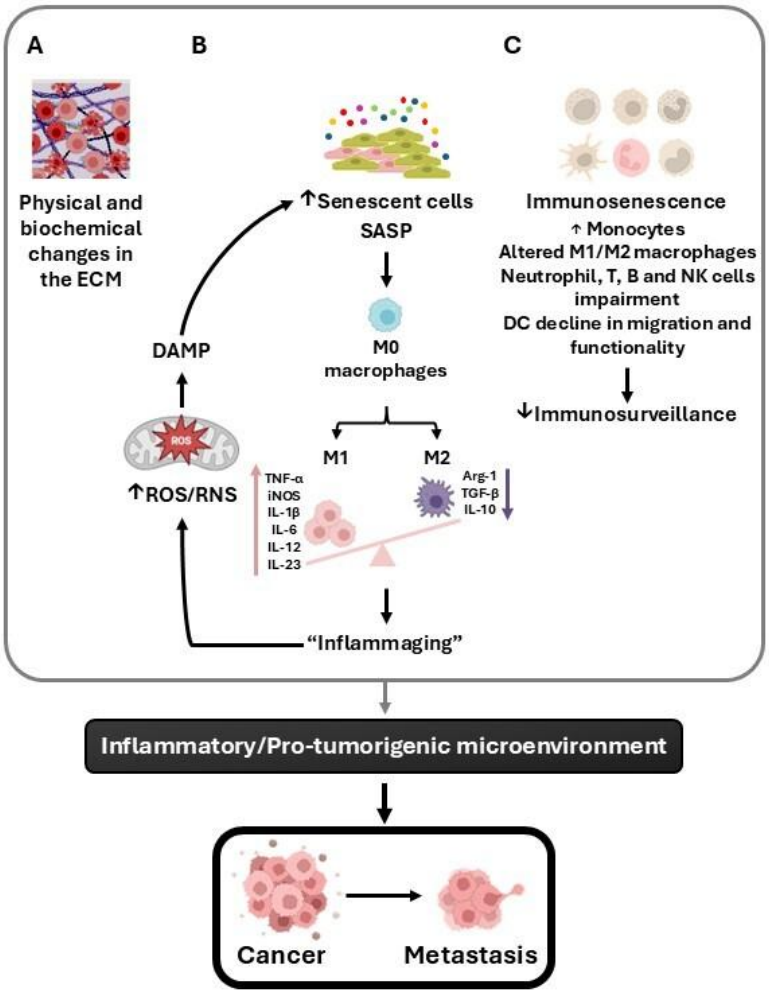

Figure 3. Processes that occur during aging that promote cancer initiation and progression: ECM modifications and "inflammaging". (A) The aging microenvironment plays an important role in the initiation and progression of cancer, mostly due to physical changes in the extracellular matrix (ECM), facilitating the invasion and metastasis of tumor cells. **(B)** Senescent cells accumulate with aging and display alterations in the secretome (i.e. senescence-associated secretory phenotype, SASP), resulting in a chronic, low-grade inflammation (i.e. "inflammaging") that can induce cancerous cell proliferation and tumor progression. SASP can transfer senescence to adjacent cells, perpetuating the inflammatory state. Inflammation promotes the generation of reactive oxygen/nitric species (ROS/RNS), inducing mutagenesis and epigenetic alterations. Reciprocally, dysfunctional mitochondria, with the production of damage-associated molecular pattern (DAMP), sustain ROS/RSN production and inflammation, promoting senescence. **(C)** Immunosenescence represents the decline in immune function with aging, it leads to a decrease in the immunosurveillance and weak anti-tumor immune responses and is associated with "inflammaging".

The impact of aging on the composition of the microenvironment has been elegantly illustrated by Li *et al*., who studied mammary epithelial and stromal changes in mice [291]. They observed a decrease in the proportion of fibroblasts with age, along with a reduced expression of ECM-related genes, suggesting an impaired ability to maintain stromal architecture. On the contrary, vascular endothelial cells exhibited a drastic age-related increase, accompanied by upregulation of genes associated with cytokines involved in the modulation of the immune microenvironment, and downregulation of genes associated with cell-cell junctions. These changes indicate altered endothelial-immune interaction, increased vascular permeability, and the establishment of an inflammatory microenvironment conducive to malignant cell proliferation and metastasis. Similarly, the intra-tumoral stroma of BC patients increases with age and can influence the response to therapy [292].

2.5.2. Inflammaging and immune microenvironment alterations

The ECM serves not only as a structural scaffold but also as a source of critical biochemical (e.g., HGF, IGFS, FGFs, TGF-β) and biomechanical cues that dictate cell growth, survival, migration and differentiation, and regulate immune function and vascular development. Given that aging is accompanied by a chronic, low-grade inflammatory state-termed "inflammaging - characterized by elevated concentrations of mediators such as interleukin (IL)-6, tumor necrosis factor-α and C-reactive protein [293], one way aging can facilitate carcinogenesis

is by inducing an inflammatory microenvironment (Fig. 3B).

Although in some instances immune cells can mediate immune surveillance and trigger anti-tumor immune responses, their permanent activation could lead to chronic inflammation, enabling and promoting the progression of several types of solid cancers [46, 294], for example PC [295].

Key cellular players in inflammaging include monocytes and macrophages. With age, there is an increase in circulating CD16+ monocytes, and aged monocytes exhibit decreased efferocytosis, migration and phagocytosis, as well as impaired resolution of inflammation due to lower expression of specific receptors, and reduced type-I IFN production. Inflammaging also alters the balance between M1 (pro-inflammatory, anti-tumorigenic) and M2 (anti-inflammatory, pro-tumorigenic, pro-angiogenic) macrophages (Fig. 3B). While macrophages in healthy elderly hepatic and adipose tissue display a more pro-inflammatory M1 phenotype, in elderly lymphoid tissues, lung and muscle, the proportion of immunosuppressive M2 macrophages increases. Interestingly, M2 macrophages trigger angiogenesis *in vivo* [296], and their number correlates with neovascularization and poor prognosis in tumor models [297] and human cancers [298].

A study on elderly BC patients found that, compared to the younger control group, those aged over 80 had a poorer tumor-immune microenvironment (TIME) and higher infiltration of M2 macrophages [299], which have been shown to promote BC cells metastasis *in vitro* and *in vivo* by secreting chitinase 3-like protein 1 [300]. Aging also reduces macrophages expression of co-receptors and major histocompatibility complex class II molecules, impairing antigen-presenting capacity [301]. Moreover, aged macrophages display increased senescence-associated markers and production of inflammatory cytokines, while phagocytosis, immune resolution, autophagy and toll-like receptors (TLRs) expression are decreased [302], changes driven by a downregulation of MYC and USF1 transcription factors [303].

Also neutrophils, which regulate T cell function, display age-associated functional impairments such as reduced phagocytic activity, impaired chemotaxis [304] and dysfunction of TLRs [305]. These changes, together with altered macrophages, have been postulated to contribute to chronic low-grade inflammation, leading to dysregulated macrophage-mediated immunosuppression and progression of a wide range of ARDs, including cancer [304]. Several studies have linked senescent neutrophils to the development and progression of prostate, lung and breast cancers, while in turn cancer cells can promote neutrophil aging, creating a vicious cycle that fosters tumor growth and metastasis [306].

Chen *et al.* have recently illustrated the negative influence of TME on CD8+ T cells functionality and their role in tumor control [307]. Reduced CD8+ T cell infiltration and function in aged mice correlate with enhanced tumor growth, and transferring T cells from young mice fails to restore tumor control in aged mice due to rapid induction of T cell dysfunction. The authors describe a tumor-infiltrating age-associated dysfunctional T cell (TTAD) state that is functionally, transcriptionally and epigenetically different from canonical T cell exhaustion. Altered natural killer (NK) cell-dendritic cell (DC)-CD8+ T cell crosstalk in aged tumors promotes a TTAD state.

Aging is accompanied not only by changes in the number of T cells, but also in their metabolism and expression of receptors, which reduces their cytotoxicity and ability to kill tumor cells [306]. In addition, although T lymphocytes mainly exert anti-tumor effects, senescent T lymphocytes facilitate immune evasion of malignant cells [282].

The expression of the immunosuppressive immune checkpoint-associated molecules (e.g., Tim-3 and TIGIT), increases with age, further contributing to tumor initiation and progression [308].

Similarly, aging alters B cells phenotype and immune function, increasing the risk of cancer and autoimmune diseases [306]. Aging-associated B cells, which exhibit a B-cell lymphoma phenotype, accumulate in older mice and humans, and particularly in elderly individuals predisposed to B-cell lymphoma [309].

NK cells, main effectors of innate immunity, display receptors that recognize stress-induced autologous proteins on cancer cells, making them critical in cancer immunity [310]. Aging alters NK cells' number, phenotype and function (e.g., lower receptor expression, diminished cytokine secretion capacity) [311, 312], contributing to an increased susceptibility to cancer in older adults. Remarkably, Peng *et al.* reported a marked reduction in cells expressing NKp30 or NKp46 in patients with pancreatic, gastric and CRC [313].

Also DCs exhibit age-related decline in migration, antigen-presentation, phagocytosis, chemotaxis and IFN production [314], reducing immune system's ability to recognize and eliminate cancer cells. Accordingly, the use of a DC hyperactivator leads to the correction of these age-related defects and restores anti-tumor activity of DCs in elderly [315].

Inflammation might drive carcinogenesis via oxidative stress and the generation of reactive oxygen species (ROS) and reactive nitric species (RNS) [316]. These reactive species damage proteins, lipids and nucleic acid, constituting the damage-associated molecular

pattern (DAMP), recognized as "non-self" by the immune system, thereby perpetuating inflammation [317]. Aging further exacerbates oxidative stress due to mitochondrial dysfunction, dysregulated NOX activity and other free-radical generating sources, leading to the formulation of the oxidative stress theory of aging [318] (Fig. 3B), supported by preclinical and observational studies linking high levels of ROS/RNS to many ARDs and cancer [319, 320].

2.5.3. Senescence and ECM

Senescent cells, which resist apoptosis, progressively accumulate in most tissues with aging [321], contributing to the loss of tissue homeostasis [322], a key hallmark of aging [322], and to the overall aging process [181]. This accumulation of noncancerous senescent cells in aged tissues might negatively affect tumor suppression and therefore exert pro-cancerous effects. For instance, senescent cancer-associated fibroblasts (senCAF) have been identified in mouse and human breast tumors, where they secrete ECM components that blunt the cytotoxicity of the NK cells, thereby promoting tumor growth. Interestingly, senCAFs are present in HER2+, ER+ and triple-negative BC, as well as in ductal carcinoma *in situ* (DCIS), where they predict tumor recurrence [323]. Beyond fibroblasts, senescent adipocytes also contribute to the TME. In the aging mammary gland, hypertrophic adipocytes promote immune cell recruitment and white adipose tissue inflammation, which increases local estrogen production. This mechanism may partially explain the higher incidence of hormone-dependent BC in older woman, despite declining systemic estrogen levels [324].

As already mentioned, a central feature of senescent cells is SASP, that can promote precancerous cell proliferation [325] and reshape the TME, including its immune component, facilitating immune evasion [283, 326] (Fig. 3B). Within the TIME, SASP can exert dual effects: on one end, it stimulates anti-tumor immunity, enhancing therapies efficacy; on the other it fosters immunosuppressive cell infiltration, thereby dampening immune surveillance [283]. In addition, SASP impairs stem cell functions, promotes cellular transdifferentiation, remodels the ECM and spreads senescence to surrounding cells, perpetuating the inflammaging [293] (Fig. 3B) and the systemic chronic inflammation [327]. The reduced efficiency of senescent cells clearance with age, further exacerbates this burden, while accelerates senescence of immune cells (i.e., macrophages) [328] weakening immune defense in older organisms [329], providing a more permissive environment for tumor growth.

SASP is both promoted by [330] and capable of [331] promoting DDR, establishing a feed-forward loop that reinforces senescence. Due to this persistent proinflammatory state [332], senescent cells have been causally linked to many ARDs [43, 333, 334].

Immunosenescence, a specialized form of senescence [335] affecting adaptive [283, 336, 337] and innate immune cells [283, 338, 339], further shapes the aged TME. It is associated with inflammaging, SASP production, increased glycolysis and ROS and reduced T-cell production [293, 340], contributing to cancer susceptibility [306] (Fig. 3C). Epigenetic regulation (e.g., DNA methylation, histone modifications, microRNA regulation) drives much of this immunosenescence [341]. Similarly, chronic SASP-driven low-grade inflammation suppresses immune cell function, further aggravating immune deterioration [342]. Also, telomere attrition and reduced telomerase activity [343], together with antigenic stimulation and thymic involution [306], can contribute to lymphocyte senescence and functional decline. The consequences on cancer progression are profound: impaired immune surveillance allows metastatic outgrowth at distant sites [344], while immunosenescence in the TME may foster tumorigenesis and reduce the effectiveness of immunotherapy [345].

2.6. Circadian system

The circadian system controls daily (~24 h) physiological and behavioral rhythms, enabling organisms to synchronize internal physiological and metabolic processes with environmental periodic cues. This temporal regulation optimizes adaptation by activating or pausing specific processes at specific times of the day [346]. Circadian control extends beyond core clock genes (e.g., *CLOCK*, *PER*, *CRY*, *BMAL1*, *REV-ERB*) to many clock-controlled genes, including genes implicated in cell cycle, DNA damage repair, important metabolic processes and oxidative stress (Fig. 4). As reviewed by Gaucher *et al*. [347], accumulating evidence suggests a complex bidirectional interplay between the circadian clock and the cell cycle. Indeed, the transcriptional core clock machinery modulates key cell cycle regulators (e.g., WEE1, P21, P16, MYC), while several cell cycle proteins exhibit rhythmic oscillations and, in turn, influence the phase and amplitude of circadian rhythms. An aging-related defective expression of circadian clock genes may impair regulation of these downstream pathways, diminishing cells susceptibility to apoptosis, increasing genomic instability and potentially inducing carcinogenesis [348, 349] (Fig. 4).

A dysfunctional circadian system has been proposed as a link between aging and cancer [350]. Aging modifies circadian system by reducing entrainment capacity, decreasing the amplitude of endogenous rhythms and modifying their phases [351]. *Bmal1* knock-out mice

exhibit premature aging phenotypes [352], although this may partly reflect the pleiotropic functions of *Bmal1* beyond circadian regulation. Similarly, loss of sirtuin 1 (SIRT1), which regulates circadian clock components by epigenetic mechanisms, results in premature aging and aging-related circadian phenotypes [353]. In the same line, the suprachiasmatic nucleus of aged mice displays lower levels of SIRT1 [354]. Noteworthy, SIRT1 dysregulation has also been linked to tumorigenesis [350].

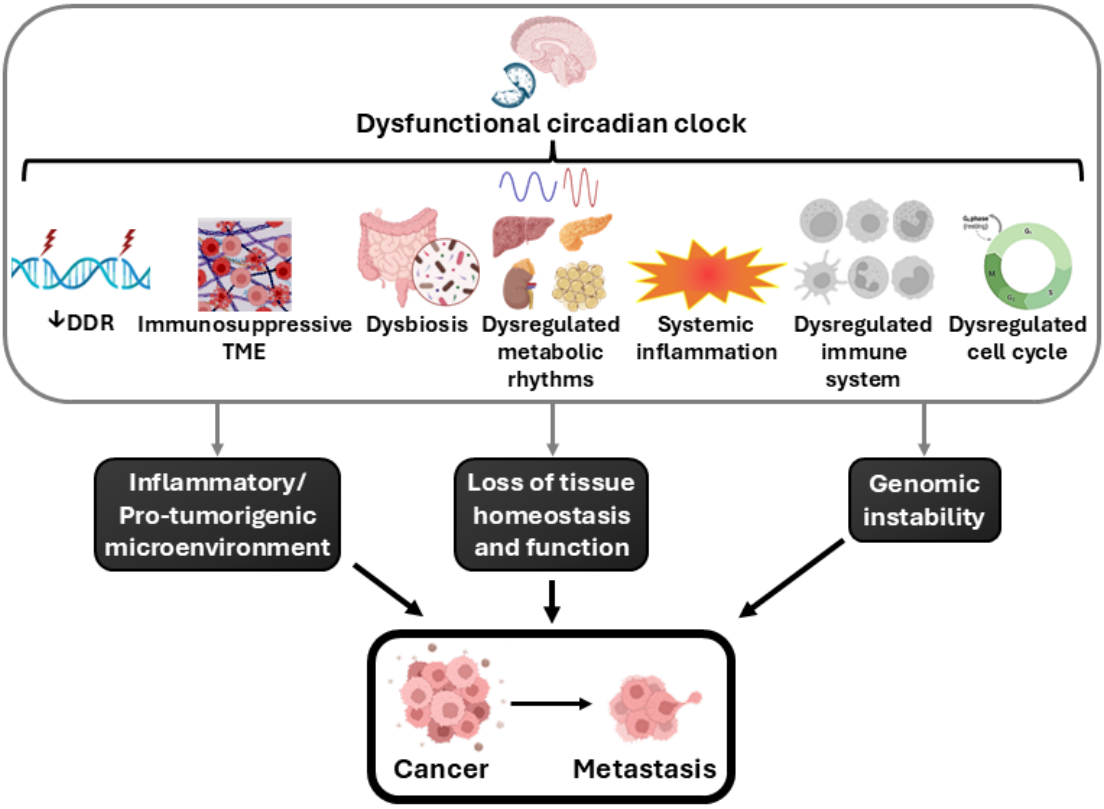

Figure 4. Age-induced dysregulation of circadian clock promotes a permissive/favoring milieu for carcinogenesis, loss of tissue homeostasis and genomic instability. Aging alters the circadian clock by disrupting the entrainment and decreasing the amplitude and modifying the phases of the endogenous rhythms. This dysregulation promotes an immunosuppressive tumor microenvironment (TME), which enhances the metastatic potential of cancer cells and results in altered metabolic rhythms that may lead to continuous activation of pro-oncogenic pathways, impaired DNA damage response (DDR) and enhanced genomic instability. Circadian misalignment may alter enteral microbiota leading to acceleration of aging and metabolic diseases, which in turn may trigger cancer development. Disturbances of the circadian clock have been also associated with systemic inflammation, dysregulation of immune systems and of the cell cycle, leading to an uncontrolled cell proliferation.

Circadian system regulates innate and adaptive immunity, two functions altered during aging and tumorigenesis [355] (Fig. 4). Aging abolishes diurnal innate immune responses and is accompanied by a loss of circadian gene transcription, a reduction in chromatin accessibility and a decrease in the diurnal expression of Kruppel-like factor 4 in macrophages [356]. Recently, it has been reported that circadian regulation of DCs trafficking to the tumor-draining lymph nodes dictates a rhythmic anti-tumor CD8+ T cell response, influencing melanoma growth; remarkably, the initial time-of-day of tumor engraftment determines subsequent tumor size in murine cancer models [357].

The comprehensive review by Xuan *et al.* describes the interactions of circadian clock with TME [358], while the review by Huang *et al.* describes in depth the mechanisms and factors by which the circadian system governs tumor development and progression, and the immune system [359]. Finally, the review by Li *et al.* describes the functions of circadian rhythms in the TME across various stages of cancer development, progression and metastasis, and points out the specific role of aging, angiogenesis and inflammation in governing circadian rhythms within the TME [360] (Fig. 4).

Clock genes alter metabolic rhythms either directly, by regulating key metabolic enzymes expression, or

indirectly, by interacting with oncogenic targets. However, their role in cancer appears to be highly tumor- and context-dependent [359]. Thus, while many preclinical studies suggest tumor-suppressing roles of the circadian clock, new studies also point to tumor-promoting functions in multiple cancer types [361]. Moreover, the clock components also exert functions not related to circadian regulation via protein–protein interactions with other pathways that are essential for carcinogenesis [361].

Chronic disruption of circadian rhythms by genetic, epigenetic and environmental factors (e.g., chronic jet lag, shift-work) heightens cancer susceptibility and disease severity [362], as well as the risk and severity of comorbidities that impact cancer therapy [361]. As reviewed recently by Su *et al.*, disrupted circadian metabolic rhythms may contribute to carcinogenesis by promoting several metabolic diseases such as obesity, type 2 diabetes mellitus, metabolic dysfunction-associated steatotic liver disease or systemic inflammation [363] (Fig. 4). Aberrant daily oscillation of metabolites may perpetuate oncogenic signaling pathways, impair DNA repair and enhance genomic instability, triggering carcinogenesis [364] (Fig. 4).

Interestingly, host circadian rhythms and gut microbiota are interrelated, constituting the "microbiome-circadian clock-axis". Diet, antibiotics, stress or aging can alter microbiota composition, disrupting circadian functions of the gastrointestinal tract, leading to metabolic diseases [365]. Conversely, circadian misalignment can reshape the microbiota, accelerating aging and several metabolic diseases [366] (Fig. 4).

2.7. Endocannabinoid system

The endocannabinoid system (ECS) comprises endocannabinoids (mainly anandamide and 2-arachidonoylglycerol [2-AG]), their receptors (i.e., cannabinoid receptors, CB1 and CB2; G protein-coupled receptor 55, GPR55; transient receptor potential vanilloid 1; nuclear receptors such as peroxisome proliferator-activated receptor gamma) and the proteins involved in the transport, degradation and synthesis of cannabinoids, such as diacylglycerol lipase (DAGL) α and β, fatty acid amide hydrolase, monoacylglycerol lipase (MAGL), and N-acylphosphatidylethanolamine-selective phospholipase D [367].

The ECS modulates many important physiological processes, and therefore its dysregulation has been linked to several ARDs, including cancer [368, 369] (Fig. 5). These conditions share common underlying mechanisms such as chronic inflammation, telomere shortening, SASP-driven inflammaging and immunosenescence. Preclinical studies suggest that the ECS contributes to healthy aging by regulating immune and inflammatory responses, suppressing oxidative stress, repressing ROS/RNS and stabilizing circadian rhythms [370]. They also improve quality of life (QoL) and general well-being in human trials [371]. Consistent with this, *Caenorhabditis elegans* studies showed that cannabinoids lengthen healthspan and lifespan, while attenuating the development of cellular senescence [371].

Age-dependent alterations of the ECS have been reported. Aged mice display a marked reduction in CB1 signaling, specifically in the hippocampus, as shown by a marked decrease in 2-AG and DAGLα protein levels [372]. Furthermore, genetic ablation of CB1 accelerates cognitive aging, induces neuronal loss and promotes hippocampal inflammation [373]. In addition, a big body of evidence implicated ECS dysregulation in the development and progression of age-related neurodegenerative diseases such as Alzheimer's, Parkinson's and Huntington's disease [374].

As previously mentioned, endocannabinoid signaling is involved in the control of several cancer hallmarks, such as cell proliferation and migration, apoptosis, angiogenesis, tumor invasiveness and metastasis [375]. Consequently, a dysfunctional ECS may induce cancer development by fostering physiological conditions that facilitate the proliferation and migration of cancer cells [369] (Fig. 5). However, their effects appear highly context-dependent, varying with type of cancer, specific genetic mutations and the TME [376]. In this context, it has been shown that cannabinoids can impact the TME in several tumor models by modulating immune infiltration, angiogenic factors, metalloproteinases and non-metalloproteinases and oxidative stress [377] (Fig. 5). For instance, cannabinoids hamper the production of angiogenic factors such as angiopoietin-2 and hypoxia-induced vascular endothelial growth factor (VEGF) and prevent angiogenesis. Recently, it has been reported that enhanced levels of endogenous 2-AG, achieved by pharmacological inhibition of MAGL, elicited a marked reduction of VEGF expression in lung cancer cells that resulted in lower migration and tube formation when HUVECs were incubated with the conditioned medium from these cancer cells [378]. Similarly, cannabinoids modulated immune infiltration and downregulated MMP-2 [379].

Noteworthy, all the immune cells express cannabinoid receptors, positioning the ECS as a key regulator of immune homeostasis and a potential gatekeeper of immune function [369]. ECS modulates the activity of NK cells [380], which are essential in the removal of senescent cells, modulation of inflammation and initiation of the adaptive immune response [381]. Xiang *et al.* reported that MAGL deficiency contributes to lipid accumulation, macrophage activation, CD8+ T

cell inhibition and tumor progression in several murine cancer models and suggested that MAGL-CB2 axis in macrophages could be a promising approach for cancer treatment. In addition, they showed that the expression of macrophage MAGL is decreased in cancer tissues and positively correlated with the survival of CRC patients [382].

Taken together, these findings support a close relation between ECS, immunosenescence and aging, suggesting that cannabinoids may hold therapeutic potential in immune disorders that are associated with various ARDs, including cancer [383].

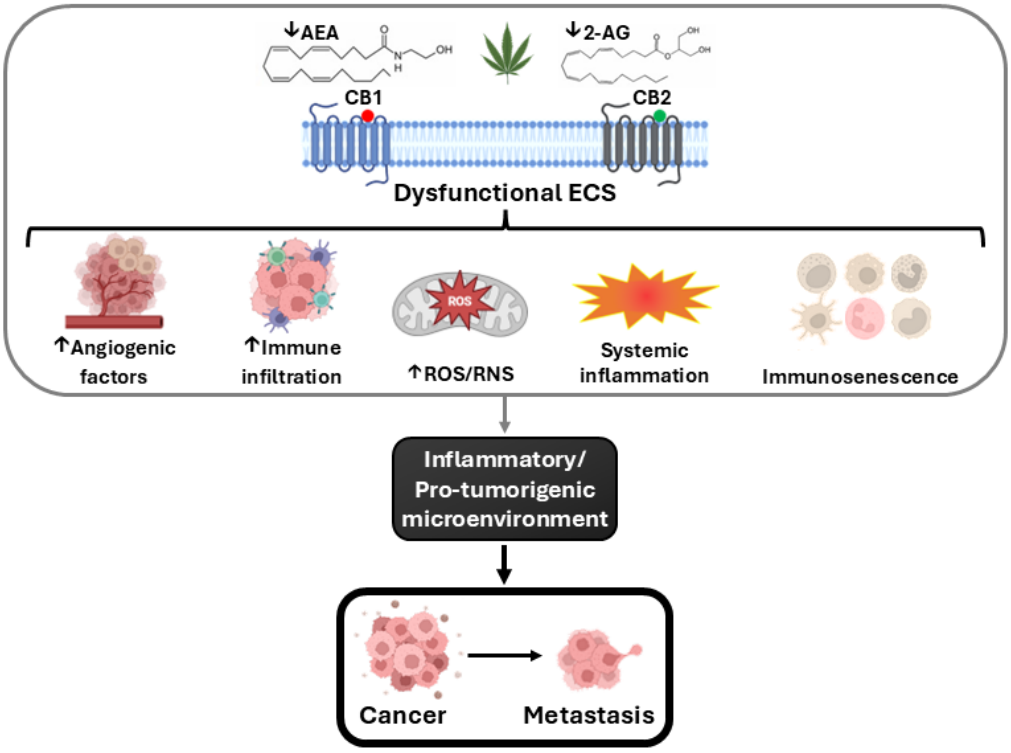

Figure 5. Age-induced dysregulation of endocannabinoid system promotes a permissive/favoring milieu for carcinogenesis. Aging blunts endocannabinoid signaling. The aged endocannabinoid system (ECS) fosters physiological conditions that facilitate the proliferation and migration of cancer cells, including enhanced secretion of angiogenic factors and MMPs, increased infiltration of immunosuppressive cells, high production of ROS/RNS, systemic inflammation and immunosenescence.

2.8. Gut microbiome

The gut microbiota, defined as the community of microorganisms inhabiting the human gastrointestinal tract, plays a fundamental role in regulating host physiology and health. Its composition changes throughout life, peaking in diversity around the age of 65 and declining thereafter, more pronouncedly in subjects over 80 years old [384]. Aging is accompanied by a gradual decrease in beneficial gut microbes and an increase of pro-inflammatory taxa, which may lead to ARDs and premature mortality [385]. For instance, the abundance of pathogenic bacteria such as *Escherichia coli*, *Butyricimonas virosa*, *Ruminococcus bicirculans*, *Bacteroides fragilis* and *Streptococcus vestibularis* increases with age in CRC, while health-associated probiotics such as *Eubacterium eligens*, decreases. Moreover, the structure and composition of the gut microbiota differ between healthy individuals and CRC patients at different ages [386].

Age-related changes in the gut microbiome are shaped by both intrinsic factors (e.g., progressive physiological decline) and extrinsic influences (e.g., therapies, diet, psychosocial factors, environmental exposures and geographic location).

Similarly, the microbiome profile is influenced by diseases. Increasing evidence links the human microbiome to cancer: microbiomes within the gut, as well as in local tissue and even within tumors, can either promote or restrain tumor progression and modulate responses to oncological therapies [387] (Fig. 6). Among the trillions of organisms comprising the human microbiota, the International Agency for Research on Cancer (IARC) currently designates only 11 as directly

carcinogenic to humans (Group 1 carcinogens) [388]. However, many others have been reported to indirectly cause cancer. A recent review by Kandalai *et al.* summarizes the diverse contributions of specific genera and species to the development and progression of several cancers [387].

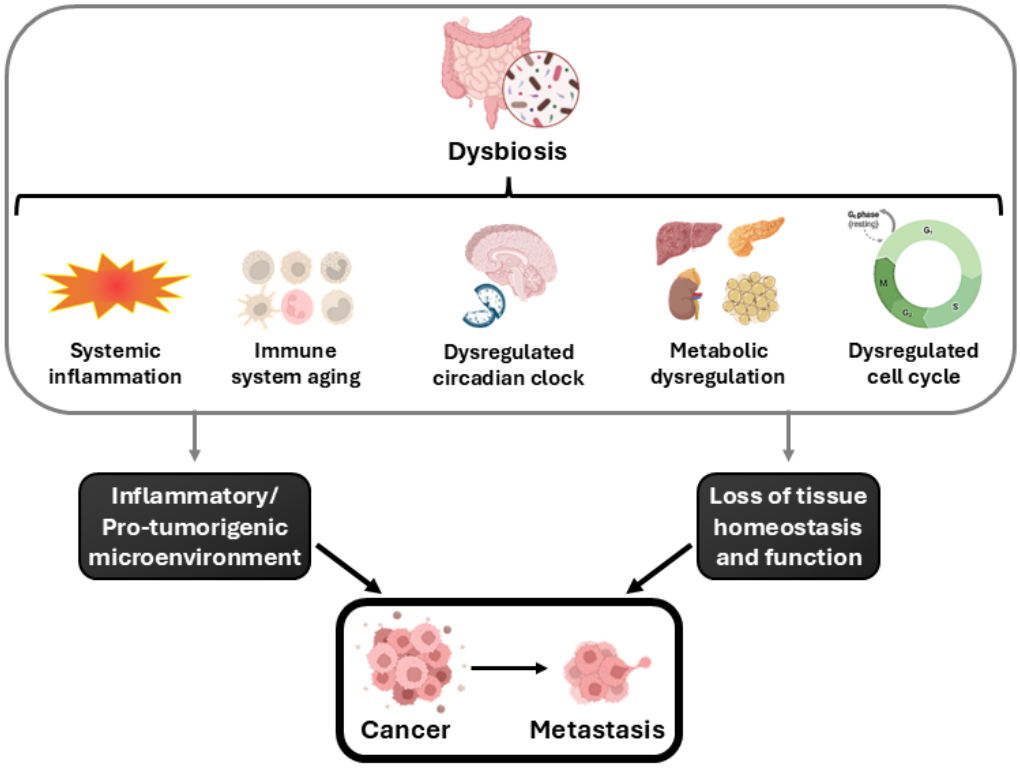

Figure 6. Age-induced dysregulation of gut microbiome promotes a permissive/favoring milieu for carcinogenesis. Aging is accompanied by dysbiosis, a gradual decline in the abundance of beneficial gut microbes and increase of pro-inflammatory microbes. Dysbiosis can promote systemic inflammation, aging of the hemato-immune system, disruption of the circadian clock, metabolic dysregulation and alterations in the cell cycle leading to cancer initiation and progression.

Age-related and disease-related decay of the gut microbiome of older individuals reflects overlapping but distinct processes [389]. Several studies suggest that alterations in the gut microbiota composition and function, known as dysbiosis, are linked to ARDs and may contribute to the aging process. Indeed, dysbiosis has been shown to affect systemic inflammation, immune function and metabolism [390], which are all hallmarks of aging (Fig. 6). In particular, dysbiosis accelerates hemato-immune aging by fostering a pro-inflammatory tissue environment, with the dominance of specific microbiota correlating with worse outcomes in hematologic malignancies [391]. Of note, centenarians often display a distinct gut microbiome composition with greater diversity and higher abundance of health-associated taxa such as *Akkermansia* and *Christensenellaceae* [392]. Conversely, non-healthy long-lived individuals tend to have higher *Streptococcus* abundance, linked to abnormal biological metabolism, whereas healthy longevity is associated with greater diversity and predominance of *Bacteroides* [393].

A recent study investigating the causal association between gut microbiota and biological age acceleration revealed that increased *Streptococcus* abundance can accelerate aging, while *Eubacterium* (*rectale group*), *Sellimonas*, *Actinomyces*, *Butyricimonas*, *Lachnospiraceae* (*FCS020 group*) had suggestive causal effects on aging acceleration, and *Lachnospira* showed potential protective effects by decelerating aging [394]. Notably, *Streptococcus* dysbiosis has been associated with several ARDs and cancers, including multiple myeloma (MM) [395], lung cancer [396], CRC [397] and gastric cancer [398]. Mechanistically, *Streptococcus* can enhance oxidative stress and induce chromatin remodeling [399], two processes implicated in both tumorigenesis and aging. Likewise, higher abundance of *Sellimonas* predicts increased risk of ER+ BC, while greater abundance of the class *Alphaproteobacteria*

correlates with a lower risk of PC [400]. *Eubacterium rectale* could trigger CRC initiation by promoting inflammation [401], whereas higher levels of *Lachnospiraceae* species are inversely correlated with CRC risk, in part through IL-10-mediated mechanisms [402]. Similarly, *Alphaproteobacteria* abundance appears protective against PC [403]. The role of *Actinomyces* remains complex: although it seems to be associated with aging acceleration, some studies report a negative correlation with esophageal cancer [404], while others identify it, along with *Butyricimonas*, as enriched in patients with recurrent esophageal cancer, suggesting that *Butyricimonas spp*. may be a biomarker of postoperative recurrence [405].

3. Clinical trials and anti-aging/cancer therapies in older adults

Although older adults (over 65 years old) are at increased risk of chemotherapy toxicity [406], studies on cancer therapy in this population remain limited. Therefore, evidence-based recommendations in everyday clinical practice are still difficult to establish. Most preclinical studies use young animals, and clinical trials (CTs) frequently underrepresent older adults [407, 408]. Recruitment in this age is particularly challenging due to comorbidities and frailty. Furthermore, randomized CTs (RCTs) should be specifically tailored for the older population, including adapted assessments and patient-reported outcomes.

Given the rapid aging of the global population, agencies for health and cancer research have undertaken a multipronged strategy to improve the evidence-based practice for cancer treatment in older adults [409-411]. In this regard, in March 2022, the Food and Drug Administration (FDA) issued guidelines on the inclusion of older adults in cancer CTs [412], underlying the importance of understanding the benefit-risk profile of drugs also in older patients, to better inform treatment decisions.

Currently, 369 studies are retrieved after entering the terms "Cancer" and "Aging", and filtering for "Older Adults (65+)" on ClinicalTrials.gov [413]. Of note, only 95 are specifically designed for older adults. Among them, 43 are completed; 11 are active, not recruiting; 18 are recruiting; 5 are not yet recruiting; 1 is enrolling by invitation; 3 have been terminated; 1 has been withdrawn; and 13 are on unknown status. Thirty-six of these CTs are observational, while 59 are interventional. Among them, 46 are randomized; 25 have supportive care as primary purpose, 11 have treatment as primary purpose and 8 are focused on prevention. Table 1 shows the main characteristics of the CTs listed in the following subsections.

3.1. CTs assessing the utility of the geriatric assessment

Geriatric oncologists face two major challenges: selecting specific patients' treatments and balancing the extension of patients' survival, while maintaining independence and QoL. To this end, the geriatric assessment (GA) is recommended to guide treatment choice in older patients [414-417]. A comprehensive GA (CGA) is a multidisciplinary evaluation encompassing functional status, comorbidity, polypharmacy, cognition, psychological status, social support and nutritional status [414, 418, 419], helping in a better estimation of the patient's overall fitness and therapy outcome. However, simplified screening tools are also available to identify patients most likely to benefit from a CGA [419, 420]. In addition, specific CGAs have been designed to predict chemotherapy side effects, including the Aging Research Group chemotoxicity calculator [421], the Chemotherapy Toxicity Tool and the Chemotherapy Risk Assessment Scale for High-Age Patients [422], the Index4 [423] or disease-specific calculators such as the Aging Research Group chemotoxicity calculator-breast cancer [424].

Table 1. Characteristics of the CTs listed in Section 3. Clinical trials and anti-aging/cancer therapies in older adults.

NCT Number (Status)	Conditions	Interventions	Phase	Allocation	Controlled	No. pts.	Age (years)	Primary outcomes	Ref.
Geriatric assessment									
NCT01472094 (Active, not recruiting)	BC under chemotherapy	Observational	N/A	N/A	No	700	≥65	Develop a predictive model of clinical and biological predictors for grade 2-5 toxicity to adjuvant and neoadjuvant chemotherapy	[424]

NCT04478916 (Unknown)	Hematologic malignancies; Solid tumor; Elderly patients	Observational	N/A	N/A	Yes	144	≥65	Number of patients received planned treatment and CGA evaluated with improved QoL	[425]
NCT03154671 (Completed)	Cancer	GAM	N/A	R	Yes	351	≥70	QoL C30 Questionnaire Global QoL scale	[426]
NCT02884375 (Recruiting)	Hematologic malignancies; Solid cancer	Observational	N/A	N/A	No	3000	≥70	Difference between initial oncologist treatment proposal and final treatment selected after GA	[427]
NCT02517034 (Active, not recruiting)	Solid neoplasm	CGA; QoLA	N/A	R	Yes	600	≥65	Rate of grade 3-5 toxicity during chemotherapy	[429]
NCT02054741 (Completed)	Adult solid neoplasm; Toxicity; Lymphoma	CGA; QoLA	N/A	R	Yes	733	≥70	QoLA (EQ-5D)	[430, 431]
NCT05919641 (Unknown)	NSCLC; Stereotactic body radiotherapy; CGA	CGA (Observational)	N/A	N/A	Yes	130	≥70	QoLA (EQ-5D)	
NCT03894917 (Recruiting)	HCC	CGA (Observational)	N/A	N/A	Yes	84	≥18	Characterize the change in disease and treatment patterns	
NCT06040801 (Recruiting)	GIC	Frailty intervention measures	N/A	NR	Yes	138	≥65	Completion rate of chemotherapy; Grade and frequency of AEs and treatment-related toxicity; QoL	
NCT04618809 (Unknown)	Metastatic gastric cancer	Didactic session; CGA; Fitness trackers for evaluation of functional status	N/A	N/A	No	100		Number of geriatric abnormalities (CGA); Percentage of treatment plan changes	
N/A	Solid malignancy at any stage	Cancer and Aging Research Group GA	N/A	N/A	No	96	≥75	Feasibility of implementing GA-guided interventions	[433]
Physical exercise									
NCT04052126 (Completed)	Aged; 80 and Over; AML; Lymphoma,NHL; Fatigue; Exercise	Individualized PA program	N/A	N/A	No	43	≥65	Compliance rate	[436]
N/A (Completed)	Curable cancer under systemic treatment	12-week mixed exercise program (aerobic+resistance); Stretching program	N/A	R	Yes	20	65-85	Feasibility	[437]
N/A	Cancer under radiotherapy and/or chemotherapy w/o bone metastasis	12-week resistance exercise	N/A	R	Yes	240	≥60	Cancer-related fatigue measures	[439]

NCT05424055 (Completed)	Cancer; Hospital acquired condition; Debility; Aging	Multicomponent exercise	N/A	R	Yes	58	≥65	Change in functional capacity; Change in cognitive function	[442]
NCT05509751 (Recruiting)	Lung cancer; GIC; Genito-urinary cancer; BC; Gynecologic cancer; Lymphoma	GAM, exercise, health education; Online chair-based exercise combined with health education	N/A	R	Yes	60	≥65	Feasability; Acceptability of the intervention	[411]
NCT03331406 (Completed)	Metastatic GIC; PA	PA program	N/A	N/A	No	20	≥18	Rate of accrual; Number of participants that adhered to PA program	[446]
Nutritional interventions									
NCT04306562 (Terminated)	Sarcopenia; Cancer	Enteral protein supplementation	N/A	R	Yes	5	≥65	Postoperative complications	
NCT00446888 (Completed)	Cancer	Standardized meals for diet stabilization; Forticare (DS); Product 4808	N/A	R	No	35	≥65	Muscle fractional synthetic rate of growth	
NCT00000611 (Completed)	Postmenopausal women w/o prior BC	Fat-restricted diet w/o CR	N/A	R	Yes	48,835	50-79	Deaths from BC	[453, 459]
NCT06496438 (Recruiting)	Depression; Anxiety disorder; Probiotics; GIC; Chemotherapy	Psychobiotics (DS); Placebo	N/A	R	Yes	270	18-85	Depression changes	
NCT06819254 (Not yet recruiting)	Fatigue	Fisetin followed by Placebo; Placebo followed by Fisetin	4	R	Yes	60	≥65	Change in Pittsburgh Fatigability Scale	
NCT04073381 (Completed)	Prehabilitation in surgical patients with abdominal cancer	Prehabilitation program	Early Phase 1	N/A	N/A	92	18-90	Length of hospital stay; Emergency room visits; Readmission; Mortality	[454]
NCT04495751 (Completed)	Fatigue	Muscadine grape extract (DS); Placebo	Early Phase 1	R	Yes	64	≥65	Patient Reported Outcomes Measurement System; Fatigue 7a questionnaire	[455, 456]
NCT04367493 (Completed)	Nutrition-related cancer; Aging	Chocolate (DS)	N/A	R	Yes	45	60-83	Change in nutritional status; Change in food ingestion; Change in body composition; Change in QoL	[458]
NCT04713332 Unknown	Radiation-induced Injuries in patients with rectal cancer	Vitamin E (DS); Hydrogen rich water (DS); Placebo (DS)	3	R	Yes	60	≥18	Total blood count; Antioxidant enzymes; Oxidative stress markers	
NCT00427193 (Completed)	Aging	CR; Control (*Ad libitum*)	N/A	R	Yes	238	21-50	Change in core body temperature; Change in resting metabolic rate	[462]

NCT03595540 (Completed)	Cancer; BC; CRC	Prolon-FMD	N/A	N/A	N/A	90	≥18	Percentage of prescribed diet consumed and intake of any extra food; Quantification of FMD-emergent AEs	[464]
NCT02970188 (Unknown)	Aging	TRF	1/2	R	Yes	12	55-79	Endothelium dependent dilation	[476]
NCT03590847 (Completed)	Overweight	TRF	N/A	N/A	N/A	10	≥65	Adherence; Retention; Safety and tolerability; Pro-inflammatory markers	[479]
N/A	Multiple myeloma	TRF; Nordic walking training	N/A	N/A	Yes	40	≥60	Microbiota composition	[480]
NCT02583269 (Completed)	Advanced malignant neoplasm; Metastatic malignant neoplasm; Unresectable malignant neoplasm	Laboratory biomarker analysis; Muscadine grape skin extract; QoLA	1	NR	No	24	≥18	Number of participants with DLT	[502]
NCT01745263 (Completed)	Improve healthy ageing in seniors; Prevent disease at older age	Vitamin D3; Omega-3 fatty acids; Strength home exercise; Flexibility home exercise	3	R	Yes	2157	≥70	Incident non-vertebral fractures; Functional muscle decline; Blood pressure change; Cognitive decline; Rate of infections	[503-506]
NCT04733534 (Active, not recruiting)	Frailty; Childhood cancer	Dasatinib+Quercetin; Fisetin	3	R	No	110	≥18	Change in walking speed; Senescent cell abundance in blood	
NCT05724329 (Active, not recruiting)	Head and neck squamous cell carcinomas	Tislelizumab+Dasatinib+Quercetin (neoadjuvant); Surgery; Tislelizumab+Dasatinib+Quercetin (adjuvant)	Yes	Yes	N/A	18-80	2	Major pathological response	[508]
Chronotherapy									
NCT04735939 (Unknown)	Glioma	Radiotherapy (Observational)	N/A	N/A	No	80	18-80	Survival time	
NCT06845267 (Not yet recruiting)	Chronic fatigue; Cancer survivors	Chronotherapy; Control	N/A	R	Yes	200	≥18	Cancer-related fatigue	
NCT02781792 (Completed)	Glioma; GM	Temozolomide; Functional assessment of cancer therapy-brain; ActTrust Condor instrument watch	2	R	No	42	≥18	Compliance with assigned administration time; Duration of response	[517]
NCT04864405 (Completed)	BC	Morning administration of ET; Evening administration of ET	4	R	No	247	≥18	Endocrine toxicity and tolerability	[518]
NCT01693861 (Completed)	mCRC	Observational	N/A	N/A	No	16	≥18	Effect of chemotherapy on urinary excretion of modified nucleosides	
NCT06850766 (Recruiting)	IDH-Wildtype Glioblastoma; Glioblastoma	Morning administration of temozolomide; Evening administration of temozolomide	N/A	R	No	50	≥18	Adherence to temozolomide dose timing protocol	

NCT06882174 (Not yet recruiting)	Metastatic NSCLC	Scheduling of the time of pembrolizumab infusions	2	R	Yes	58	≥18	Rate of deviation from scheduling intervention; Dropout rate	
NCT06418139 (Not yet recruiting)	Non-Metastatic BC	Observational	N/A	N/A	No	450	18-100	Residual cancer burden class	
NCT00852228 (Unknown)	mCRC; Liver metastases; Hepatic lesions	IV cetuximab; HAI chronomodulated chemotherapy; HAI conventional chemotherapy	2	NR	Yes	60	≥18	Incidence of complete macroscopic resections of unresectable liver metastases	[519]
NCT04263948 (Recruiting)	Pancreas cancer	Picado system internet platform and connected objects	N/A	N/A	No	42		Toxicity-related emergency hospitalization rate; Rates and grades toxicity and early tumor responses	[550]
NCT04374721 (Unknown)	Cushing syndrome; Adrenal insufficiency; Addison disease	Circadian gene expression evaluation	N/A	NR	Yes	44	18-80	CLOCK and ARNTL expression	
NCT00519168 (Completed)	Advanced BC	Urine and saliva sample; Electrode sleep recorder; Phlebotomy (Observational)	N/A	N/A	Yes	123	45-75	Home and in-hospital polysomnography ; Actigraphy; Self-report of sleep; Endocrine measures	[551]
Epigenetic modifiers									
NCT03220347 (Terminated)	NHL; Neoplasms	CC-90010	1	N/A	N/A	139	≥18	AEs; DLT; Maximum tolerated dose	[534]
NCT00404508 (Completed)	Refractory solid tumors	Hydralazine and magnesium valproate	2	NR	N/A	15	≥18	Clinical benefit; Safety	[535]
NCT00532818 (Unknown)	Metastatic cervical cancer	Hydralazine and magnesium valproate; Placebo	3	R	Yes	143	≥18	Progression-free survival	[536]
NCT02717884 (Unknown)	AML; Myelodysplastic syndrome	Tanylcypromine+All-trans retinoic acid+ Cytarabine	1/2	N/A	N/A	60	≥65	MTD determination of Tanylcypromine in combination with ATRA and with Cytarabine	[537]
NCT01829503 (Completed)	AML	Decitabine and cytarabine; Supportive care	2	N/A	N/A	44	≥60	Number of participants with best clinical response; Proportion of participants with clinical response	[538]
NCT05958719 (Recruiting)	Peripheral T-cell lymphoma; Epigenetic repression	Chidamide; Azacitidine; Liposomal mitoxantrone; Prednisone	2	NR	N/A	37	≥18	ORR; Number of participants with treatment-related AEs	
NCT02395627 (Terminated)	Stage IV ER+ BC	Tamoxifen; Vorinostat; Pembrolizumab	2	R	No	38	≥18	ORR; Number of participants with Treatment-related AE	[540]
NCT03903458 (Unknown)	Malignant melanoma	Tinostamustine+Nivolumab	1	N/A	No	21	≥18	Safety and DLT	[541]
NCT04407741 (Recruiting)	Solid tumor; Lymphoma	SHR2554+SHR1701; SHR1701	1/2	R	Yes	100	18-70	Median amount of time subject survives without	[542, 543]

								disease progression	
Cannabinoids									
NCT01812603 NCT01812616 (Completed)	GM	Sativex+Temozolomide	1/2	N/A	N/A	21	≥18	Incidence of AEs	[548]
NCT04428203 (Completed)	Recurrent prostate cancer	Epidiolex oral liquid product	1	NR	N/A	21	≥18	Number of participants with DLT	[547]
NCT05629702 (Recruiting)	Glioblastoma; Brain tumor	Nabiximols; Temozolomide; Nabiximols-matched placebo	2	R	Yes	120	≥16	Overall survival time	
NCT05525455 (Terminated)	Advanced solid tumor	TT-816; TT-816+PD-1 inhibitor	1/2	NR	N/A	9	≥18	ORR; Incidence of AEs and serious AEs; Incidence and nature of DLT; MTD; Recommended Phase 2 dose	
NCT02255292 (Unknown)	Solid tumor	Cannabidiol	2	N/A	N/A	60	≥18	ORR	
NCT06601218 (Recruiting)	Cancer; Cancer pain	Oral cannabis low THC; Oral cannabis high THC; Oral cannabis THC/CBD; Placebo comparator	1	R	Yes	80	≥18	Percent of participants that withdraw from the study or are removed due to AEs	
NCT02423239 (Unknown)	HCC; Pancreatic cancer	Dexanabinol; Sorafenib; Nab-paclitaxel	1	NR	No	112	≥18	MTD of dexanabinol+standard chemotherapies; Number of AEs	
NCT06266611 (Recruiting)	Sleep; Anxiety; Depression	fsCBD Cannabidiol; bsCBD Cannabidiol; Placebo	2	R	Yes	185	≥25	Pain interference; Pain intensity; Sleep disturbance; Fatigue	
NCT05246670 (Active, not recruiting)	CIPN; Hematopoietic and lymphoid cell neoplasm; Malignant solid neoplasm	Palmidrol; Placebo; QoLA	2	R	Yes	88	≥18	Mean change in QoLA	
NCT05822362 (Recruiting)	Mild cognitive impairment	Cannabidiol; Placebo	2	R	Yes	236	55-85	Neurocognitive function; Biomarkers of Alzheimer's disease progression	
NCT05188404 (Completed)	Cannabis use	Choice of cannabis product (Observational)	N/A	N/A	Yes	326		Change in patient global impression of change; Change in FACT-Cog; Balance task	

AEs: Adverse events; AML: Acute myeloid leukemia; BC: Breast cancer; CGA: Comprehensive geriatric assessment; CIPN: Chemotherapy-induced peripheral neuropathy; CR: Calorie restriction; CRC: Colorectal cancer; DLT: Dose-limiting toxicity; DS: Dietary supplement; ET: Endocrine therapy; FMD: Fasting mimicking diet; GA: Geriatric assessment; GAM: Geriatric assessment and management; GIC: Gastrointestinal cancer; GM: Glioma multiforme; HCC: Hepatocellular carcinoma; mCRC: Metastatic CRC; MTD: Maximum tolerated dose; N/A: Not applicable; No.: Number; NHL: Non-Hodgkin lymphoma; NSCLC: Non-small cell lung cancer; ORR: Overall response rate; PA: Physical activity; pts.: Patients; QoL: Quality of life; QoLA: Quality of life assessment; Ref.: Reference; TRF: Time-restricted feeding.

Several trials have tested the importance of GA and CGA in relation to cancer therapy in older adults [424-428]. They incorporate both physiological and cognitive/behavioral effects to build a predictive model for chemotherapy toxicity. Two large RCTs demonstrated that identifying and addressing vulnerabilities through GA reduced chemotherapy-related toxicities by 10%-20% and increased treatment adherence [429, 430]. The results

of the RCT done by Li et *al.* (NCT02517034) in ≥ 65 years patients with solid malignancies showed that GA-driven intervention (GAIN) significantly reduced grade ≥ 3 chemotherapy-related toxicities [429]. Similarly, the RCT NCT02054741 in patients over 70 years with incurable solid tumors, including stage III & IV lung cancer, or lymphoma, showed that providing a GA summary and management recommendations significantly improved treatment tolerability [430, 431].

Additional CTs are currently ongoing to assess the impact of CGA or GAIN on the management of old and frail oncologic patients, including NCT05919641 (localized non-small cell lung cancer), NCT04478916 (onco-haematological patients candidates for complex therapies) [425], NCT03894917 (hepatocellular carcinoma), NCT06040801 (frail patients with gastric, biliary and pancreatic cancer receiving palliative chemotherapy) and NCT04618809 (metastatic gastric cancer) [432]. Furthermore, a recent prospective pilot study demonstrated the feasibility of implementing GAIN among hospitalized older adults with cancer to identify vulnerabilities and to guide the interventions in the inpatient oncology setting [433].

3.2. CTs assessing physical exercise

Several studies are focusing on lifestyle interventions aimed at reducing side effects of cancer therapy associated with both aging and cancer. For example, different trials point out that physical exercise during or after radiotherapy and chemotherapy decreased molecular aging and tumor markers, while improving patients' fitness and QoL [434-436]. Evidence indicates that physical exercise can reduce pain, toxicity, fatigue, and improve mental state, QoL and mobility, as well as adherence to treatment [437-439]. In line with these findings, an integrative literature review showed that combined aerobic and resistance exercise protocols improved the functional capacity of older cancer patients [440]. Similarly, a recent systematic review confirmed the effectiveness of physical exercise, as part of a holistic management of the patient, for preventing disability, improving QoL, and partially reducing all-cause mortality [441]. Furthermore, the RCT NCT05424055 showed that an individualized multicomponent exercise program (twice daily for five days) in hospitalized older adults with cancer (mean age 74.4 years) was not only feasible, but also improved functional abilities and reduced fatigue in comparison to standard hospital care [442]. Moreover, physical exercise on chemotherapy treatment days is safe and potentially effective in reducing neuropathy and maintaining physical well-being [443, 444]. Additional benefits include decreased hospital admissions and shorter hospital stays [445].

Particular attention must be given to frail older adults undergoing cancer treatment, given that they are at heightened risk of adverse outcomes. Nonetheless, older cancer patients usually report low levels of physical activity, and poor adherence to recommendations provided by health centers. Consequently, trials are also exploring how to better involve older people with cancer in structured exercise programs (NCT04052126 [436], NCT05509751 [411], NCT03331406 [446]). Of note is the recent systematic review and meta-analysis showing that the potential harms of exercise during systemic cancer treatment are uncertain, and current evidence is insufficient to establish robust risk-benefit profiles for the application of structured exercise in this population [447].

Therefore, larger controlled RCTs are needed to evaluate the impact of physical activity on cancer progression, treatment-related side effects, post-operative recovery, long-term outcomes and QoL in older cancer patients, while accounting for their comorbidities and functional decline. These studies, which should incorporate patient-reported outcomes, will provide evidence-based guidance for a safe inclusion of physical activity in the holistic management of older cancer patients. In the field of prevention, large and long-term studies in young/adult subjects are warranted to evaluate whether different physical activity regimens promote healthy aging and thereby reduce cancer risk.

3.3. CTs assessing nutritional interventions

Epigenetic alterations are involved in both cancer and aging, and diet and nutrition are known modulators of epigenetic mechanisms [448]. Thus, epigenetics could provide a link between nutrition and cancer therapy in older adults [449]. Despite the general use of dietary supplements after cancer diagnosis, there is no consensus regarding their recommendation by medical authorities, including the World Cancer Research Fund and the American Cancer Society [450]. Therefore, different studies are testing the impact of modified food regimens and dietary supplements on aging, cancer incidence and survival, chemotherapy-induced toxicity, hospitalization rates and infections (e.g., NCT04306562, NCT00446888, NCT00000611 [451-453], NCT06496438, NCT06819254, NCT04073381 [454], NCT04495751 [455, 456]) [457]. In this context, it has been proved that, in older cancer patients receiving palliative care, the consumption of chocolate with high cocoa content improved nutritional status and physical/mental functionality (NCT04367493) [458]. Antioxidant interventions are also being explored, such as hydrogen-rich water or vitamin E, which may mitigate radiotherapy-related side effects in old colon cancer patients (NCT04713332).

Dietary fat reduction has been specifically evaluated in the WHI DM trial (NCT00000611), which randomized 48,835 postmenopausal women (50-79 years) without prior BC to a low-fat dietary intervention or to a usual diet [459]. Although the 8.5-year intervention phase showed a nonsignificant trend toward reduced, in an extended follow-up (19.6 years), BC incidence and mortality displayed a statistically significant reduction in all-cause mortality following BC, as well as in BC-specific mortality [460].

Caloric restriction (CR, sustained 10-40% reduction in daily energy intake), without malnutrition, has been shown to slow aging [461, 462] and extend lifespan. Therefore, CR may reduce the risk of many ARDs, including cancer [463]. In addition, CR, along with other nutritional interventions (e.g., short-term fasting, fasting-mimicking diet [FMD]), seems also to have beneficial effects in combination with cancer therapy [464-468]. However, in non-obese older patients, CR is rarely feasible due to frailty and comorbidities [469], and it may cause lean mass and bone density loss, damped immune system function and increased risk of malnutrition.

Intermittent fasting (IF), which alternates unrestricted feeding with shorter periods of restricted intake, and short-term fasting or FMD (5-day low calorie intervention, typically plant-based, designed to mimic the metabolic effects of a water-only fast while still providing necessary nutrients) are considered potential CR-mimicking lifestyle strategies in humans [464-467, 470]. Their metabolic benefits are likely achieved by impacting (i) modifiable lifestyle behaviors (e.g. sleep), (ii) gut microbiome, (iii) immune responses, (iv) circulating cytokines/adipokines and (v) circadian biology [467, 471].

A particular form of IF is time-restricted feeding (TRF) in animals, or time-restricted eating (TRE) in humans, which involves consuming normal daily calories amount within a limited time window (3-12 h) and fasting during the rest of the day [471]. Common TRE protocols include the 16/8, 18/6 and 20/4 schedules, which result in an 8 h, 6 h and 4 h eating window, respectively [472]. Importantly, the eating window should be aligned with the circadian rhythms (i.e., eating during active daytime hours) to optimize metabolic processes [473]. Notably, TRF maximizes the physiological benefits of CR, while minimizing its adverse effects in older adults, given that, unlike all other forms of IF, it does not require caloric reduction [470]. This feature may also facilitate the long-term adherence to this eating pattern [474]. Indeed, a pilot study with 10 overweight, sedentary older adults, instructed to fast for approximately 16 h per day for 4 weeks, showed a high level of adherence, few reported adverse events (AEs) and clinically meaningful improvements in walking speed and QoL [475]. Similarly, a randomized, controlled pilot study of short-term TRE (eating < 8 h per day for 6 weeks) in healthy, non-obese midlife and older adults demonstrated that this approach is safe and well-tolerated, and associated with high adherence, without impacting lean mass, bone density or nutrient intake [476]. Importantly, TRE exerts tumor-suppressive effects in healthy individuals and is feasible and acceptable by cancer patients, improves QoL and may have oncological benefits [477]. In this line, it has been reported that elderly individuals with the shortest fasting duration (≤ 7.5 h) display higher risks of both cancer and other-cause mortality, and that fasting duration of 11.49 h correlates with the lowest mortality risk [478]. Of relevance, a recent pilot study in overweight older adults suggests that TRE could reduce inflammation and oxidative stress [479]. Furthermore, a 10/14 TRE regimen combined with 6-week Nordic walking training program was able to change the gut microbiota of MM patients, which was predominantly represented by the phyla *Firmicutes*, *Actinobacteria*, *Verrucomicrobia*, *Proteobacteria* and *Bacteroidetes*, toward the pattern of the control healthy group [480]. Collectively, these findings suggest that TRE could be a promising therapeutic approach for the management of older cancer patients.

In the context of cancer prevention, larger CTs, with longer follow-up, using CR, FMD, IF or TRE should be performed to evaluate the potential of these interventions to promote healthy aging and eventually decrease the risk of cancer development in the elderly. These studies could generate evidence-based data that would allow health authorities to develop prevention programs to reduce the economic and health burden due to cancer.

3.4. CTs assessing calorie restriction mimetics

Calorie restriction mimetics (CRMs) are both bioactive food components and non-dietary substances (e.g., metformin, hydroxycitrate, spermidine, rapamycin, aspirin and natural polyphenols such as resveratrol) that replicate the biochemical and signaling pathways triggered by CR. CRMs elicit antitumor activity enhancing anticancer immunosurveillance and modulating energy and nutrient-sensing pathways, chaperone-mediated autophagy and epigenetic factors [481-483]. They also enhance the therapeutic efficacy of chemo-immunotherapies (e.g. immune checkpoint inhibitors targeting PD-1) [484]. CRMs are well tolerated, with metformin and aspirin showing the strongest evidence for reducing cancer risk in a selected group of patients.

Currently, there are 46 CTs registered in ClinicalTrials.gov evaluating CRMs. Although all of them include older adults, only 16 are specifically

designed for subjects aged over 65, and only 1 was conducted in cancer settings (Table 2). This CT (NCT02642094) tested the effect of sirolimus (mTOR inhibitor) in human breast tissue. While no effect was observed on basal cell population, luminal cell population was reduced, particularly in postmenopausal patients. Most importantly, it also significantly reduced prognostic biomarkers associated with BC progression from ductal carcinoma *in situ* to invasive BC (i.e., p16INK4A, COX-2, Ki67), as well as markers of the SASP, thereby conceivably preventing early BC progression [485].

Table 2. Clinical trials studying calorie restriction mimetics (CRMs) in older adults.

NCT Number	Status	Conditions	Interventions	Age (years)	Phase	Ref.
NCT06459310	Recruiting	Metformin; Aging	Metformin hydrochloride tablet; Placebo	18-65	2	
NCT02432287	Completed	Aging	Metformin; Placebo	≥60	4	
NCT02308228	Completed	Aging	Progressive resistance training; Metformin	≥65	1	[552]
NCT03861767	Terminated	Aging	Metformin ER; Placebo	≥18	3	[553]
NCT03072485	Completed	Aging	Sirolimus; Metformin; Diclofenac	≥55	1	
NCT03451006	Terminated	Aging; Inflammation; Frailty	Metformin; Placebo	≥60	2	
NCT03309007	Completed	Prediabetes; Aging	Metformin; Placebo	30-70	3	
NCT03713801	Completed	Aging; Vaccine response impaired	Metformin; Placebo	63-90	1	
NCT03996538	Completed	Aging; Age-related immunodeficiency; Vaccine response impaired	Metformin hydrochloride ER Tablets; Influenza vaccine	≥65	1	[554]
NCT01765946	Completed	IR; Prediabetes; Aging; Inflammation	Metformin; Placebo	40-75	4	[555]
NCT04264897	Completed	Aging; Insulin sensitivity; Chronic disease; Mitochondria; IR	Metformin; Placebo	40-75	3	[556]
NCT04994561	Withdrawn	Aging	Metformin+Dasatinib+Bio-Quercetin+Bio-Fisetin+Glucosamine+Nicotinamide riboside+Trans-Resveratrol	≥65	1	
NCT06463743	Not yet recruiting	Multiple sclerosis	Metformin; Placebo	55-75	2	
NCT03107884	Active, not recruiting	Muscle atrophy; IR	Metformin (Bed rest); Placebo (Bed rest); Metformin (2 week run-in only); Placebo (2 week run-in only)	≥60	1	[557, 558]
NCT04221750	Active, not recruiting	Frailty; Sarcopenic obesity; Aging	Metformin hydrochloride; Placebo; Lifestyle therapy	65-85	3	[559]
NCT05893849	Unknown	Aging	Clinical probes	≥60	Ob	[560]
NCT02745886	Unknown	Overweight; Aging	Metformin; CR	18-60	4	
NCT04375657	Recruiting	Epigenetic aging; Immunosenescence	Somatropin+Metformin+Deidroepiandrosterone; Metformin+ Deidroepiandrosterone	40-80	2	
NCT06999343	Not yet recruiting	COPD	Metformin 850Mg Tab; Placebo	40-75	3	
NCT06445569	Completed	Prediabetes; Aging	KH-1 (DS); Placebo	≥50	NA	
NCT06550271	Completed	Aging	Rapamycin	40-120	Ob	
NCT02874924	Completed	Aging	Rapamycin; Placebo	70-95	2	[561]
NCT04488601	Completed	Aging	Rapamycin; Placebo	50-85	2	[562]
NCT04742777	Recruiting	Aging	Rapamycin	70-95	2	
NCT01649960	Completed	Aging; CAD	Rapamycin	≥60	1	[563]
NCT06658093	Not yet recruiting	Aging	Rapamycin; Everolimus; Placebo	65-90	1	
NCT02642094	Terminated	Breast cancer	Rapamycin	18-80	2	[485]
NCT06727305	Not yet recruiting	Aging	Sirolimus; Everolimus	65-80	1/2	
NCT05949658	Recruiting	Aging	Sirolimus; Everolimus	55-89	1	
NCT05835999	Recruiting	Aging; IR	Everolimus; Placebo	18-80	2	
NCT00891696	Completed	Sarcopenia	Everolimus; Physical training	18-85	2	[564]
NCT04608448	Completed	Aging; Epigenetics; Inflammatory mediators	Rapamycin topical ointment; Placebo	65-95	1	
NCT05237687	Recruiting	Aging	Sirolimus	65-80	2	
NCT04284397	Recruiting	Aging	Low dose Aspirin; Control	≥18	1	
NCT02523274	Completed	Aging	Resveratrol; Placebo; Exercise	≥65	2	[565]

NCT05981053	Completed	Aging; Healthy aging; Sarcopenia; Obesity	Wine enriched with Resveratrol	40-80	Ob	[566]
NCT05500742	Unknown	Aging	Coenzyme Q10 (DS); Selenium (DS); Resveratrol (DS); TA-65 MD (DS); Placebo-1; Placebo-2	65-80	NA	[567]
NCT02909699	Completed	Aging	Resveratrol	65-99	Ob	
NCT00823381	Completed	Obesity; Metabolic syndrome; Diabetes; Aging	Resveratrol (DS); Placebo; CR	35-70	NA	[568]
NCT01842399	Terminated	Vascular resistance; Hypertension	Resveratrol (DS); Placebo	≥50	1/2	
NCT01126229	Completed	Memory	Placebo; Low dose Resveratrol; High dose Resveratrol	≥65	1	[569]
NCT00996229	Unknown	Healthy	CR; Omega-3 (fish oil capsules); Resveratrol (DS); Placebo	50-80	3	[570]
NCT02095873	Completed	Glucose Intolerance; Aortic stiffness; Vasodilation	Glyoxalase 1 inducer (DS); Placebo	18-80	1/2	[571]
NCT06585865	Recruiting	Sarcopenia; Anabolic resistance	Resistance training; Resveratrol (DS); Placebo	≥60	NA	
NCT02123121	Completed	Mitochondrial function; Physical function	Resveratrol 1000 mg/day; Resveratrol 1500 mg/day; Vegetable cellulose (Placebo)	≥65	2	
NCT02001831	Unknown	Physical disability	DS: ω-3 PUFAs+Vitamin D3+Resveratrol	≥70	NA	[572]

DS: Dietary supplement; ER: Extended-release; IR: Insulin resistance; KH-1: Nutraceutical comprised of spermidine, spermidine derivatives and probiotics; NA: Not applicable. Ob: Observational; Ref.: Reference. Source: ClinicalTrials.gov, accessed on 2025/07/02.

3.4.1. CTs assessing senotherapeutics

Senotherapeutics are a particular class of CRMs, which either selectively kill senescent cells (senolytics) or suppress the SASP (senomorphics) [486-488]. Since cellular senescence is implicated in aging-related phenotypes [489] and in the onset of ARDs, in particular cancer [323, 490-492], pharmacological interventions targeting senescent cells have been proposed to delay age-driven tumorigenesis [492-494].

The first senolytics identified were dasatinib (a pan-inhibitor of tyrosine kinase receptors) and quercetin (a flavonoid targeting Bcl-2 family members), which combination reduced senescent cells burden and ARDs in progeroid mice [495]. Since then, additional classes of senolytics have been reported, including kinase inhibitors (e.g., saracatinib, nintedanib), natural compounds (e.g. fisetin), Bcl-2 family inhibitors (e.g. navitoclax), p53 binding inhibitors (e.g., UBX0101, FOXO4-DRI, P22077/P5091), heat shock protein 90 (HSP90) inhibitors (e.g., 17AAG, 17-DMAG), Na+/K+ ATPase pumps inhibitors (e.g., ouabain, digitoxin), galactose modified prodrugs (e.g., duocarmycin, gemcitabine) and histone deacetylase (HDAC) inhibitors (e.g. panobinostat) [487, 491, 496].

In cancer therapy, senolytics have been proven to reduce chemo- and radiotherapy adverse effects, and to rejuvenate chemotherapy-induced aged tissues [497, 498]. Currently, the combination of dasatinib and quercetin is being investigated in adults who survived childhood cancer and present an accelerated aging phenotype (NCT04733534). Table 3 shows a list of the interventional CTs testing quercetin and/or fisetin in the context of cancer and/or aging. Remarkably, only 5 CTs were specifically conducted in patients aged ≥ 65 years.

However, first-generation senolytics, largely derived from drug repurposing, exhibit limited efficacy, underscoring the need for next-generation, tissue- and disease-specific senolytic strategies. Promising approaches include cell therapy and immunological strategies, such as antibody-drug conjugates, CAR-T cells or vaccines [496].

Senomorphics, also known as senostatics or SASP inhibitors, work by disrupting the connection between proinflammatory, proapoptotic senescent cells and disease, without acting directly on senescent cells. Senomorphics are inhibitors of ATM, p38 MAPK, JAK/STAT, mitochondrial complex 1- or 4-related and the NF-κB and mTOR pathways, and they include rapamycin, metformin, curcumin and ellagic acid, among others. Other senomorphics inhibit HSP90, modulate NAD+/NADH metabolism or neutralize SASP factors or their receptors [499]. Unlike senolytics, senomorphics require continuous administration because they suppress SASP activity but do not eliminate senescent cells [500].

Table 3. Interventional clinical trials studying quercetin and fisetin, two natural senolytics, in the context of cancer or aging.

NCT Number	Status	Conditions	Interventions	Age (years)	Phase	Ref.
Cancer						
NCT02989129	Withdrawn	Polyneuropathies and other disorders of the peripheral nervous system; Chemotherapy-induced neuropathic pain	Quercetin	≥18	1	
NCT05680662	Unknown	BC	Quercetin+EGCG+Metformin+Zinc	18-70	1	
NCT01732393	Completed	Chemotherapy-induced oral mucositis	Quercetin; Placebo	15-40	1/2	[573]
NCT04733534	Recruiting	Frailty; Childhood cancer	Dasatinib+Quercetin; Fisetin	≥18	2	
NCT03476330	Active, not recruiting	Fanconi anemia; Squamous cell carcinoma	Quercetin (DS)	≥2	2	
NCT01538316	Unknown	Primary prevention of PC	Quercetin (DS); Genistein (DS); Placebo	18-65	N/A	
NCT00003365	Terminated	CRC	Curcumin (DS); Rutin (DS); Quercetin; Sulindac	≥18	N/A	
NCT05724329	Active, not recruiting	Head and neck squamous cell carcinomas	Tislelizumab+Dasatinib+Quercetin (neoadjuvant); Surgery; Tislelizumab+Dasatinib+Quercetin (adjuvant)	18-80	2	[508]
NCT05456022	Unknown	Tongue cancer	Quercetin; Doxorubicin	Any	2	
NCT06615752	Terminated	Metastatic castration-resistant PC	Green tea+Quercetin+Docetaxel; Placebo+Docetaxel	≥18	1/2	
NCT01912820	Completed	PC	Green tea extract (DS); Quercetin; Placebo; Surgery	40-75	1	[574]
NCT06209229	Completed	NSCLC	Sodium nucleinate (DS)	40-65	1	
NCT06355037	Recruiting	Triple-negative BC	Quercetin; Dasatinib; Taxane/Anthracycline/Eribulin mesylate/Vinorelbine/Capecitabine/Carboplatin/UTD1/Platinum	18-70	2	
NCT06940297	Recruiting	Recurrent MM; Refractory MM	Cyclophosphamide; Dasatinib; Fludarabine; Quercetin	≥18	2	
NCT02195232	Completed	Thromboembolism of Vein VTE in CRC; in Pancreatic cancer and in NSCLC	Isoquercetin	≥18	2/3	[575]
NCT03493997	Completed	PC	Radiotherapy+IAluril®+Laluril Soft Gels®; Radiotherapy	≥18	2	[576]
NCT05651321	Unknown	Follicular lymphoma	ω-3 fatty acids; Selenium; Garlic extract; Ellagic acid; Resveratrol+Quercetin; EGCG	≥18	2	
NCT06819254	Not yet recruiting	Fatigue in cancer survivors	Fisetin followed by Placebo; Placebo followed by Fisetin	≥65	4	
NCT05595499	Recruiting	Stage I-III BC	Fisetin; Placebo	≥60	2	[577]
NCT06113016	Recruiting	Stage I-III BC	Fisetin; Placebo	≥50	2	[578]
NCT07025226	Not yet recruiting	Glioma	Dasatinib; Fisetin; Fluorodopa F 18; Quercetin; Temozolomide	≥18	1	
NCT01879878	Unknown	Pancreatic Ductal Adenocarcinoma	Verum, broccoli sprout grain; Placebo	≥18	N/A	
NCT02446795	Unknown	Renal Cell Carcinoma; Kidney Cancer	Sunitinib; Isoquercetin; Placebo	≥18	1/2	
NCT00455416	Unknown	Follicular Lymphoma	Omega 3 fatty acids; L-Selenomethionine; Allicin; Ellagic acid; Resveratrol, Quercetin; Epigallocathechin gallate	≥18	2	
Aging						

NCT04946383	Unknown	Aging	Dasatinib+Quercetin	≥40	2	[579]
NCT05422885	Completed	Aging	Dasatinib; Quercetin	≥65	1/2	[580, 581]
NCT05297032	Terminated	Lipid metabolism; Aging	Quercetin phytosome (DS)	20-70	N/A	
NCT05838560	Recruiting	Premature aging; Schizophrenia; Treatment resistant depression	Dasatinib; Quercetin	≥50	2	
NCT01376011	Completed	Stroke; Problem of Aging	Quercetin (DS); Placebo	18-75	1	
NCT04994561	Withdrawn	Aging	Metformin+Dasatinib+Rapamycin+Bio-Quercetin+Bio-Fisetin+Glucosamine+Nicotinamide riboside+Trans-Resveratrol	≥65	1	
NCT01752868	Completed	Healthy	Curcumin+Fish oil+Resveratrol+Sesamin+Acetyl-L-carnitine+Lipoic acid+Green and black teas+Quercetin+Pomegranate+Cinnamon bark	40-60	N/A	
NCT06133634	Recruiting	Aging; Endothelial dysfunction; Arterial stiffness	Fisetin (DS); Placebo	≥65	1/2	
NCT06399809	Recruiting	Peripheral arterial disease; Aging; Peripheral vascular diseases; Walking; Difficulty; Claudication	Fisetin; Placebo	≥50	2	
NCT03675724	Enrolling by invitation	Frail elderly syndrome	Fisetin (DS); Placebo	≥70	2	
NCT05838560	Recruiting	Schizophrenia; Treatment Resistant Depression; Aging, Premature	Dasatinib; Quercetin	≥50	2	[582]
NCT07000734	Not yet recruiting	Aging; Cognitive decline; Older adults; Immune senescence; Motor function; Sedentary behaviors	Dasatinib; Quercetin; Vortioxetine; Risk managment	50-70	2	
NCT06990256	Not yet recruiting	Sleep disorder; Aging	Fisetin; Placebo; Urolithin A	45-70	N/A	

BC: Breast cancer; CRC: Colorectal cancer; DS: Dietary supplement; EGCG: Epigallocatechin gallate; MM: Multiple myeloma; NA: Not applicable; NR: Nonrandomized; NSCLC: Non-small cell lung cancer; PC: Prostate cancer; R: Randomized; Ref.: Reference. Source: ClinicalTrials.gov, 2025/07/02.

A recent work compared the effects of senolytics and of senomorphics in rescuing radiotherapy-induced frailty phenotype in a mouse model. Prolonged metformin administration delayed frailty and improved short-term memory, achieving benefits comparable to senolytic administration [501].

Among natural compounds, the muscadine grape extract (MGE) is under investigation for its anticancer properties. This extract is a mixture of senotherapeutic polyphenols (e.g., gallic acid, quercetin, cyanidin, delphinidin, ellagic acid) contained in the grapes of *Vitis rotundifolia,* and has been proven as an effective anticancer therapy in different *in vitro* cancer models and has been reported safe and well-tolerated in heavily pre-treated and older cancer patients (NCT02583269) [502]. Currently, the clinical trial NCT04495751 is investigating whether MGE improves fatigue in people over 70 years who have a history of treated cancer [455].

The DO-HEALTH trial, further investigated the geroprotective effects of vitamin D (2,000 IU per day) and/or omega-3 (1 g per day) and/or a home exercise program in generally healthy and active adults aged ≥ 70 years. Results showed that omega-3 supplementation alone reduced the rate of falls by 10% [503] and the rate of infections by 13% [504]. When combined, all three interventions showed a significant additive benefit on reducing pre-frailty by 39% [505] and incident invasive cancer by 61% [503] over a 3-year follow-up. Remarkably, a post *hoc* analysis on the effect of these treatments on four next-generation DNA methylation

(DNAm) measures of biological aging (GrimAge, GrimAge2, DunedinPACE and PhenoAge) revealed that, over 3 years, omega-3 alone slowed the DNAm clocks GrimAge2, DunedinPACE and PhenoAge, and all three treatments had additive benefits on PhenoAge. These results support the notion that targeted nutritional strategies can have distinct epigenetic aging effects. Moreover, the observation that subjects with lower starting levels of omega-3 displayed larger epigenetic shifts further strengthens the use of personalized strategies [506]. These observations also endorse the geroscience hypothesis that slowing biological aging can contribute to prevent chronic diseases [507].

The preliminary results of a phase 2 CT (NCT05724329) combining anti-PD-1 therapy (tislelizumab) with dasatinib and quercetin in patients with head and neck squamous cell carcinoma show a favorable safety profile and therapeutic efficacy of the combination, with a reduction in AEs and alleviated immunosenescence [508].

As previously mentioned, nutritional interventions, which imply CR, are difficult to implement in older cancer patients, who very often present conditions such as frailty, sarcopenia and cachexia. CRMs are a feasible alternative, since they are well tolerated. While CR and CRMs show promising effects in anticancer therapy, strong evidence is still needed to support their integration in standard-of-care treatments [509]. This is particularly true in the case of older cancer patients, who are often polymedicated and thus at greater risk of adverse drug reactions. Therefore, large RCTs specifically designed for this population should be conducted to assess not only the feasibility of these interventions, but also the interactions of the CRMs with the most common medications taken by these patients. Once demonstrated the safety, RCTs should be conducted to evaluate the efficacy of these drugs in combination with standard cancer therapies.

3.5. CTs assessing chronotherapy

Over 80% of the FDA-approved drugs target molecules that display daily rhythms. Therefore, the timing of drug administration should be considered to enhance the efficacy and safety of anti-aging and oncological drugs acting on oscillating targets [510]. This concept constitutes the base of the so called “chronotherapy or circadian medicine” [511].

As reviewed by Acosta-Rodríguez *et al.*, chronotherapy in aging rests on three main observations: (i) aging is accompanied by a decline in circadian rhythms, (ii) aging-related pathways oscillate along the day and (iii) disruption of circadian rhythms results in metabolic disorders and reduce lifespan, whereas circadian rhythms restoration improves health and longevity [510]. Sulli *et al.* have proposed that restoring the balance of metabolic rhythms improves cancer therapies. Such restoration can be achieved by (i) drugging the clock by targeting core clock components, (ii) clocking the drug by optimizing the time of administration for optimal efficacy (chronotherapy), and (iii) training the clock by reinforcing daily rhythms through behavioral cycles (light exposure, sleep, physical exercise and feeding) [512]. A summary of these interventions can be found in the review by Zhu *et al.* [361]. Currently, there are 10 CTs assessing chronotherapy [513], 15 evaluating circadian dysregulation [514] and 2 studying clock genes dysregulation [515] in the context of cancer. To date, 6 CTs study circadian dysregulation in the context of aging [516], while no trial investigating chronotherapy and aging is currently registered in ClinicalTrials.gov.

In the RCT conducted by Damato *et al.* (NCT02781792), 35 glioma patients (mean age 56.31, 20-81) were randomized to receive temozolomide either before 10 a.m. or after 8 p.m. Compliance data proved the feasibility of timed temozolomide dosing, but no significant differences in AEs, QoL or survival between the groups were observed. However, the authors claimed that a larger study is required to validate the effect of chronotherapy on clinical efficacy [517].

Another RCT (NCT04864405) randomized 245 women (mean age 61.1) starting adjuvant endocrine therapy for BC to either morning or evening administration. There were no statistical differences in endocrine toxicity/tolerability measured by the change in total Functional Assessment of Cancer Therapy-Endocrine Subscale (FACT-ES) score from baseline to 12-weeks, nor in QoL [518].

The NCT00852228 CT was conducted in patients (median age 58, 33-76) with unresectable liver metastases (LM) from *wt KRAS* CRC to test whether hepatic artery infusion (HAI) with triplet chemotherapy and systemic cetuximab could increase the rate of conversion of previously unresectable LM to curative intent in previously treated patients. To that aim, 46 patients were assigned to conventional HAI and 24 to chronomodulated HAI. Objective response rates (ORR) were markedly higher, and the rate of early responses was twice as large on chronomodulated when compared with conventional delivery (38.9% *vs.* 19.6%) [519].

Chronoimmunotherapy has also emerged as a promising anticancer strategy. Recent studies demonstrated that patients with stage IV malignant melanoma or metastatic non-small-cell lung cancer receiving immune checkpoint inhibitors exhibit time-of-day dependent OS [520, 521].

Available data on possible administration-time differences in drug dynamics in the elderly is very sparse,

although the chronopharmacologic mismatch is one of the main contributors to poor therapeutic outcomes and treatment-related AEs. Therefore, additional prospective studies are needed to fully characterize the chronodinamics and chronokinetics of commonly used anticancer drugs in the elderly. Such studies will clarify whether administration-time effects are amplified or attenuated with age in comparison with young subjects, allowing to exploit the potential of the chronotherapy already suggested in young/adult patients to reduce toxicity while enhancing efficacy in older cancer patients.

Evidence for the impact of time-of-day on radiotherapy outcomes is even more limited and often with inconsistent results [522]. Furthermore, not all the studies include older adults. Two prospective RCTs conducted in head and neck cancer patients showed that afternoon treatments were associated with faster progression to a higher grade of mucositis, while the median time to develop grade III/IV mucositis was significantly longer in morning-treated patients [523, 524]. Conversely, a prospective RCT in cervical cancer patients found higher rates of severe gastrointestinal mucositis in patients treated in the morning compared with those treated in the afternoon [525].

The scarcity of RCTs and the disparity of the results of the studies carried out to date make necessary studies conducted under much more standardized conditions, using similar sources of irradiation, time intervals for morning/afternoon groups, symptoms used as the primary endpoint, as well as the use of consensus guidelines to evaluate treatment outcome.

3.6. CTs assessing epigenetic modifiers

As noted above, epigenetic alterations during aging contribute to several ARDs, including cancer. Epigenetics is a reversible process that can be countered by environmental factors, diet (epigenetic diet or "epidiet", e.g., epigallocatechin-3-gallate, curcumin, resveratrol, genistein, sulforaphane) and epigenetic drugs, also known as "epidrugs" (e.g., azacitidine, decitabine, vorinostat, romidepsin, belinostat, panobinostat, tazemetostat, enasidenib and ivosidenib). Most epidrugs act as inhibitors of DNA methyltransferases, histone demethylases, histone acetyltransferases, HDACs and protein arginine methyltransferases, although in some contexts they can also act as activators [526, 527].

Epigenetic therapy impacts energy metabolism and induces cell differentiation, cell cycle arrest and cell death, thereby influencing multiple genes and proteins [527]. When used alone or in combination with chemotherapy, oncometabolites or immunotherapy, epidrugs enhance anti-tumor activity, reduce drug resistance and stimulate the host immune response in several hematological and solid tumors (e.g., breast, skin, colon, prostate) [528]. Some of them have already been approved by the FDA for different cancers and ARDs treatments, while others are in different phases of CTs [529, 530]. Currently, there are 192 ongoing or completed CTs assessing epidrugs in the context of cancer, of which 174 include older adults. Remarkably, none of them are specifically designed for older adults [531].

Several preclinical and clinical studies have shown the potential of epidrugs, epidiets and its combination in cancer prevention and therapy [532, 533]. For instance, the CT NCT03220347 tested CC-90010, a reversible and orally active BET inhibitor, in patients with advanced or unresectable solid tumors or relapsed/refractory diffuse large B-cell lymphoma (R/R-DLBCL). CC-90010 monotherapy displayed antitumor activity, with an ORR of 13.0% in patients with R/R-DLBC and a clinical benefit rate (CBR) of 31.7% in patients with advanced solid tumors, while toxicities were generally manageable [534]. Similarly, the CT NCT00404508 assessing the response and toxicity of hydralazine and magnesium valproate in patients with solid tumors receiving chemotherapy showed clinical benefit in 80% of the patients. A reduction in global DNA methylation, HDAC activity and promoter demethylation was also observed, while treatment was well-tolerated, despite the fact that the study population was heavily pre-treated [535]. A RCT (NCT00532818) enrolling 143 patients with metastatic, persistent or recurrent cervical cancer without previous systemic treatment demonstrated improved PFS for epigenetic therapy with hydralazine and valproate plus standard cisplatin+topotecan over cisplatin+topotecan [536].

The CT NCT02717884 is one of the few CTs specifically designed to test epidrugs in elderly patients (median age 75 years). It evaluates the efficacy of tranylcypromine (a first-generation histone demethylase LSD1 [KDM1A] inhibitor) in combination with ATRA and cytarabine in elderly, non-fit AML patients resistant to prior hypomethylating agent (HMA) treatment. The combination was feasible, even at the highest tranylcypromine dose. While the ORR was modest, 48% of the patients achieved partial remission or stable disease with this 3-drug combination, indicating limited cross-resistance with prior azanucleosides treatment [537]. The phase 2 study NCT01829503 is another trial conducted specifically in older adults. It was designed to determine the efficacy of an induction regimen using decitabine as an epigenetic primer followed by cytarabine in the treatment of 44 older patients (median age 76 years) with newly diagnosed AML. Complete response was achieved by 26 patients (66.7% of evaluable patients). Fourteen of 21 (66.7%) patients with adverse cytogenetics achieved a complete response. The 4- and 8-week mortality rates

were 2.3% and 9.1%, respectively, with median OS of 10.7 months. There were no treatment-related mortalities. The authors suggest that epigenetic priming with decitabine followed by cytarabine should be considered as first-line option for older AML patients [538]. The ongoing CT NCT05958719 investigates the ORR of a new combination therapy called CAMP (chidamide, azacitidine, liposomal mitoxantrone and prednisone) as first-line therapy for untreated angioimmunoblastic T-cell lymphoma (AITL). It compares CAMP's safety and efficacy to standard treatments. Younger patients (≤ 70) receive the full CAMP regimen, while older patients receive a modified version (CAMP-light).

The combined use of epidrugs with immune checkpoint inhibitors (e.g., atezolizmab, avelumab, cemiplimab, durvalumb, ipilimumab, nivolumab, pembrolizmab) provides a novel and promising option for cancer treatment [529, 539]. For instance, a RCT (NCT02395627) in patients with therapy resistant ER+ BC tested the safety and response rate of the combination of a HDAC inhibitor (vorinostat), an anti-estrogen (tamoxifen) and a PD-1 inhibitor (pembrolizumab). Among evaluable patients who received all three agents, 3.7% achieved a complete response, with a CBR of 18.5% and an ORR of 3.7% [540]. Similarly, the NCT03903458 trial tested the combination of tinostamustine (EDO-S101) and the anti-PD-1 monoclonal antibody nivolumab in 17 patients with refractory, locally advanced or metastatic melanoma. This treatment resulted in 54% disease stabilization and 23% confirmed partial responses [541]. The CT NCT04407741 evaluates the EZH2 inhibitor SHR2554 in combination with the anti-PD-L1/TGFβ antibody SHR1701 in patients with advanced or metastatic solid tumors and relapsed/refractory B-cell lymphomas. In the efficacy-evaluable population, ORR was 57.7%, including 2 complete responses achieved by patients with metastatic renal cell carcinoma and classical Hodgkin lymphoma (cHL). Out of 14 cHL-evaluable patients, ORR was 100% and the complete response rate was 7.1%. [542, 543].

Table 4 shows a list of the interventional CTs evaluating epidrugs in the context of cancer and/or aging. Notably, only 3 CTs were specifically conducted in patients aged ≥ 65, highlighting the paucity of safety and efficacy data in this population. Dedicated CTs are needed to characterize the pharmacokinetics and pharmacodynamics of epidrugs in elderly patients, as age-related epigenetic alterations may increase the risk of treatment-related AEs and reduce the efficacy of cancer therapies and other medications. RCTs enrolling young/adult and older adults would help identify age-specific epigenetic changes and support the development of more targeted and effective therapies. Additionally, further research is required to address resistance mechanisms, off-target effects of epidrugs and the optimal combination with other anti-cancer therapies. Incorporating the evaluation of markers of epigenetic regulation into these studies will be essential to clarify mechanisms of action. Finally, innovative dosing strategies, like controlled release formulations or real-time monitoring of drug levels, could represent a step forward to increase overall effectiveness of these therapies.

Table 4. Interventional clinical trials studying epidrugs in the context of cancer and/or aging.

NCT Number	Status	Conditions	Interventions	Age (years)	Phase	Ref.
			Cancer			
NCT01200004	Terminated	Advanced cancers	Azacitidine; Lenalidomide; *Grifola frondosa*	≥13	1	
NCT05178693	Recruiting	Neuroendocrine tumors	ASTX727; Lutathera	18-99	1	[583]
NCT02395627	Terminated	Stage IV ER+ BC	Tamoxifen; Vorinostat; Pembrolizumab	≥18	2	[540]
NCT03220477	Active, not recruiting	NSCLC	Pembrolizumab; Guadecitabine; Mocetinostat	≥18	1	
NCT01534598	Completed	Neoplasms	FdCyd+THU	≥18	1	[584]
NCT03220347	Terminated	NHL; Neoplasms	CC-90010	≥18	1	[534, 585]
NCT00404508	Completed	Refractory solid tumors	Hydralazine+Magnesium valproate	≥18	2	[535]
NCT04257448	Unknown	Metastatic PDAC	Romidepsin; Azacytidine; Nab-Paclitaxel; Gemcitabine; Durvalumab; Lenalidomide capsule	≥18	1/2	[586]
NCT04648826	Withdrawn	Sarcomas; Melanomas; Germ cell tumors; Epithelial malignancies (excluding lung and renal cell carcinomas);	Bintrafusp alfa; Azacitidine	≥18	1/2	

		Pulmonary metastases				
NCT01700569	Terminated	Grade IV astrocytoma; Glioblastoma	Temozolomide; folinic acid; High voltage radiation therapy	18-70	1	[587]
NCT03612739	Withdrawn	AML; MDS	NKR-2 CAR-T cells+5-azacytidine	≥18	1	
NCT02374099	Terminated	BC	CC-486; Fulvestrant	≥18	2	[588]
NCT02664181	Completed	NSCLC	Nivolumab; Decitabine; THU	≥18	2	
NCT00533299	Unknown	Ovarian cancer	Hydralazine+Magnesium valproate; Placebo	≥18	3	
NCT01194908	Terminated	BC	Decitabine; LBH589; Tamoxifen	≥18	1/2	
NCT03903458	Unknown	Malignant melanoma	Tinostamustine	≥18	1	[541]
NCT04611711	Unknown	Digestive system tumors resistant to PD-1 inhibitors	Decitabine+TQB2450 injection; Decitabine+TQB2450 injection+Anlotinib	≥18	1/2	
NCT04965129	Recruiting	Lung cancer	Fish oil; Placebo	20-90	N/A	
NCT05680662	Unknown	BC	Quercetin+EGCG+Metformin+Zinc	18-70	1	
NCT00978432	Terminated	DLBCL	RAD001; LBH589; RAD001+LBH589	≥18	2	
NCT01121757	Terminated	Follicular lymphoma; Marginal zone lymphoma	Azacitidine; Lenalidomide	≥18	2	
NCT03682029	Active, not recruiting	MDS; CML; Cytopenia	Vitamin C (DS); Placebo	≥18	N/A	
NCT04190056	Terminated	Stage IV BC	Pembrolizumab; Tamoxifen; Vorinostat	≥18	2	
NCT00404326	Completed	Cervical cancer	Hydralazine+Magnesium valproate	18-70	2	
NCT01743560	Completed	ER+ advanced BC	RAD001; Exemestane	≥18	4	
NCT06694454	Not yet recruiting	NSCLC	Azacytidine; Carboplatin; Paclitaxel; Durvalumab; Cisplatin; Gemcitabine; Pemetrexed	18-120	1/2	
NCT00532818	Unknown	Metastatic cervical cancer	Hydralazine+Magnesium valproate; Placebo	≥18	3	[536]
NCT03765229	Completed	Melanoma	Entinostat; Pembrolizumab	18-99	2	
NCT04173585	Completed	AML	Bortezomib; Gemtuzumab ozogamicin	18-100	2	
NCT04355858	Unknown	BC	SHR7390; Famitinib; SHR3162, Pyrotinib; Capecitabine; SHR1210; Everolimus; Nab-Paclitaxel; SHR2554; SHR3680; SHR6390; SHR1701; SERD; AI; VEGFi	18-75	2	[589]
NCT02497404	Completed	Acute leukemia erythroblastic; MDS	5-Azacytidine; Fludarabine; Melphalan; Alemtuzumab; Total body irradiation	≥18	2	
NCT06714357	Recruiting	Metastatic CRC	Irinotecan; Panitumumab; VPA	≥18	2	
NCT00395655	Terminated	Locally advanced BC	Hydralazine+Magnesium valproate	≥18	2	[590]
NCT02717884	Unknown	AML; MDS	Tranylcypromine; All-trans retinoic acid; Cytarabine	≥18	1/2	[537]
NCT02951156	Terminated	DLBCL	Avelumab; Utomilumab; Rituximab; Azacitidine; Bendamustine; Gemcitabine; Oxaliplatin	≥18	3	[591]
NCT01016990	Unknown	Leukemia; Lymphoma	VPA	≥18	2	
NCT01607645	Terminated	Leukemia; Refractory anemia with excess blasts	Decitabine; Idarubicin; Cytarabine	≥18	2	
NCT02546986	Active, not recruiting	NSCLC	CC-486; Pembrolizumab; Placebo	≥18	2	[592]
NCT01729845	Completed	Previously treated MDS; AML	Cytarabine; Decitabine; Etoposide; Mitoxantrone hydrochloride	≥18	1/2	[593]
NCT02159820	Unknown	Primary malignant neoplasm of ovary; FIGO stages II to IV	Decitabine; Paclitaxel+Carboplatin	18-80	2/3	
NCT02846935	Completed	T-cell lymphoma; Aggressive B-cell lymphoma; NHL; Indolent B-cell lymphoma	Decitabine; THU	≥18	1	
NCT04407741	Recruiting	Solid tumor; Lymphoma	SHR2554+SHR1701; SHR1701	18-70	1/2	[542, 543]
NCT02847000	Completed	Metastatic pancreatic adenocarcinoma	THU; Decitabine	≥18	1	
NCT03366116	Recruiting	Neoplasms; Solid tumors	5-aza-4'-Thio-2'-Deoxycytidine	18-120	1	[594]

NCT02423057	Suspended	Neoplasms; Solid tumors	4'-Thio-2'-Deoxycytidine	18-120	1	
NCT00359606	Completed	Neoplasms	FdCyd; THU	≥18	1	
NCT00978250	Completed	Head and neck neoplasms; Lung neoplasms; Urinary bladder neoplasms; Breast neoplasms	FdCyd+THU	18-120	2	
NCT04741945	Recruiting	Preleukemia; Preleukemic Anemia; Myelodysplastic neoplasm; Cytopenia	Metformin	≥18	2	
NCT04553393	Unknown	Refractory or relapsed aggressive r/r B-NHL with huge tumor burden	Chidamide; Decitabine; Chidamide+Decitabine; Decitabine-primed Tandem CAR19/20 engineered T cells	16-65	1/2	
NCT02959437	Terminated	Solid tumors; advanced malignancies; metastatic cancer	Azacitidine; Pembrolizumab; Epacadostat; INCB057643; Pembrolizumab; Epacadostat; INCB059872	≥18	1/2	[595]
NCT01935947	Terminated	Recurrent NSCLC; Stage IIIA NSCLC; Stage IIIB NSCLC;	Azacitidine; Azacitidine; Docetaxel; Entinostat; Gemcitabine hydrochloride; Irinotecan hydrochloride; Pemetrexed disodium; Laboratory biomarker analysis	≥18	2	
NCT03903458	Unknown	Malignant melanoma	Tinostamustine	≥18	1	
NCT02518958	Completed	Malignant solid tumor; Lymphoma	RRx-001; Drug: Nivolumab	≥18	1	
NCT00925132	Terminated	Metastatic melanoma	Temozolomide+Decitabine+Panobinostat	≥18	1/2	[596]
NCT02900560	Terminated	Epithelial ovarian cancer	CC-486; Pembrolizumab	≥18	2	
NCT04896073	Completed	Pancreatic adenosquamous carcinoma	Minnelide	≥18	2	[597]
NCT06646809	Recruiting	CRC	Alpha-ketoglutarate; Placebo	≥45	3	
NCT06454448	Recruiting	Metastatic pancreatic cancer	Adebrelimab+Decitabine	18-72	1/2	
NCT05958719	Recruiting	PTCL; Epigenetic repression	Chidamide; Azacitidine; Liposomal mitoxantrone; Prednisone	≥18	2	
NCT01933061	Withdrawn	Metastatic melanoma	Abraxane; Abraxane+CC-486	≥18	2	
NCT01834248	Completed	AML; Alkylating agent-related AML; CML; MDS; Refractory anemia with excess blasts in transformation	DEC-205/NY-ESO-1 fusion protein CDX-1401; Decitabine; Poly ICLC	≥18	1	
NCT01265953	Completed	Prostate cancer prevention	Sulforaphane-rich broccoli sprout extract capsules; Gelatin capsule containing microcrystalline cellulose	≥21	NA	[598]
NCT03417427	Unknown	AML	Decitabine+Ara-C; Ara-C	14-60	2	
NCT02724202	Unknown	Metastatic colon cancer	Curcumin; 5-flurorouracil	≥18	1	
NCT02786875	Unknown	BC	High level Vitamin D; normal level Vitamin D	30-74	3	[599]
NCT00005639	Completed	Lymphoma; Small intestine cancer; Unspecified adult solid tumor	Azacitidine injection; Sodium phenylbutyrate	18-120	1	
NCT06930118	Recruiting	Advanced CRC in the third-line treatment and beyond; pMMR/MSS advanced CRC	Chidamide+Regorafenib+Iparomlimab/Tuvonralimab	≥18	2	
NCT02250326	Completed	NSCLC	*nab*-paclitaxel IV; CC-486; Duravalumab	≥18	2	[600]
NCT04541277	Unknown	AML in relapse or refractory; AML in unfit elderly; AML with positive	Tislelizumab+Decitabine+Azacitidine	≥18	2	[601]

		minimal residual disease				
NCT03240211	Recruiting	PTCL; Cutaneous T-cell lymphoma	Pembrolizumab; Pralatrexate; Decitabine	18-90	1	
NCT02452970	Terminated	Cholangiocarcinoma	RRx-001; Gemcitabine+Cisplatin	≥18	2	
NCT02705469	Completed	mCRPC	ZEN003694	≥18	1	
NCT05896813	Unknown	Newly diagnosed PTCL	CHOP+Chidamide	18-80	NA	
NCT05497453	Terminated	Hepatocellular carcinoma; Solid tumors	OTX-2002; TKI o; TKI two; Immune checkpoint inhibitor	≥18	1/2	[602]
NCT02711956	Completed	mCRPC	ZEN003694; Enzalutamide	≥18	1/2	
NCT03900871	Unknown	Esophageal squamous cell carcinoma	Acetylsalicylic acid	18-70	1	
NCT01301820	Completed	AML	Azacitidine; Lenalidomide	60-75	2	[603]
NCT04831710	Unknown	Angioimmunoblastic T-cell lymphoma	Sintilimab; Chidamide	18-75	2	
NCT04414969	Unknown	Early-stage extranodal natural killer/T-cell lymphoma	Anti-PD-1 antibody+Peg-Asparaginase+Chidamide	18-75	2	[604]
NCT03999723	Recruiting	MDS; AML; CML	Vitamin C (DS); Placebo (DS)	≥18	2	
NCT01829503	Completed	AML	Decitabine+Cytarabine; Supportive care	≥60	2	[538]
NCT02489929	Unknown	Myeloid Leukemia; MDS	Azacytidine	18-85	NA	
NCT06705686	Not yet recruiting	mCRPC	(R)-9bMS	≥18	1	
NCT03206047	Completed	Platinum-resistant fallopian tube carcinoma; Platinum-resistant ovarian carcinoma; Platinum-resistant primary peritoneal carcinoma; Recurrent fallopian tube carcinoma; Recurrent ovarian carcinoma; Recurrent primary peritoneal carcinoma	Atezolizumab; DEC-205/NY-ESO-1 Fusion Protein CDX-1401; Guadecitabine; Poly ICLC	≥18	1/2	
NCT05772728	Unknown	T-Cell lymphoma	Cidapenem+Azacitidine+Mitoxantrone liposome (CAM) regimen	18-75	N/A	
NCT03709550	Withdrawn	CRPC; Metastatic prostate carcinoma in soft tissue; Prostate carcinoma metastatic in bone	Decitabine; Enzalutamide	≥18	1/2	
NCT01358045	Completed	Basal cell carcinoma	Diclofenac; Diclofenac+Calcitriol; Calcitriol	≥18	2	
NCT02085408	Completed	AML; Different types of leukemia; Erythroleukemia	Daunorubicin; Cytarabine; Clofarabine; Decitabine	≥60	3	
NCT04022005	Completed	Diffuse large B-cell lymphoma	Chidamide+Rituximab+Gemcitabine+Oxaliplatin	18-75	2	
NCT06696378	Recruiting	Female BC; Older adults; Exercise training program	Melatonin 6 mg (DS); Placebo (DS)	60-80	N/A	[605]
			Aging			
NCT04608448	Completed	Aging; Epigenetics; Inflammatory mediators	Rapamycin topical ointment; Placebo	65-95	1	
NCT04375657	Recruiting	Epigenetic aging; Immunosenescence	TRIIM; Active control	40-80	2	
NCT04946383	Unknown	Aging	Dasatinib+Quercetin	≥40	2	[579]
NCT05310123	Unknown	Aging	AC-11 (DS)	≥55	2	
NCT05110313	Completed	Psoriasis; Aging; Epigenetic disorder, Skin inflammation	TILDRAKIZUMAB	≥35	4	

NCT05964920	Recruiting	Healthy aging; Age-related sarcopenia; Testosterone deficiency	Saline; Testosterone undecanoate; Saline+Resistance exercise training; Testosterone undecanoate+Resistance exercise training	55-70	2/3	
NCT06411366	Completed	Frailty; Aging	Follistatin plasmid	≥22	1	
NCT05593939	Completed	Aging	Exercise; Time restricted feeding; Nicotinamide riboside (DS)	≥65	2	
NCT01754012	Completed	Aging	Nutrient-rich diet+Cholecalciferol	65-79	N/A	[606]
NCT06613542	Active, not recruiting	Biological aging; Longevity; Physical activity; Metabolic health	Taurine; Placebo	55-75	N/A	
NCT04110028	Completed	Inflammation; Acute illness	Nicotinamide riboside; Placebo	≥18	1/2	
NCT05294835	Unknown	Depression; Post traumatic stress disorder	Ketamine	18-64	2	
NCT05706389	Unknown	Aging	Calcium Alpha-Ketoglutarate (Ca-AKG) (DS)	40-60	2	
NCT06789900	Recruiting	Postmenopausal women	Everolimus	45-60	N/A	

FdCyd: 5-Fluoro-2'-Deoxycytidine; AI: Aromatase inhibitor; AML: Acute myeloid leukemia; BC: Breast cancer; CML: Chronic myelomonocytic leukemia; CRC: Colorectal cancer; DLBCL: Diffuse large B cell lymphoma; DS: Dietary supplement; ER: Estrogen receptor; GBM: Glioblastoma multiforme; mCRPC: Metastatic castration-resistant prostate cancer; MDS: Myelodysplastic syndrome; NA: Not applicable; NSCLC: Non-small cell lung cancer; PDAC: Pancreatic ductal adenocarcinoma; PTCL: Peripheral T-cell lymphoma; SERD: Selective estrogen receptor degraders; THU: Tetrahydrouridine; TKI: Tyrosine kinase inhibitor; VPA: Valproic acid. Source: ClinicalTrials.gov, accessed on 2025/07/02.

3.7. CTs assessing cannabinoids

Nowadays, cannabinoids are indicated in cancer patients to ameliorate chemotherapy-induced nausea and vomiting, cancer-related pain, insomnia and mood disorders, anorexia and cachexia [544]. At present, there are 43 ongoing or completed CTs studying cannabinoids in cancer patients, 39 of them include older adults [545] both as palliative/supportive care or therapy, and 2 trials are now recruiting subjects to evaluate the role of cannabinoids in aging [546]. However, none of them are focused exclusively on older adults.

Of particular interest is cannabidiol, a non-psychoactive cannabinoid with anti-inflammatory properties, which improves healthspan parameters, including lessening age-related behavioral dysfunction, in models of both healthy and accelerated aging. These benefits likely occur through activation of antioxidative pathways and induction of autophagy [371]. A recent open-label, phase 1 dose-escalation study (NCT 04428203) in patients with recurrent PC following prostatectomy and/or salvage radiotherapy or primary definitive radiotherapy demonstrated the safety of cannabidiol at doses of 600 and 800 mg. Furthermore, at 12 weeks, 16 of 18 patients maintained stable biochemical markers [547]. Similarly, a randomized, placebo-controlled trial (NCT01812603/NCT01812616), involving 21 patients with recurrent glioblastoma multiforme, showed a longer survival when temozolomide was combined with nabiximols (Δ-9-tetrahydrocannabinol plus cannabidiol), compared with the combination of temozolomide with a placebo [548].

As highlighted in a recent review [549], most current preclinical and clinical studies focus on the interactions and potential risks of cannabinoids when combined with different anticancer therapies. Nevertheless, existing data also suggest that cannabinoids may increase the efficacy of chemotherapeutic agents while reducing their side effects. To date, most studies focus mainly on cytotoxicity, underscoring the need for additional research evaluating the effects of such combinations on the immune system, angiogenesis, invasion and metastasis.

CTs on the potential use of cannabinoids is of particular relevance in aged population, as it represents the fastest-growing group of medical marijuana users for the symptomatic management of various diseases and treatment-related AEs. To take advantage of the anticancer potential of cannabinoids in older adults, robust RCTs are required to evaluate the interactions between cannabinoids and the most common drugs taken by these polimedicated patients, including those for depression, cardiovascular disease, cholesterol, high blood pressure and blood thinning. These trials should also examine potential cognitive and psychological impacts, particularly in subjects with pre-existing conditions, as well as the effects on motor control.

In addition, given that the available data come mainly from studies performed in BC, glioblastoma and hematological malignancies, clinical research should be expanded to other cancer types with high incidence in older adults, such as lung, prostate and CRC. Given the interindividual variability in responses to cannabinoids, these trials should include large cohorts in order to generate high quality data on safety, efficacy and optimal cannabinoid dosing. Finally, considering the suggested impact of cannabinoids on aging process, long-term RCTs

aimed at evaluating the use of these compounds to promote healthspan should be conducted.

4. Concluding remarks

Aging is considered one of the main risk factors for cancer development. Accordingly, the increase in cancer incidence is intimately associated with lifespan lengthening and with the consequent growth of the aging population. By 2050, the number of people aged 60 years and older is projected to reach 2.1 billion, with the number of subjects aged 80 years or older expected to reach 426 million. As a consequence, cancer incidence, especially among older adults, is expected to rise dramatically in the next years, representing one of the greatest challenges for public health systems.

In this context, elucidating the specific mechanisms that connect aging with carcinogenesis is of great importance. A better understanding of these mechanisms will not only help the development of more effective oncology therapies, but also of interventions aimed at delaying, reversing and stopping aging process itself.

There are many aging-associated changes in key physiological processes and systems that have been proposed to be on the root of cancer initiation and progression. These include somatic mutations, genome instability, DNA damage repair deficiency, aberrant microenvironment, senescence, telomere attrition, oxidative stress, defective adaptive and innate immunity, systemic inflammation, epigenetic changes, circadian clock disruption, dysfunctional endocannabinoid system, aberrant gut microbiome and metabolic dysregulation. The crosstalk between some of these systems and mechanisms (e.g., circadian clock-cell cycle, microbiome-circadian clock, ECS-immunosenescence) adds another layer of complexity to the picture.

In older adults, particular attention must be given to the selection of their treatments and to the preservation of mental and physical status during and after cancer therapy. The relevance of conducting CTs in older adults to issue evidence-based recommendations for clinical practice must be pointed out. Currently, there are several anti-aging therapies in older cancer patients that have been proven not only to improve patients' fitness and QoL, but also to reduce chemo and radiotherapy adverse effects and/or to have oncological benefits. These interventions include lifestyle-related strategies, such as exercise and nutritional approaches (e.g., TRE), and pharmacological treatments, including CRMs, senolytics, senomorphics, epidrugs and cannabinoids, especially cannabidiol, given its anti-inflammatory properties. Probably, due to the reversible nature of the epigenetic modifications, one of the most promising anti-aging compounds to treat cancer and reverse drug resistance are the epidrugs, especially when given in combination with immune checkpoint inhibitors. Similarly, gut microbiome-based therapeutics for older subjects, aimed at reverting the unhealthy microbiome to a healthy one, represent a rapidly growing and promising area of research. Finally, given that many targets of anti-aging drugs display daily oscillations, it must be highlighted that dosage timing should be taken into account to optimize both efficacy and safety of anti-aging and oncological drugs.

Beyond anti-aging drugs discovery and clinical development, public health policies designed to promote prevention and healthy aging must also be prioritized.

Acknowledgements

This work was supported by Associazione Italiana per la Ricerca sul Cancro (AIRC; #22098 to A.N. and MFAG#26482 to I.C.) and the Marie Skłodowska-Curie Postdoctoral Fellowship (Grant Agreement No. 101154600 to G.A).

Author contributions

A.G., G.A. and I.C. wrote the manuscript. A.G., G.A., A.N. and I.C. developed, conceived and critically reviewed the manuscript. L.P. critically reviewed the manuscript.

Competing interests

A.N. and I.C. hold intellectual property rights on medical uses of MF regimens. All authors have read and agreed to the published version of the manuscript.

References

[1] Lopez-Otin C, Blasco MA, Partridge L, Serrano M, Kroemer G (2013). The hallmarks of aging. Cell, 153:1194-1217.

[2] Cagan A, Baez-Ortega A, Brzozowska N, Abascal F, Coorens THH, Sanders MA, et al. (2022). Somatic mutation rates scale with lifespan across mammals. Nature, 604:517-524.

[3] Gensler HL, Bernstein H (1981). DNA damage as the primary cause of aging. Q Rev Biol, 56:279-303.

[4] Pinto M, Moraes CT (2015). Mechanisms linking mtDNA damage and aging. Free Radic Biol Med, 85:250-258.

[5] Spadaro O, Youm Y, Shchukina I, Ryu S, Sidorov S, Ravussin A, et al. (2022). Caloric restriction in humans reveals immunometabolic regulators of health span. Science, 375:671-677.

[6] Lee GD, Wilson MA, Zhu M, Wolkow CA, de Cabo R, Ingram DK, et al. (2006). Dietary deprivation extends lifespan in Caenorhabditis elegans. Aging Cell, 5:515-

524.

[7] Martens CR, Denman BA, Mazzo MR, Armstrong ML, Reisdorph N, McQueen MB, et al. (2018). Chronic nicotinamide riboside supplementation is well-tolerated and elevates NAD(+) in healthy middle-aged and older adults. Nat Commun, 9:1286.

[8] Kiss T, Nyul-Toth A, Balasubramanian P, Tarantini S, Ahire C, Yabluchanskiy A, et al. (2020). Nicotinamide mononucleotide (NMN) supplementation promotes neurovascular rejuvenation in aged mice: transcriptional footprint of SIRT1 activation, mitochondrial protection, anti-inflammatory, and anti-apoptotic effects. Geroscience, 42:527-546.

[9] Ma S, Sun S, Geng L, Song M, Wang W, Ye Y, et al. (2020). Caloric Restriction Reprograms the Single-Cell Transcriptional Landscape of Rattus Norvegicus Aging. Cell, 180:984-1001 e1022.

[10] Ocampo A, Reddy P, Martinez-Redondo P, Platero-Luengo A, Hatanaka F, Hishida T, et al. (2016). In Vivo Amelioration of Age-Associated Hallmarks by Partial Reprogramming. Cell, 167:1719-1733 e1712.

[11] Jazwinski SM, Kim S (2019). Examination of the Dimensions of Biological Age. Front Genet, 10:263.

[12] Zhang Q (2023). An interpretable biological age. Lancet Healthy Longev, 4:e662-e663.

[13] Elliott ML, Caspi A, Houts RM, Ambler A, Broadbent JM, Hancox RJ, et al. (2021). Disparities in the pace of biological aging among midlife adults of the same chronological age have implications for future frailty risk and policy. Nat Aging, 1:295-308.

[14] Rattan SI (2014). Aging is not a disease: implications for intervention. Aging Dis, 5:196-202.

[15] Maltoni R, Ravaioli S, Bronte G, Mazza M, Cerchione C, Massa I, et al. (2022). Chronological age or biological age: What drives the choice of adjuvant treatment in elderly breast cancer patients? Transl Oncol, 15:101300.

[16] Feltes BC, de Faria Poloni J, Bonatto D (2011). The developmental aging and origins of health and disease hypotheses explained by different protein networks. Biogerontology, 12:293-308.

[17] Bonafe M, Sabbatinelli J, Olivieri F (2020). Exploiting the telomere machinery to put the brakes on inflamm-aging. Ageing Res Rev, 59:101027.

[18] Li L, Shan T, Zhang D, Ma F (2024). Nowcasting and forecasting global aging and cancer burden: analysis of data from the GLOBOCAN and Global Burden of Disease Study. J Natl Cancer Cent, 4:223-232.

[19] Lahti L, Huovari J, Kainu M, Biecek P (2017). Retrieval and analysis of Eurostat open data with the eurostat. Version 3.3.1.3 package. R Journal. , 9:385–392.

[20] Pilleron S, Sarfati D, Janssen-Heijnen M, Vignat J, Ferlay J, Bray F, et al. (2019). Global cancer incidence in older adults, 2012 and 2035: A population-based study. Int J Cancer, 144:49-58.

[21] White MC, Holman DM, Goodman RA, Richardson LC (2019). Cancer Risk Among Older Adults: Time for Cancer Prevention to Go Silver. Gerontologist, 59:S1-S6.

[22] World Health Organization (WHO). Ageing and health. Available at https://www.who.int/news-room/fact-sheets/detail/ageing-and-health#:~:text=In%202020%2C%20the%20number%20of,from%2012%25%20to%2022%25. Accessed on July 2, 2025.

[23] Kontis V, Bennett JE, Mathers CD, Li G, Foreman K, Ezzati M (2017). Future life expectancy in 35 industrialised countries: projections with a Bayesian model ensemble. Lancet, 389:1323-1335.

[24] Collaborators GBDD (2020). Global age-sex-specific fertility, mortality, healthy life expectancy (HALE), and population estimates in 204 countries and territories, 1950-2019: a comprehensive demographic analysis for the Global Burden of Disease Study 2019. Lancet, 396:1160-1203.

[25] Foreman KJ, Marquez N, Dolgert A, Fukutaki K, Fullman N, McGaughey M, et al. (2018). Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016-40 for 195 countries and territories. Lancet, 392:2052-2090.

[26] World Population Prospects 2024. Summary of Results. United Nations. Department of Economic and Social Affairs. Population Division. 2024. UN DESA/POP/2024/TR/NO. 9. Available at https://population.un.org/wpp/assets/Files/WPP2024_Summary-of-Results.pdf. Accessed on July 2, 2025.

[27] National Cancer Institute. Cancer statistics. Available at: https://www.cancer.gov/about-cancer/understanding/statistics. Accessed on July 2, 2025.

[28] Loughran EA, Leonard AK, Hilliard TS, Phan RC, Yemc MG, Harper E, et al. (2018). Aging Increases Susceptibility to Ovarian Cancer Metastasis in Murine Allograft Models and Alters Immune Composition of Peritoneal Adipose Tissue. Neoplasia, 20:621-631.

[29] Smetana K, Jr., Lacina L, Szabo P, Dvorankova B, Broz P, Sedo A (2016). Ageing as an Important Risk Factor for Cancer. Anticancer Res, 36:5009-5017.

[30] White MC, Holman DM, Boehm JE, Peipins LA, Grossman M, Henley SJ (2014). Age and cancer risk: a potentially modifiable relationship. Am J Prev Med, 46:S7-15.

[31] Laconi E, Marongiu F, DeGregori J (2020). Cancer as a disease of old age: changing mutational and microenvironmental landscapes. Br J Cancer, 122:943-952.

[32] Deng F, Xu X, Lv M, Ren B, Wang Y, Guo W, et al. (2017). Age is associated with prognosis in serous ovarian carcinoma. J Ovarian Res, 10:36.

[33] Lu CH, Lee SH, Liu KH, Hung YS, Wang CH, Lin YC, et al. (2018). Older age impacts on survival outcome in patients receiving curative surgery for solid cancer. Asian J Surg, 41:333-340.

[34] Migkou M, Kastritis E, Roussou M, Gkotzamanidou M, Gavriatopoulou M, Nikitas N, et al. (2011). Short progression-free survival predicts for poor overall survival in older patients with multiple myeloma treated upfront with novel agent-based therapy. Eur J

Haematol, 87:323-329.
[35] Pham J, Conron M, Wright G, Mitchell P, Ball D, Philip J, et al. (2021). Excess mortality and undertreatment in elderly lung cancer patients: treatment nihilism in the modern era? ERJ Open Res, 7.
[36] Thigpen T, Brady MF, Omura GA, Creasman WT, McGuire WP, Hoskins WJ, et al. (1993). Age as a prognostic factor in ovarian carcinoma. The Gynecologic Oncology Group experience. Cancer, 71:606-614.
[37] Burkhalter MD, Rudolph KL, Sperka T (2015). Genome instability of ageing stem cells--Induction and defence mechanisms. Ageing Res Rev, 23:29-36.
[38] Calcinotto A, Kohli J, Zagato E, Pellegrini L, Demaria M, Alimonti A (2019). Cellular Senescence: Aging, Cancer, and Injury. Physiol Rev, 99:1047-1078.
[39] Cassidy LD, Narita M (2022). Autophagy at the intersection of aging, senescence, and cancer. Mol Oncol, 16:3259-3275.
[40] Yin D, Chen K (2005). The essential mechanisms of aging: Irreparable damage accumulation of biochemical side-reactions. Exp Gerontol, 40:455-465.
[41] Cai Y, Song W, Li J, Jing Y, Liang C, Zhang L, et al. (2022). The landscape of aging. Sci China Life Sci, 65:2354-2454.
[42] Clarke TL, Mostoslavsky R (2022). DNA repair as a shared hallmark in cancer and ageing. Mol Oncol, 16:3352-3379.
[43] Lopez-Otin C, Blasco MA, Partridge L, Serrano M, Kroemer G (2023). Hallmarks of aging: An expanding universe. Cell, 186:243-278.
[44] Montegut L, Lopez-Otin C, Kroemer G (2024). Aging and cancer. Mol Cancer, 23:106.
[45] Risques RA, Kennedy SR (2018). Aging and the rise of somatic cancer-associated mutations in normal tissues. PLoS Genet, 14:e1007108.
[46] Hanahan D, Weinberg RA (2011). Hallmarks of cancer: the next generation. Cell, 144:646-674.
[47] Trastus LA, d'Adda di Fagagna F (2025). The complex interplay between aging and cancer. Nat Aging, 5:350-365.
[48] Chatterjee N, Walker GC (2017). Mechanisms of DNA damage, repair, and mutagenesis. Environ Mol Mutagen, 58:235-263.
[49] De Bont R, van Larebeke N (2004). Endogenous DNA damage in humans: a review of quantitative data. Mutagenesis, 19:169-185.
[50] Fromme JC, Verdine GL (2004). Base excision repair. Adv Protein Chem, 69:1-41.
[51] Kimsey IJ, Petzold K, Sathyamoorthy B, Stein ZW, Al-Hashimi HM (2015). Visualizing transient Watson-Crick-like mispairs in DNA and RNA duplexes. Nature, 519:315-320.
[52] Kunkel TA (2009). Evolving views of DNA replication (in)fidelity. Cold Spring Harb Symp Quant Biol, 74:91-101.
[53] Poetsch AR (2020). The genomics of oxidative DNA damage, repair, and resulting mutagenesis. Comput Struct Biotechnol J, 18:207-219.
[54] Heidenreich E, Novotny R, Kneidinger B, Holzmann V, Wintersberger U (2003). Non-homologous end joining as an important mutagenic process in cell cycle-arrested cells. EMBO J, 22:2274-2283.
[55] Basu AK (2018). DNA Damage, Mutagenesis and Cancer. Int J Mol Sci, 19.
[56] Lopez-Gil L, Pascual-Ahuir A, Proft M (2023). Genomic Instability and Epigenetic Changes during Aging. Int J Mol Sci, 24.
[57] Negrini S, Gorgoulis VG, Halazonetis TD (2010). Genomic instability--an evolving hallmark of cancer. Nat Rev Mol Cell Biol, 11:220-228.
[58] Maslov AY, Vijg J (2009). Genome instability, cancer and aging. Biochim Biophys Acta, 1790:963-969.
[59] Kirkwood TB (1989). DNA, mutations and aging. Mutat Res, 219:1-7.
[60] Szilard L (1959). On the Nature of the Aging Process. Proc Natl Acad Sci U S A, 45:30-45.
[61] Martincorena I, Campbell PJ (2015). Somatic mutation in cancer and normal cells. Science, 349:1483-1489.
[62] Stratton MR, Campbell PJ, Futreal PA (2009). The cancer genome. Nature, 458:719-724.
[63] Garraway LA, Lander ES (2013). Lessons from the cancer genome. Cell, 153:17-37.
[64] Vogelstein B, Papadopoulos N, Velculescu VE, Zhou S, Diaz LA, Jr., Kinzler KW (2013). Cancer genome landscapes. Science, 339:1546-1558.
[65] Tomasetti C, Li L, Vogelstein B (2017). Stem cell divisions, somatic mutations, cancer etiology, and cancer prevention. Science, 355:1330-1334.
[66] Ostroverkhova D, Przytycka TM, Panchenko AR (2023). Cancer driver mutations: predictions and reality. Trends Mol Med, 29:554-566.
[67] Beroukhim R, Mermel CH, Porter D, Wei G, Raychaudhuri S, Donovan J, et al. (2010). The landscape of somatic copy-number alteration across human cancers. Nature, 463:899-905.
[68] Scheble VJ, Braun M, Beroukhim R, Mermel CH, Ruiz C, Wilbertz T, et al. (2010). ERG rearrangement is specific to prostate cancer and does not occur in any other common tumor. Mod Pathol, 23:1061-1067.
[69] Zhou C, Li J, Li Q (2017). CDKN2A methylation in esophageal cancer: a meta-analysis. Oncotarget, 8:50071-50083.
[70] Cancer Genome Atlas Research N (2012). Comprehensive genomic characterization of squamous cell lung cancers. Nature, 489:519-525.
[71] Cancer Genome Atlas N (2015). Comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature, 517:576-582.
[72] Cancer Genome Atlas Research N (2014). Comprehensive molecular profiling of lung adenocarcinoma. Nature, 511:543-550.
[73] Xu W, Ji JY (2011). Dysregulation of CDK8 and Cyclin C in tumorigenesis. J Genet Genomics, 38:439-452.
[74] Harvey-Jones E, Raghunandan M, Robbez-Masson L, Magraner-Pardo L, Alaguthurai T, Yablonovitch A, et al. (2024). Longitudinal profiling identifies co-

occurring BRCA1/2 reversions, TP53BP1, RIF1 and PAXIP1 mutations in PARP inhibitor-resistant advanced breast cancer. Ann Oncol, 35:364-380.
[75] Nussinov R, Tsai CJ (2015). 'Latent drivers' expand the cancer mutational landscape. Curr Opin Struct Biol, 32:25-32.
[76] Li Y, Tollefsbol TO (2016). Age-related epigenetic drift and phenotypic plasticity loss: implications in prevention of age-related human diseases. Epigenomics, 8:1637-1651.
[77] Martincorena I, Fowler JC, Wabik A, Lawson ARJ, Abascal F, Hall MWJ, et al. (2018). Somatic mutant clones colonize the human esophagus with age. Science, 362:911-917.
[78] Milholland B, Auton A, Suh Y, Vijg J (2015). Age-related somatic mutations in the cancer genome. Oncotarget, 6:24627-24635.
[79] Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SA, Behjati S, Biankin AV, et al. (2013). Signatures of mutational processes in human cancer. Nature, 500:415-421.
[80] Blokzijl F, de Ligt J, Jager M, Sasselli V, Roerink S, Sasaki N, et al. (2016). Tissue-specific mutation accumulation in human adult stem cells during life. Nature, 538:260-264.
[81] Hoang ML, Kinde I, Tomasetti C, McMahon KW, Rosenquist TA, Grollman AP, et al. (2016). Genome-wide quantification of rare somatic mutations in normal human tissues using massively parallel sequencing. Proc Natl Acad Sci U S A, 113:9846-9851.
[82] Tomasetti C, Vogelstein B (2015). Cancer etiology. Variation in cancer risk among tissues can be explained by the number of stem cell divisions. Science, 347:78-81.
[83] Lynch M (2010). Rate, molecular spectrum, and consequences of human mutation. Proc Natl Acad Sci U S A, 107:961-968.
[84] Tomasetti C, Vogelstein B, Parmigiani G (2013). Half or more of the somatic mutations in cancers of self-renewing tissues originate prior to tumor initiation. Proc Natl Acad Sci U S A, 110:1999-2004.
[85] Zhu L, Finkelstein D, Gao C, Shi L, Wang Y, Lopez-Terrada D, et al. (2016). Multi-organ Mapping of Cancer Risk. Cell, 166:1132-1146 e1137.
[86] Tomasetti C, Marchionni L, Nowak MA, Parmigiani G, Vogelstein B (2015). Only three driver gene mutations are required for the development of lung and colorectal cancers. Proc Natl Acad Sci U S A, 112:118-123.
[87] Alexandrov LB, Jones PH, Wedge DC, Sale JE, Campbell PJ, Nik-Zainal S, et al. (2015). Clock-like mutational processes in human somatic cells. Nat Genet, 47:1402-1407.
[88] Ren P, Dong X, Vijg J (2022). Age-related somatic mutation burden in human tissues. Front Aging, 3:1018119.
[89] Welch JS, Ley TJ, Link DC, Miller CA, Larson DE, Koboldt DC, et al. (2012). The origin and evolution of mutations in acute myeloid leukemia. Cell, 150:264-278.
[90] Sun S, Wang Y, Maslov AY, Dong X, Vijg J (2022). SomaMutDB: a database of somatic mutations in normal human tissues. Nucleic Acids Res, 50:D1100-D1108.
[91] Franco I, Revechon G, Eriksson M (2022). Challenges of proving a causal role of somatic mutations in the aging process. Aging Cell, 21:e13613.
[92] Franco I, Helgadottir HT, Moggio A, Larsson M, Vrtacnik P, Johansson A, et al. (2019). Whole genome DNA sequencing provides an atlas of somatic mutagenesis in healthy human cells and identifies a tumor-prone cell type. Genome Biol, 20:285.
[93] Brazhnik K, Sun S, Alani O, Kinkhabwala M, Wolkoff AW, Maslov AY, et al. (2020). Single-cell analysis reveals different age-related somatic mutation profiles between stem and differentiated cells in human liver. Sci Adv, 6:eaax2659.
[94] Li R, Di L, Li J, Fan W, Liu Y, Guo W, et al. (2021). A body map of somatic mutagenesis in morphologically normal human tissues. Nature, 597:398-403.
[95] Zhang L, Vijg J (2018). Somatic Mutagenesis in Mammals and Its Implications for Human Disease and Aging. Annu Rev Genet, 52:397-419.
[96] Vijg J (2021). From DNA damage to mutations: All roads lead to aging. Ageing Res Rev, 68:101316.
[97] Levy O, Amit G, Vaknin D, Snir T, Efroni S, Castaldi P, et al. (2020). Age-related loss of gene-to-gene transcriptional coordination among single cells. Nat Metab, 2:1305-1315.
[98] Lans H, Hoeijmakers JHJ, Vermeulen W, Marteijn JA (2019). The DNA damage response to transcription stress. Nat Rev Mol Cell Biol, 20:766-784.
[99] Debattista J, Grech L, Scerri C, Grech G (2023). Copy Number Variations as Determinants of Colorectal Tumor Progression in Liquid Biopsies. Int J Mol Sci, 24.
[100] Oketch DJA, Giulietti M, Piva F (2023). Copy Number Variations in Pancreatic Cancer: From Biological Significance to Clinical Utility. Int J Mol Sci, 25.
[101] Shahrouzi P, Forouz F, Mathelier A, Kristensen VN, Duijf PHG (2024). Copy number alterations: a catastrophic orchestration of the breast cancer genome. Trends Mol Med, 30:750-764.
[102] Shlien A, Malkin D (2009). Copy number variations and cancer. Genome Med, 1:62.
[103] Stephens PJ, Greenman CD, Fu B, Yang F, Bignell GR, Mudie LJ, et al. (2011). Massive genomic rearrangement acquired in a single catastrophic event during cancer development. Cell, 144:27-40.
[104] Pellestor F, Gaillard JB, Schneider A, Puechberty J, Gatinois V (2022). Chromoanagenesis, the mechanisms of a genomic chaos. Semin Cell Dev Biol, 123:90-99.
[105] Campbell PJ, Yachida S, Mudie LJ, Stephens PJ, Pleasance ED, Stebbings LA, et al. (2010). The patterns and dynamics of genomic instability in metastatic pancreatic cancer. Nature, 467:1109-1113.
[106] Yang L, Luquette LJ, Gehlenborg N, Xi R, Haseley PS, Hsieh CH, et al. (2013). Diverse mechanisms of

somatic structural variations in human cancer genomes. Cell, 153:919-929.

[107] Zhuang J, Weng Z (2015). Local sequence assembly reveals a high-resolution profile of somatic structural variations in 97 cancer genomes. Nucleic Acids Res, 43:8146-8156.

[108] Fujimoto A, Wong JH, Yoshii Y, Akiyama S, Tanaka A, Yagi H, et al. (2021). Whole-genome sequencing with long reads reveals complex structure and origin of structural variation in human genetic variations and somatic mutations in cancer. Genome Med, 13:65.

[109] Consortium ITP-CAoWG (2020). Pan-cancer analysis of whole genomes. Nature, 578:82-93.

[110] Li Y, Roberts ND, Wala JA, Shapira O, Schumacher SE, Kumar K, et al. (2020). Patterns of somatic structural variation in human cancer genomes. Nature, 578:112-121.

[111] Yi K, Ju YS (2018). Patterns and mechanisms of structural variations in human cancer. Exp Mol Med, 50:1-11.

[112] Dubois F, Sidiropoulos N, Weischenfeldt J, Beroukhim R (2022). Structural variations in cancer and the 3D genome. Nat Rev Cancer, 22:533-546.

[113] Mitchell E, Spencer Chapman M, Williams N, Dawson KJ, Mende N, Calderbank EF, et al. (2022). Clonal dynamics of haematopoiesis across the human lifespan. Nature, 606:343-350.

[114] Cosenza MR, Rodriguez-Martin B, Korbel JO (2022). Structural Variation in Cancer: Role, Prevalence, and Mechanisms. Annu Rev Genomics Hum Genet, 23:123-152.

[115] Totoki Y, Tatsuno K, Covington KR, Ueda H, Creighton CJ, Kato M, et al. (2014). Trans-ancestry mutational landscape of hepatocellular carcinoma genomes. Nat Genet, 46:1267-1273.

[116] Rustad EH, Yellapantula VD, Glodzik D, Maclachlan KH, Diamond B, Boyle EM, et al. (2020). Revealing the impact of structural variants in multiple myeloma. Blood Cancer Discov, 1:258-273.

[117] Supek F, Lehner B (2015). Differential DNA mismatch repair underlies mutation rate variation across the human genome. Nature, 521:81-84.

[118] De S, Michor F (2011). DNA replication timing and long-range DNA interactions predict mutational landscapes of cancer genomes. Nat Biotechnol, 29:1103-1108.

[119] Zavacka K, Plevova K, Jarosova M, Pospisilova S (2019). Chromothripsis - Extensive Chromosomal Rearrangements and Their Significance in Cancer. Klin Onkol, 32:101-108.

[120] Luijten MNH, Lee JXT, Crasta KC (2018). Mutational game changer: Chromothripsis and its emerging relevance to cancer. Mutat Res Rev Mutat Res, 777:29-51.

[121] Rosswog C, Bartenhagen C, Welte A, Kahlert Y, Hemstedt N, Lorenz W, et al. (2021). Chromothripsis followed by circular recombination drives oncogene amplification in human cancer. Nat Genet, 53:1673-1685.

[122] Rode A, Maass KK, Willmund KV, Lichter P, Ernst A (2016). Chromothripsis in cancer cells: An update. Int J Cancer, 138:2322-2333.

[123] Pastorczak A, Urbanska Z, Styka B, Miarka-Walczyk K, Sedek L, Wypyszczak K, et al. (2024). Genetic hallmarks and clinical implications of chromothripsis in childhood T-cell acute lymphoblastic leukemia. Leukemia, 38:2344-2354.

[124] Northcott PA, Shih DJ, Peacock J, Garzia L, Morrissy AS, Zichner T, et al. (2012). Subgroup-specific structural variation across 1,000 medulloblastoma genomes. Nature, 488:49-56.

[125] Parker M, Mohankumar KM, Punchihewa C, Weinlich R, Dalton JD, Li Y, et al. (2014). C11orf95-RELA fusions drive oncogenic NF-kappaB signalling in ependymoma. Nature, 506:451-455.

[126] Shoshani O, Brunner SF, Yaeger R, Ly P, Nechemia-Arbely Y, Kim DH, et al. (2021). Chromothripsis drives the evolution of gene amplification in cancer. Nature, 591:137-141.

[127] Zhang Q, Yang L, Xiao H, Dang Z, Kuang X, Xiong Y, et al. (2023). Pan-cancer analysis of chromothripsis-related gene expression patterns indicates an association with tumor immune and therapeutic agent responses. Front Oncol, 13:1074955.

[128] Cortes-Ciriano I, Lee JJ, Xi R, Jain D, Jung YL, Yang L, et al. (2020). Comprehensive analysis of chromothripsis in 2,658 human cancers using whole-genome sequencing. Nat Genet, 52:331-341.

[129] Voronina N, Wong JKL, Hubschmann D, Hlevnjak M, Uhrig S, Heilig CE, et al. (2020). The landscape of chromothripsis across adult cancer types. Nat Commun, 11:2320.

[130] Fontana MC, Marconi G, Feenstra JDM, Fonzi E, Papayannidis C, Ghelli Luserna di Rora A, et al. (2018). Chromothripsis in acute myeloid leukemia: biological features and impact on survival. Leukemia, 32:1609-1620.

[131] Cai H, Kumar N, Bagheri HC, von Mering C, Robinson MD, Baudis M (2014). Chromothripsis-like patterns are recurring but heterogeneously distributed features in a survey of 22,347 cancer genome screens. BMC Genomics, 15:82.

[132] Fraser M, Sabelnykova VY, Yamaguchi TN, Heisler LE, Livingstone J, Huang V, et al. (2017). Genomic hallmarks of localized, non-indolent prostate cancer. Nature, 541:359-364.

[133] Behjati S, Tarpey PS, Haase K, Ye H, Young MD, Alexandrov LB, et al. (2017). Recurrent mutation of IGF signalling genes and distinct patterns of genomic rearrangement in osteosarcoma. Nat Commun, 8:15936.

[134] Hart RW, Setlow RB (1974). Correlation between deoxyribonucleic acid excision-repair and life-span in a number of mammalian species. Proc Natl Acad Sci U S A, 71:2169-2173.

[135] Doria G, Frasca D (2001). Age-related changes of DNA damage recognition and repair capacity in cells of the immune system. Mech Ageing Dev, 122:985-998.

[136] Stead ER, Bjedov I (2021). Balancing DNA repair to

prevent ageing and cancer. Exp Cell Res, 405:112679.
[137] Coolbaugh-Murphy MI, Xu J, Ramagli LS, Brown BW, Siciliano MJ (2005). Microsatellite instability (MSI) increases with age in normal somatic cells. Mech Ageing Dev, 126:1051-1059.
[138] Neri S, Gardini A, Facchini A, Olivieri F, Franceschi C, Ravaglia G, et al. (2005). Mismatch repair system and aging: microsatellite instability in peripheral blood cells from differently aged participants. J Gerontol A Biol Sci Med Sci, 60:285-292.
[139] Hsieh P, Yamane K (2008). DNA mismatch repair: molecular mechanism, cancer, and ageing. Mech Ageing Dev, 129:391-407.
[140] Parsons R, Li GM, Longley M, Modrich P, Liu B, Berk T, et al. (1995). Mismatch repair deficiency in phenotypically normal human cells. Science, 268:738-740.
[141] Nakagawa H, Nuovo GJ, Zervos EE, Martin EW, Jr., Salovaara R, Aaltonen LA, et al. (2001). Age-related hypermethylation of the 5' region of MLH1 in normal colonic mucosa is associated with microsatellite-unstable colorectal cancer development. Cancer Res, 61:6991-6995.
[142] Jenkins MA, Hayashi S, O'Shea AM, Burgart LJ, Smyrk TC, Shimizu D, et al. (2007). Pathology features in Bethesda guidelines predict colorectal cancer microsatellite instability: a population-based study. Gastroenterology, 133:48-56.
[143] Starostik P, Greiner A, Schwarz S, Patzner J, Schultz A, Muller-Hermelink HK (2000). The role of microsatellite instability in gastric low- and high-grade lymphoma development. Am J Pathol, 157:1129-1136.
[144] Maruvka YE, Mouw KW, Karlic R, Parasuraman P, Kamburov A, Polak P, et al. (2017). Analysis of somatic microsatellite indels identifies driver events in human tumors. Nat Biotechnol, 35:951-959.
[145] Temko D, Tomlinson IPM, Severini S, Schuster-Bockler B, Graham TA (2018). The effects of mutational processes and selection on driver mutations across cancer types. Nat Commun, 9:1857.
[146] Piegu B, Bire S, Arensburger P, Bigot Y (2015). A survey of transposable element classification systems--a call for a fundamental update to meet the challenge of their diversity and complexity. Mol Phylogenet Evol, 86:90-109.
[147] Goodier JL, Kazazian HH, Jr. (2008). Retrotransposons revisited: the restraint and rehabilitation of parasites. Cell, 135:23-35.
[148] Romano G, Veneziano D, Acunzo M, Croce CM (2017). Small non-coding RNA and cancer. Carcinogenesis, 38:485-491.
[149] Burns KH (2022). Repetitive DNA in disease. Science, 376:353-354.
[150] Mendez-Dorantes C, Zeng X, Karlow JA, Schofield P, Turner S, Kalinowski J, et al. (2024). Chromosomal rearrangements and instability caused by the LINE-1 retrotransposon. bioRxiv.
[151] Tubio JMC, Li Y, Ju YS, Martincorena I, Cooke SL, Tojo M, et al. (2014). Mobile DNA in cancer. Extensive transduction of nonrepetitive DNA mediated by L1 retrotransposition in cancer genomes. Science, 345:1251343.
[152] Rodriguez-Martin B, Alvarez EG, Baez-Ortega A, Zamora J, Supek F, Demeulemeester J, et al. (2020). Pan-cancer analysis of whole genomes identifies driver rearrangements promoted by LINE-1 retrotransposition. Nat Genet, 52:306-319.
[153] Mendez-Dorantes C, Burns KH (2023). LINE-1 retrotransposition and its deregulation in cancers: implications for therapeutic opportunities. Genes Dev, 37:948-967.
[154] Rodic N, Sharma R, Sharma R, Zampella J, Dai L, Taylor MS, et al. (2014). Long interspersed element-1 protein expression is a hallmark of many human cancers. Am J Pathol, 184:1280-1286.
[155] McKerrow W, Wang X, Mendez-Dorantes C, Mita P, Cao S, Grivainis M, et al. (2022). LINE-1 expression in cancer correlates with p53 mutation, copy number alteration, and S phase checkpoint. Proc Natl Acad Sci U S A, 119.
[156] Miki Y, Nishisho I, Horii A, Miyoshi Y, Utsunomiya J, Kinzler KW, et al. (1992). Disruption of the APC gene by a retrotransposal insertion of L1 sequence in a colon cancer. Cancer Res, 52:643-645.
[157] Shukla R, Upton KR, Munoz-Lopez M, Gerhardt DJ, Fisher ME, Nguyen T, et al. (2013). Endogenous retrotransposition activates oncogenic pathways in hepatocellular carcinoma. Cell, 153:101-111.
[158] Ewing AD, Gacita A, Wood LD, Ma F, Xing D, Kim MS, et al. (2015). Widespread somatic L1 retrotransposition occurs early during gastrointestinal cancer evolution. Genome Res, 25:1536-1545.
[159] Solyom S, Ewing AD, Rahrmann EP, Doucet T, Nelson HH, Burns MB, et al. (2012). Extensive somatic L1 retrotransposition in colorectal tumors. Genome Res, 22:2328-2338.
[160] Helman E, Lawrence MS, Stewart C, Sougnez C, Getz G, Meyerson M (2014). Somatic retrotransposition in human cancer revealed by whole-genome and exome sequencing. Genome Res, 24:1053-1063.
[161] Gorbunova V, Seluanov A, Mita P, McKerrow W, Fenyo D, Boeke JD, et al. (2021). The role of retrotransposable elements in ageing and age-associated diseases. Nature, 596:43-53.
[162] Burns KH (2020). Our Conflict with Transposable Elements and Its Implications for Human Disease. Annu Rev Pathol, 15:51-70.
[163] Li X, Yu H, Li D, Liu N (2024). LINE-1 transposable element renaissance in aging and age-related diseases. Ageing Res Rev, 100:102440.
[164] De Cecco M, Criscione SW, Peckham EJ, Hillenmeyer S, Hamm EA, Manivannan J, et al. (2013). Genomes of replicatively senescent cells undergo global epigenetic changes leading to gene silencing and activation of transposable elements. Aging Cell, 12:247-256.
[165] Lee JH, Kim EW, Croteau DL, Bohr VA (2020). Heterochromatin: an epigenetic point of view in aging. Exp Mol Med, 52:1466-1474.

[166] Schumacher B, Pothof J, Vijg J, Hoeijmakers JHJ (2021). The central role of DNA damage in the ageing process. Nature, 592:695-703.
[167] Shaw AC, Joshi S, Greenwood H, Panda A, Lord JM (2010). Aging of the innate immune system. Curr Opin Immunol, 22:507-513.
[168] Barbosa MC, Grosso RA, Fader CM (2018). Hallmarks of Aging: An Autophagic Perspective. Front Endocrinol (Lausanne), 9:790.
[169] Pizarro JG, Cristofari G (2016). Post-Transcriptional Control of LINE-1 Retrotransposition by Cellular Host Factors in Somatic Cells. Front Cell Dev Biol, 4:14.
[170] Guo H, Chitiprolu M, Gagnon D, Meng L, Perez-Iratxeta C, Lagace D, et al. (2014). Autophagy supports genomic stability by degrading retrotransposon RNA. Nat Commun, 5:5276.
[171] Peze-Heidsieck E, Bonnifet T, Znaidi R, Ravel-Godreuil C, Massiani-Beaudoin O, Joshi RL, et al. (2021). Retrotransposons as a Source of DNA Damage in Neurodegeneration. Front Aging Neurosci, 13:786897.
[172] Saul D, Kosinsky RL (2021). Epigenetics of Aging and Aging-Associated Diseases. Int J Mol Sci, 22.
[173] Booth LN, Brunet A (2016). The Aging Epigenome. Mol Cell, 62:728-744.
[174] Blaudin de Thé FX, Rekaik H, Peze-Heidsieck E, Massiani-Beaudoin O, Joshi RL, Fuchs J, et al. (2018). Engrailed homeoprotein blocks degeneration in adult dopaminergic neurons through LINE-1 repression. EMBO J, 37.
[175] Rockwood LD, Felix K, Janz S (2004). Elevated presence of retrotransposons at sites of DNA double strand break repair in mouse models of metabolic oxidative stress and MYC-induced lymphoma. Mutat Res, 548:117-125.
[176] Van Meter M, Kashyap M, Rezazadeh S, Geneva AJ, Morello TD, Seluanov A, et al. (2014). SIRT6 represses LINE1 retrotransposons by ribosylating KAP1 but this repression fails with stress and age. Nat Commun, 5:5011.
[177] Lu AT, Fei Z, Haghani A, Robeck TR, Zoller JA, Li CZ, et al. (2023). Universal DNA methylation age across mammalian tissues. Nat Aging, 3:1144-1166.
[178] Reale A, Tagliatesta S, Zardo G, Zampieri M (2022). Counteracting aged DNA methylation states to combat ageing and age-related diseases. Mech Ageing Dev, 206:111695.
[179] Pereira B, Correia FP, Alves IA, Costa M, Gameiro M, Martins AP, et al. (2024). Epigenetic reprogramming as a key to reverse ageing and increase longevity. Ageing Res Rev, 95:102204.
[180] Cruickshanks HA, McBryan T, Nelson DM, Vanderkraats ND, Shah PP, van Tuyn J, et al. (2013). Senescent cells harbour features of the cancer epigenome. Nat Cell Biol, 15:1495-1506.
[181] Childs BG, Gluscevic M, Baker DJ, Laberge RM, Marquess D, Dananberg J, et al. (2017). Senescent cells: an emerging target for diseases of ageing. Nat Rev Drug Discov, 16:718-735.
[182] Wood JG, Hillenmeyer S, Lawrence C, Chang C, Hosier S, Lightfoot W, et al. (2010). Chromatin remodeling in the aging genome of Drosophila. Aging Cell, 9:971-978.
[183] De Cecco M, Ito T, Petrashen AP, Elias AE, Skvir NJ, Criscione SW, et al. (2019). L1 drives IFN in senescent cells and promotes age-associated inflammation. Nature, 566:73-78.
[184] Wood JG, Jones BC, Jiang N, Chang C, Hosier S, Wickremesinghe P, et al. (2016). Chromatin-modifying genetic interventions suppress age-associated transposable element activation and extend life span in Drosophila. Proc Natl Acad Sci U S A, 113:11277-11282.
[185] LaRocca TJ, Cavalier AN, Wahl D (2020). Repetitive elements as a transcriptomic marker of aging: Evidence in multiple datasets and models. Aging Cell, 19:e13167.
[186] De Cecco M, Criscione SW, Peterson AL, Neretti N, Sedivy JM, Kreiling JA (2013). Transposable elements become active and mobile in the genomes of aging mammalian somatic tissues. Aging (Albany NY), 5:867-883.
[187] Alexandrov LB, Nik-Zainal S, Wedge DC, Campbell PJ, Stratton MR (2013). Deciphering signatures of mutational processes operative in human cancer. Cell Rep, 3:246-259.
[188] Alexandrov LB, Stratton MR (2014). Mutational signatures: the patterns of somatic mutations hidden in cancer genomes. Curr Opin Genet Dev, 24:52-60.
[189] Bartkova J, Horejsi Z, Koed K, Kramer A, Tort F, Zieger K, et al. (2005). DNA damage response as a candidate anti-cancer barrier in early human tumorigenesis. Nature, 434:864-870.
[190] Jiang M, Jia K, Wang L, Li W, Chen B, Liu Y, et al. (2020). Alterations of DNA damage repair in cancer: from mechanisms to applications. Ann Transl Med, 8:1685.
[191] Zhao Y, Simon M, Seluanov A, Gorbunova V (2023). DNA damage and repair in age-related inflammation. Nat Rev Immunol, 23:75-89.
[192] Groelly FJ, Fawkes M, Dagg RA, Blackford AN, Tarsounas M (2023). Targeting DNA damage response pathways in cancer. Nat Rev Cancer, 23:78-94.
[193] Wengner AM, Scholz A, Haendler B (2020). Targeting DNA Damage Response in Prostate and Breast Cancer. Int J Mol Sci, 21.
[194] Ciriello G, Miller ML, Aksoy BA, Senbabaoglu Y, Schultz N, Sander C (2013). Emerging landscape of oncogenic signatures across human cancers. Nat Genet, 45:1127-1133.
[195] Reinhardt HC, Jiang H, Hemann MT, Yaffe MB (2009). Exploiting synthetic lethal interactions for targeted cancer therapy. Cell Cycle, 8:3112-3119.
[196] Loeb LA, Loeb KR, Anderson JP (2003). Multiple mutations and cancer. Proc Natl Acad Sci U S A, 100:776-781.
[197] Loeb LA, Bielas JH, Beckman RA (2008). Cancers exhibit a mutator phenotype: clinical implications. Cancer Res, 68:3551-3557; discussion 3557.

[198] Dietlein F, Thelen L, Reinhardt HC (2014). Cancer-specific defects in DNA repair pathways as targets for personalized therapeutic approaches. Trends Genet, 30:326-339.
[199] Hayes MN, Cohen-Gogo S, Kee L, Xiong X, Weiss A, Layeghifard M, et al. (2025). DNA damage response deficiency enhances neuroblastoma progression and sensitivity to combination PARP and ATR inhibition. Cell Rep, 44:115537.
[200] de Boer J, Andressoo JO, de Wit J, Huijmans J, Beems RB, van Steeg H, et al. (2002). Premature aging in mice deficient in DNA repair and transcription. Science, 296:1276-1279.
[201] Milosic F, Hengstschlager M, Osmanagic-Myers S (2023). Premature aging in genetic diseases: what conclusions can be drawn for physiological aging. Front Aging, 4:1327833.
[202] Cleaver JE (2005). Cancer in xeroderma pigmentosum and related disorders of DNA repair. Nat Rev Cancer, 5:564-573.
[203] Crabbe L, Jauch A, Naeger CM, Holtgreve-Grez H, Karlseder J (2007). Telomere dysfunction as a cause of genomic instability in Werner syndrome. Proc Natl Acad Sci U S A, 104:2205-2210.
[204] Ellis NA, Sander M, Harris CC, Bohr VA (2008). Bloom's syndrome workshop focuses on the functional specificities of RecQ helicases. Mech Ageing Dev, 129:681-691.
[205] Deakyne JS, Mazin AV (2011). Fanconi anemia: at the crossroads of DNA repair. Biochemistry (Mosc), 76:36-48.
[206] McKinnon PJ (2004). ATM and ataxia telangiectasia. EMBO Rep, 5:772-776.
[207] Edifizi D, Nolte H, Babu V, Castells-Roca L, Mueller MM, Brodesser S, et al. (2017). Multilayered Reprogramming in Response to Persistent DNA Damage in C. elegans. Cell Rep, 20:2026-2043.
[208] Vitale I, Manic G, De Maria R, Kroemer G, Galluzzi L (2017). DNA Damage in Stem Cells. Mol Cell, 66:306-319.
[209] Zhang L, Mack R, Breslin P, Zhang J (2020). Molecular and cellular mechanisms of aging in hematopoietic stem cells and their niches. J Hematol Oncol, 13:157.
[210] de Haan G, Lazare SS (2018). Aging of hematopoietic stem cells. Blood, 131:479-487.
[211] Latchney SE, Calvi LM (2017). The aging hematopoietic stem cell niche: Phenotypic and functional changes and mechanisms that contribute to hematopoietic aging. Semin Hematol, 54:25-32.
[212] Beerman I (2017). Accumulation of DNA damage in the aged hematopoietic stem cell compartment. Semin Hematol, 54:12-18.
[213] Rossi DJ, Bryder D, Seita J, Nussenzweig A, Hoeijmakers J, Weissman IL (2007). Deficiencies in DNA damage repair limit the function of haematopoietic stem cells with age. Nature, 447:725-729.
[214] Beerman I, Seita J, Inlay MA, Weissman IL, Rossi DJ (2014). Quiescent hematopoietic stem cells accumulate DNA damage during aging that is repaired upon entry into cell cycle. Cell Stem Cell, 15:37-50.
[215] Kramer A, Challen GA (2017). The epigenetic basis of hematopoietic stem cell aging. Semin Hematol, 54:19-24.
[216] Pezone A, Olivieri F, Napoli MV, Procopio A, Avvedimento EV, Gabrielli A (2023). Inflammation and DNA damage: cause, effect or both. Nat Rev Rheumatol, 19:200-211.
[217] Armanios M, Blackburn EH (2012). The telomere syndromes. Nat Rev Genet, 13:693-704.
[218] Chakravarti D, LaBella KA, DePinho RA (2021). Telomeres: history, health, and hallmarks of aging. Cell, 184:306-322.
[219] Kocak H, Ballew BJ, Bisht K, Eggebeen R, Hicks BD, Suman S, et al. (2014). Hoyeraal-Hreidarsson syndrome caused by a germline mutation in the TEL patch of the telomere protein TPP1. Genes Dev, 28:2090-2102.
[220] Walne AJ, Vulliamy T, Kirwan M, Plagnol V, Dokal I (2013). Constitutional mutations in RTEL1 cause severe dyskeratosis congenita. Am J Hum Genet, 92:448-453.
[221] Stanley SE, Armanios M (2015). The short and long telomere syndromes: paired paradigms for molecular medicine. Curr Opin Genet Dev, 33:1-9.
[222] Fumagalli M, Rossiello F, Clerici M, Barozzi S, Cittaro D, Kaplunov JM, et al. (2012). Telomeric DNA damage is irreparable and causes persistent DNA-damage-response activation. Nat Cell Biol, 14:355-365.
[223] Rossiello F, Jurk D, Passos JF, d'Adda di Fagagna F (2022). Telomere dysfunction in ageing and age-related diseases. Nat Cell Biol, 24:135-147.
[224] Gorgoulis V, Adams PD, Alimonti A, Bennett DC, Bischof O, Bishop C, et al. (2019). Cellular Senescence: Defining a Path Forward. Cell, 179:813-827.
[225] Maciejowski J, Li Y, Bosco N, Campbell PJ, de Lange T (2015). Chromothripsis and Kataegis Induced by Telomere Crisis. Cell, 163:1641-1654.
[226] Maciejowski J, de Lange T (2017). Telomeres in cancer: tumour suppression and genome instability. Nat Rev Mol Cell Biol, 18:175-186.
[227] Lansdorp PM (2022). Telomeres, aging, and cancer: the big picture. Blood, 139:813-821.
[228] Carneiro MC, Henriques CM, Nabais J, Ferreira T, Carvalho T, Ferreira MG (2016). Short Telomeres in Key Tissues Initiate Local and Systemic Aging in Zebrafish. PLoS Genet, 12:e1005798.
[229] Lopes-Bastos B, Nabais J, Ferreira T, Allavena G, El Mai M, Bird M, et al. (2024). The absence of telomerase leads to immune response and tumor regression in zebrafish melanoma. Cell Rep, 43:115035.
[230] Kane AE, Sinclair DA (2019). Epigenetic changes during aging and their reprogramming potential. Crit Rev Biochem Mol Biol, 54:61-83.
[231] Molina-Serrano D, Kyriakou D, Kirmizis A (2019). Histone Modifications as an Intersection Between Diet

and Longevity. Front Genet, 10:192.
[232] Kabacik S, Lowe D, Fransen L, Leonard M, Ang SL, Whiteman C, et al. (2022). The relationship between epigenetic age and the hallmarks of aging in human cells. Nature Aging, 2:484–493.
[233] Feinberg AP, Ohlsson R, Henikoff S (2006). The epigenetic progenitor origin of human cancer. Nat Rev Genet, 7:21-33.
[234] Choudhari R, Sedano MJ, Harrison AL, Subramani R, Lin KY, Ramos EI, et al. (2020). Long noncoding RNAs in cancer: From discovery to therapeutic targets. Adv Clin Chem, 95:105-147.
[235] Daniel M, Tollefsbol TO (2015). Epigenetic linkage of aging, cancer and nutrition. J Exp Biol, 218:59-70.
[236] Locke WJ, Guanzon D, Ma C, Liew YJ, Duesing KR, Fung KYC, et al. (2019). DNA Methylation Cancer Biomarkers: Translation to the Clinic. Front Genet, 10:1150.
[237] Teschendorff AE, Menon U, Gentry-Maharaj A, Ramus SJ, Weisenberger DJ, Shen H, et al. (2010). Age-dependent DNA methylation of genes that are suppressed in stem cells is a hallmark of cancer. Genome Res, 20:440-446.
[238] Benayoun BA, Pollina EA, Brunet A (2015). Epigenetic regulation of ageing: linking environmental inputs to genomic stability. Nat Rev Mol Cell Biol, 16:593-610.
[239] Guo M, Peng Y, Gao A, Du C, Herman JG (2019). Epigenetic heterogeneity in cancer. Biomark Res, 7:23.
[240] Beekman R, Chapaprieta V, Russinol N, Vilarrasa-Blasi R, Verdaguer-Dot N, Martens JHA, et al. (2018). The reference epigenome and regulatory chromatin landscape of chronic lymphocytic leukemia. Nat Med, 24:868-880.
[241] Heide T, Househam J, Cresswell GD, Spiteri I, Lynn C, Mossner M, et al. (2022). The co-evolution of the genome and epigenome in colorectal cancer. Nature, 611:733-743.
[242] Zabransky DJ, Jaffee EM, Weeraratna AT (2022). Shared genetic and epigenetic changes link aging and cancer. Trends Cell Biol, 32:338-350.
[243] Peleg S, Feller C, Ladurner AG, Imhof A (2016). The Metabolic Impact on Histone Acetylation and Transcription in Ageing. Trends Biochem Sci, 41:700-711.
[244] Fennell L, Kane A, Liu C, McKeone D, Hartel G, Su C, et al. (2022). Braf mutation induces rapid neoplastic transformation in the aged and aberrantly methylated intestinal epithelium. Gut, 71:1127-1140.
[245] Tao Y, Kang B, Petkovich DA, Bhandari YR, In J, Stein-O'Brien G, et al. (2019). Aging-like Spontaneous Epigenetic Silencing Facilitates Wnt Activation, Stemness, and Braf(V600E)-Induced Tumorigenesis. Cancer Cell, 35:315-328 e316.
[246] Miyano M, Sayaman RW, Shalabi SF, Senapati P, Lopez JC, Angarola BL, et al. (2021). Breast-Specific Molecular Clocks Comprised of ELF5 Expression and Promoter Methylation Identify Individuals Susceptible to Cancer Initiation. Cancer Prev Res (Phila), 14:779-794.
[247] Rideout WM, 3rd, Coetzee GA, Olumi AF, Jones PA (1990). 5-Methylcytosine as an endogenous mutagen in the human LDL receptor and p53 genes. Science, 249:1288-1290.
[248] Debernardi C, Libera L, Berrino E, Sahnane N, Chiaravalli AM, Laudi C, et al. (2021). Evaluation of global and intragenic hypomethylation in colorectal adenomas improves patient stratification and colorectal cancer risk prediction. Clin Epigenetics, 13:154.
[249] Duan R, Fu Q, Sun Y, Li Q (2022). Epigenetic clock: A promising biomarker and practical tool in aging. Ageing Res Rev, 81:101743.
[250] Oblak L, van der Zaag J, Higgins-Chen AT, Levine ME, Boks MP (2021). A systematic review of biological, social and environmental factors associated with epigenetic clock acceleration. Ageing Res Rev, 69:101348.
[251] Bell CG, Lowe R, Adams PD, Baccarelli AA, Beck S, Bell JT, et al. (2019). DNA methylation aging clocks: challenges and recommendations. Genome Biol, 20:249.
[252] Teschendorff AE, Horvath S (2025). Epigenetic ageing clocks: statistical methods and emerging computational challenges. Nat Rev Genet.
[253] Yu M, Hazelton WD, Luebeck GE, Grady WM (2020). Epigenetic Aging: More Than Just a Clock When It Comes to Cancer. Cancer Res, 80:367-374.
[254] Horvath S, Raj K (2018). DNA methylation-based biomarkers and the epigenetic clock theory of ageing. Nat Rev Genet, 19:371-384.
[255] Liu Z, Leung D, Thrush K, Zhao W, Ratliff S, Tanaka T, et al. (2020). Underlying features of epigenetic aging clocks in vivo and in vitro. Aging Cell, 19:e13229.
[256] Chen L, Ganz PA, Sehl ME (2022). DNA Methylation, Aging, and Cancer Risk: A Mini-Review. Front Bioinform, 2:847629.
[257] Perez RF, Tejedor JR, Fernandez AF, Fraga MF (2022). Aging and cancer epigenetics: Where do the paths fork? Aging Cell, 21:e13709.
[258] Chen S, Jiang Y, Wang C, Tong S, He Y, Lu W, et al. (2024). Epigenetic clocks and gliomas: unveiling the molecular interactions between aging and tumor development. Front Mol Biosci, 11:1446428.
[259] Yang Z, Wong A, Kuh D, Paul DS, Rakyan VK, Leslie RD, et al. (2016). Correlation of an epigenetic mitotic clock with cancer risk. Genome Biol, 17:205.
[260] Levine ME, Hosgood HD, Chen B, Absher D, Assimes T, Horvath S (2015). DNA methylation age of blood predicts future onset of lung cancer in the women's health initiative. Aging (Albany NY), 7:690-700.
[261] Curtius K, Wong CJ, Hazelton WD, Kaz AM, Chak A, Willis JE, et al. (2016). A Molecular Clock Infers Heterogeneous Tissue Age Among Patients with Barrett's Esophagus. PLoS Comput Biol, 12:e1004919.
[262] Morales Berstein F, McCartney DL, Lu AT, Tsilidis KK, Bouras E, Haycock P, et al. (2022). Assessing the causal role of epigenetic clocks in the development of multiple cancers: a Mendelian randomization study.

Elife, 11.
[263] Casado-Pelaez M, Bueno-Costa A, Esteller M (2022). Single cell cancer epigenetics. Trends Cancer, 8:820-838.
[264] Mehrmohamadi M, Sepehri MH, Nazer N, Norouzi MR (2021). A Comparative Overview of Epigenomic Profiling Methods. Front Cell Dev Biol, 9:714687.
[265] Kresovich JK, Xu Z, O'Brien KM, Shi M, Weinberg CR, Sandler DP, et al. (2022). Blood DNA methylation profiles improve breast cancer prediction. Mol Oncol, 16:42-53.
[266] Trapp A, Kerepesi C, Gladyshev VN (2021). Profiling epigenetic age in single cells. Nat Aging, 1:1189-1201.
[267] Herzog CMS, Redl E, Barrett J, Aminzadeh-Gohari S, Weber DD, Tevini J, et al. (2025). Functionally enriched epigenetic clocks reveal tissue-specific discordant aging patterns in individuals with cancer. Commun Med (Lond), 5:98.
[268] de Visser KE, Joyce JA (2023). The evolving tumor microenvironment: From cancer initiation to metastatic outgrowth. Cancer Cell, 41:374-403.
[269] Yuan S, Almagro J, Fuchs E (2024). Beyond genetics: driving cancer with the tumour microenvironment behind the wheel. Nat Rev Cancer, 24:274-286.
[270] Pickup MW, Mouw JK, Weaver VM (2014). The extracellular matrix modulates the hallmarks of cancer. EMBO Rep, 15:1243-1253.
[271] Socovich AM, Naba A (2019). The cancer matrisome: From comprehensive characterization to biomarker discovery. Semin Cell Dev Biol, 89:157-166.
[272] Ewald CY (2020). The Matrisome during Aging and Longevity: A Systems-Level Approach toward Defining Matreotypes Promoting Healthy Aging. Gerontology, 66:266-274.
[273] Statzer C, Park JYC, Ewald CY (2023). Extracellular Matrix Dynamics as an Emerging yet Understudied Hallmark of Aging and Longevity. Aging Dis, 14:670-693.
[274] McCullough KD, Coleman WB, Smith GJ, Grishan JW (1994). Age-dependent regulation of the tumorigenic potential of neoplastically transformed rat liver epithelial cells by the liver microenvironment. Cancer Res, 54:3668-3671.
[275] Hendrix MJ, Seftor EA, Seftor RE, Kasemeier-Kulesa J, Kulesa PM, Postovit LM (2007). Reprogramming metastatic tumour cells with embryonic microenvironments. Nat Rev Cancer, 7:246-255.
[276] Turrell FK, Orha R, Guppy NJ, Gillespie A, Guelbert M, Starling C, et al. (2023). Age-associated microenvironmental changes highlight the role of PDGF-C in ER(+) breast cancer metastatic relapse. Nat Cancer, 4:468-484.
[277] Fane ME, Chhabra Y, Smith AG, Sturm RA (2019). BRN2, a POUerful driver of melanoma phenotype switching and metastasis. Pigment Cell Melanoma Res, 32:9-24.
[278] Fane ME, Chhabra Y, Alicea GM, Maranto DA, Douglass SM, Webster MR, et al. (2022). Stromal changes in the aged lung induce an emergence from melanoma dormancy. Nature, 606:396-405.
[279] Anisimov VN (2003). The relationship between aging and carcinogenesis: a critical appraisal. Crit Rev Oncol Hematol, 45:277-304.
[280] Krtolica A, Campisi J (2002). Cancer and aging: a model for the cancer promoting effects of the aging stroma. Int J Biochem Cell Biol, 34:1401-1414.
[281] Bianchi-Frias D, Damodarasamy M, Hernandez SA, Gil da Costa RM, Vakar-Lopez F, Coleman IM, et al. (2019). The Aged Microenvironment Influences the Tumorigenic Potential of Malignant Prostate Epithelial Cells. Mol Cancer Res, 17:321-331.
[282] Jiang X, Shen H, Shang X, Fang J, Lu Y, Lu Y, et al. (2022). Recent Advances in the Aging Microenvironment of Breast Cancer. Cancers (Basel), 14.
[283] Zhao B, Wu B, Feng N, Zhang X, Zhang X, Wei Y, et al. (2023). Aging microenvironment and antitumor immunity for geriatric oncology: the landscape and future implications. J Hematol Oncol, 16:28.
[284] Baghy K, Ladanyi A, Reszegi A, Kovalszky I (2023). Insights into the Tumor Microenvironment-Components, Functions and Therapeutics. Int J Mol Sci, 24.
[285] Lampi MC, Reinhart-King CA (2018). Targeting extracellular matrix stiffness to attenuate disease: From molecular mechanisms to clinical trials. Sci Transl Med, 10.
[286] Marino GE, Weeraratna AT (2020). A glitch in the matrix: Age-dependent changes in the extracellular matrix facilitate common sites of metastasis. Aging Cancer, 1:19-29.
[287] Ishihara S, Haga H (2022). Matrix Stiffness Contributes to Cancer Progression by Regulating Transcription Factors. Cancers (Basel), 14.
[288] Fisher GJ, Quan T, Purohit T, Shao Y, Cho MK, He T, et al. (2009). Collagen fragmentation promotes oxidative stress and elevates matrix metalloproteinase-1 in fibroblasts in aged human skin. Am J Pathol, 174:101-114.
[289] Kaur A, Ecker BL, Douglass SM, Kugel CH, 3rd, Webster MR, Almeida FV, et al. (2019). Remodeling of the Collagen Matrix in Aging Skin Promotes Melanoma Metastasis and Affects Immune Cell Motility. Cancer Discov, 9:64-81.
[290] Liu H, Kato Y, Erzinger SA, Kiriakova GM, Qian Y, Palmieri D, et al. (2012). The role of MMP-1 in breast cancer growth and metastasis to the brain in a xenograft model. BMC Cancer, 12:583.
[291] Li CM, Shapiro H, Tsiobikas C, Selfors LM, Chen H, Rosenbluth J, et al. (2020). Aging-Associated Alterations in Mammary Epithelia and Stroma Revealed by Single-Cell RNA Sequencing. Cell Rep, 33:108566.
[292] Vangangelt KMH, Kramer CJH, Bastiaannet E, Putter H, Cohen D, van Pelt GW, et al. (2020). The intra-tumoural stroma in patients with breast cancer increases with age. Breast Cancer Res Treat, 179:37-45.
[293] Franceschi C, Bonafe M, Valensin S, Olivieri F, De Luca M, Ottaviani E, et al. (2000). Inflamm-aging. An

evolutionary perspective on immunosenescence. Ann N Y Acad Sci, 908:244-254.
[294] Grivennikov SI, Greten FR, Karin M (2010). Immunity, inflammation, and cancer. Cell, 140:883-899.
[295] Sfanos KS, Yegnasubramanian S, Nelson WG, De Marzo AM (2018). The inflammatory microenvironment and microbiome in prostate cancer development. Nat Rev Urol, 15:11-24.
[296] Jetten N, Verbruggen S, Gijbels MJ, Post MJ, De Winther MP, Donners MM (2014). Anti-inflammatory M2, but not pro-inflammatory M1 macrophages promote angiogenesis in vivo. Angiogenesis, 17:109-118.
[297] Lin EY, Li JF, Gnatovskiy L, Deng Y, Zhu L, Grzesik DA, et al. (2006). Macrophages regulate the angiogenic switch in a mouse model of breast cancer. Cancer Res, 66:11238-11246.
[298] Torisu H, Ono M, Kiryu H, Furue M, Ohmoto Y, Nakayama J, et al. (2000). Macrophage infiltration correlates with tumor stage and angiogenesis in human malignant melanoma: possible involvement of TNFalpha and IL-1alpha. Int J Cancer, 85:182-188.
[299] Okano M, Oshi M, Mukhopadhyay S, Qi Q, Yan L, Endo I, et al. (2021). Octogenarians' Breast Cancer Is Associated with an Unfavorable Tumor Immune Microenvironment and Worse Disease-Free Survival. Cancers (Basel), 13.
[300] Chen Y, Zhang S, Wang Q, Zhang X (2017). Tumor-recruited M2 macrophages promote gastric and breast cancer metastasis via M2 macrophage-secreted CHI3L1 protein. J Hematol Oncol, 10:36.
[301] Liang S, Domon H, Hosur KB, Wang M, Hajishengallis G (2009). Age-related alterations in innate immune receptor expression and ability of macrophages to respond to pathogen challenge in vitro. Mech Ageing Dev, 130:538-546.
[302] De Maeyer RPH, Chambers ES (2021). The impact of ageing on monocytes and macrophages. Immunol Lett, 230:1-10.
[303] Moss CE, Johnston SA, Kimble JV, Clements M, Codd V, Hamby S, et al. (2024). Aging-related defects in macrophage function are driven by MYC and USF1 transcriptional programs. Cell Rep, 43:114073.
[304] Jackaman C, Tomay F, Duong L, Abdol Razak NB, Pixley FJ, Metharom P, et al. (2017). Aging and cancer: The role of macrophages and neutrophils. Ageing Res Rev, 36:105-116.
[305] Qian F, Guo X, Wang X, Yuan X, Chen S, Malawista SE, et al. (2014). Reduced bioenergetics and toll-like receptor 1 function in human polymorphonuclear leukocytes in aging. Aging (Albany NY), 6:131-139.
[306] Wang L, Tang D (2025). Immunosenescence promotes cancer development: from mechanisms to treatment strategies. Cell Commun Signal, 23:128.
[307] Chen ACY, Jaiswal S, Martinez D, Yerinde C, Ji K, Miranda V, et al. (2024). The aged tumor microenvironment limits T cell control of cancer. Nat Immunol, 25:1033-1045.
[308] Cai L, Li Y, Tan J, Xu L, Li Y (2023). Targeting LAG-3, TIM-3, and TIGIT for cancer immunotherapy. J Hematol Oncol, 16:101.
[309] Perez RF, Jimenez-Martinez V, Martin-Subero JI (2024). Lymphoma lurks within aged B cells. Nat Aging, 4:1343-1345.
[310] Wolf NK, Kissiov DU, Raulet DH (2023). Roles of natural killer cells in immunity to cancer, and applications to immunotherapy. Nat Rev Immunol, 23:90-105.
[311] Almeida-Oliveira A, Smith-Carvalho M, Porto LC, Cardoso-Oliveira J, Ribeiro Ados S, Falcao RR, et al. (2011). Age-related changes in natural killer cell receptors from childhood through old age. Hum Immunol, 72:319-329.
[312] Brauning A, Rae M, Zhu G, Fulton E, Admasu TD, Stolzing A, et al. (2022). Aging of the Immune System: Focus on Natural Killer Cells Phenotype and Functions. Cells, 11.
[313] Peng YP, Zhu Y, Zhang JJ, Xu ZK, Qian ZY, Dai CC, et al. (2013). Comprehensive analysis of the percentage of surface receptors and cytotoxic granules positive natural killer cells in patients with pancreatic cancer, gastric cancer, and colorectal cancer. J Transl Med, 11:262.
[314] Agrawal A, Gupta S (2011). Impact of aging on dendritic cell functions in humans. Ageing Res Rev, 10:336-345.
[315] Zhivaki D, Kennedy SN, Park J, Boriello F, Devant P, Cao A, et al. (2024). Correction of age-associated defects in dendritic cells enables CD4(+) T cells to eradicate tumors. Cell, 187:3888-3903 e3818.
[316] Locati M, Curtale G, Mantovani A (2020). Diversity, Mechanisms, and Significance of Macrophage Plasticity. Annu Rev Pathol, 15:123-147.
[317] Sobhon P, Savedvanich G, Weerakiet S (2023). Oxidative stress and inflammation: the root causes of aging. Exploration of Medicine, 4:127-156.
[318] Pomatto LCD, Davies KJA (2018). Adaptive homeostasis and the free radical theory of ageing. Free Radic Biol Med, 124:420-430.
[319] Glorieux C, Liu S, Trachootham D, Huang P (2024). Targeting ROS in cancer: rationale and strategies. Nat Rev Drug Discov, 23:583-606.
[320] Mijatovic S, Savic-Radojevic A, Pljesa-Ercegovac M, Simic T, Nicoletti F, Maksimovic-Ivanic D (2020). The Double-Faced Role of Nitric Oxide and Reactive Oxygen Species in Solid Tumors. Antioxidants (Basel), 9.
[321] Bussian TJ, Aziz A, Meyer CF, Swenson BL, van Deursen JM, Baker DJ (2018). Clearance of senescent glial cells prevents tau-dependent pathology and cognitive decline. Nature, 562:578-582.
[322] Baker DJ, Childs BG, Durik M, Wijers ME, Sieben CJ, Zhong J, et al. (2016). Naturally occurring p16(Ink4a)-positive cells shorten healthy lifespan. Nature, 530:184-189.
[323] Ye J, Baer JM, Faget DV, Morikis VA, Ren Q, Melam A, et al. (2024). Senescent CAFs Mediate Immunosuppression and Drive Breast Cancer Progression. Cancer Discov, 14:1302-1323.

[324] Iyengar NM, Morris PG, Zhou XK, Gucalp A, Giri D, Harbus MD, et al. (2015). Menopause is a determinant of breast adipose inflammation. Cancer Prev Res (Phila), 8:349-358.
[325] Campisi J, d'Adda di Fagagna F (2007). Cellular senescence: when bad things happen to good cells. Nat Rev Mol Cell Biol, 8:729-740.
[326] Dong Z, Luo Y, Yuan Z, Tian Y, Jin T, Xu F (2024). Cellular senescence and SASP in tumor progression and therapeutic opportunities. Mol Cancer, 23:181.
[327] Tchkonia T, Zhu Y, van Deursen J, Campisi J, Kirkland JL (2013). Cellular senescence and the senescent secretory phenotype: therapeutic opportunities. J Clin Invest, 123:966-972.
[328] Hall BM, Balan V, Gleiberman AS, Strom E, Krasnov P, Virtuoso LP, et al. (2016). Aging of mice is associated with p16(Ink4a)- and beta-galactosidase-positive macrophage accumulation that can be induced in young mice by senescent cells. Aging (Albany NY), 8:1294-1315.
[329] Prattichizzo F, Bonafe M, Olivieri F, Franceschi C (2016). Senescence associated macrophages and "macroph-aging": are they pieces of the same puzzle? Aging (Albany NY), 8:3159-3160.
[330] Rodier F, Coppe JP, Patil CK, Hoeijmakers WA, Munoz DP, Raza SR, et al. (2009). Persistent DNA damage signalling triggers senescence-associated inflammatory cytokine secretion. Nat Cell Biol, 11:973-979.
[331] Victorelli S, Lagnado A, Halim J, Moore W, Talbot D, Barrett K, et al. (2019). Senescent human melanocytes drive skin ageing via paracrine telomere dysfunction. EMBO J, 38:e101982.
[332] Coppe JP, Patil CK, Rodier F, Sun Y, Munoz DP, Goldstein J, et al. (2008). Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. PLoS Biol, 6:2853-2868.
[333] Pignolo RJ, Passos JF, Khosla S, Tchkonia T, Kirkland JL (2020). Reducing Senescent Cell Burden in Aging and Disease. Trends Mol Med, 26:630-638.
[334] Mylonas A, O'Loghlen A (2022). Cellular Senescence and Ageing: Mechanisms and Interventions. Front Aging, 3:866718.
[335] Pawelec G, Solana R (1997). Immunosenescence. Immunol Today, 18:514-516.
[336] Frasca D, Blomberg BB (2011). Aging affects human B cell responses. J Clin Immunol, 31:430-435.
[337] Nikolich-Zugich J (2005). T cell aging: naive but not young. J Exp Med, 201:837-840.
[338] Guo Z, Tilburgs T, Wong B, Strominger JL (2014). Dysfunction of dendritic cells in aged C57BL/6 mice leads to failure of natural killer cell activation and of tumor eradication. Proc Natl Acad Sci U S A, 111:14199-14204.
[339] Nguyen M, Pace AJ, Koller BH (2005). Age-induced reprogramming of mast cell degranulation. J Immunol, 175:5701-5707.
[340] Lian J, Yue Y, Yu W, Zhang Y (2020). Immunosenescence: a key player in cancer development. J Hematol Oncol, 13:151.
[341] Sidler C, Woycicki R, Ilnytskyy Y, Metz G, Kovalchuk I, Kovalchuk O (2013). Immunosenescence is associated with altered gene expression and epigenetic regulation in primary and secondary immune organs. Front Genet, 4:211.
[342] Guan Y, Zhang C, Lyu G, Huang X, Zhang X, Zhuang T, et al. (2020). Senescence-activated enhancer landscape orchestrates the senescence-associated secretory phenotype in murine fibroblasts. Nucleic Acids Res, 48:10909-10923.
[343] Fali T, Papagno L, Bayard C, Mouloud Y, Boddaert J, Sauce D, et al. (2019). New Insights into Lymphocyte Differentiation and Aging from Telomere Length and Telomerase Activity Measurements. J Immunol, 202:1962-1969.
[344] Fulop T, Kotb R, Fortin CF, Pawelec G, de Angelis F, Larbi A (2010). Potential role of immunosenescence in cancer development. Ann N Y Acad Sci, 1197:158-165.
[345] Maggiorani D, Le O, Lisi V, Landais S, Moquin-Beaudry G, Lavallee VP, et al. (2024). Senescence drives immunotherapy resistance by inducing an immunosuppressive tumor microenvironment. Nat Commun, 15:2435.
[346] Finger AM, Kramer A (2021). Mammalian circadian systems: Organization and modern life challenges. Acta Physiol (Oxf), 231:e13548.
[347] Gaucher J, Montellier E, Sassone-Corsi P (2018). Molecular Cogs: Interplay between Circadian Clock and Cell Cycle. Trends Cell Biol, 28:368-379.
[348] Masri S, Sassone-Corsi P (2018). The emerging link between cancer, metabolism, and circadian rhythms. Nat Med, 24:1795-1803.
[349] Rana S, Mahmood S (2010). Circadian rhythm and its role in malignancy. J Circadian Rhythms, 8:3.
[350] Jung-Hynes B, Reiter RJ, Ahmad N (2010). Sirtuins, melatonin and circadian rhythms: building a bridge between aging and cancer. J Pineal Res, 48:9-19.
[351] Buijink MR, Olde Engberink AHO, Wit CB, Almog A, Meijer JH, Rohling JHT, et al. (2020). Aging Affects the Capacity of Photoperiodic Adaptation Downstream from the Central Molecular Clock. J Biol Rhythms, 35:167-179.
[352] Zhao J, Warman GR, Cheeseman JF (2019). The functional changes of the circadian system organization in aging. Ageing Res Rev, 52:64-71.
[353] Wang RH, Zhao T, Cui K, Hu G, Chen Q, Chen W, et al. (2016). Negative reciprocal regulation between Sirt1 and Per2 modulates the circadian clock and aging. Sci Rep, 6:28633.
[354] Chang HC, Guarente L (2013). SIRT1 mediates central circadian control in the SCN by a mechanism that decays with aging. Cell, 153:1448-1460.
[355] Wang C, Lutes LK, Barnoud C, Scheiermann C (2022). The circadian immune system. Sci Immunol, 7:eabm2465.
[356] Blacher E, Tsai C, Litichevskiy L, Shipony Z, Iweka CA, Schneider KM, et al. (2022). Aging disrupts circadian gene regulation and function in macrophages. Nat Immunol, 23:229-236.

[357] Wang C, Barnoud C, Cenerenti M, Sun M, Caffa I, Kizil B, et al. (2023). Dendritic cells direct circadian anti-tumour immune responses. Nature, 614:136-143.
[358] Xuan W, Khan F, James CD, Heimberger AB, Lesniak MS, Chen P (2021). Circadian regulation of cancer cell and tumor microenvironment crosstalk. Trends Cell Biol, 31:940-950.
[359] Huang C, Zhang C, Cao Y, Li J, Bi F (2023). Major roles of the circadian clock in cancer. Cancer Biol Med, 20:1-24.
[360] Li D, Yu Q, Wu R, Tuo Z, Zhu W, Wang J, et al. (2025). Chronobiology of the Tumor Microenvironment: Implications for Therapeutic Strategies and Circadian-Based Interventions. Aging Dis, 16:645-657.
[361] Zhu X, Maier G, Panda S (2024). Learning from circadian rhythm to transform cancer prevention, prognosis, and survivorship care. Trends Cancer, 10:196-207.
[362] Hadadi E, Taylor W, Li XM, Aslan Y, Villote M, Riviere J, et al. (2020). Chronic circadian disruption modulates breast cancer stemness and immune microenvironment to drive metastasis in mice. Nat Commun, 11:3193.
[363] Su K, Zeng D, Zhang W, Peng F, Cui B, Liu Q (2025). Integrating cancer medicine into metabolic rhythms. Trends Endocrinol Metab.
[364] Shafi AA, Knudsen KE (2019). Cancer and the Circadian Clock. Cancer Res, 79:3806-3814.
[365] Thaiss CA, Zeevi D, Levy M, Zilberman-Schapira G, Suez J, Tengeler AC, et al. (2014). Transkingdom control of microbiota diurnal oscillations promotes metabolic homeostasis. Cell, 159:514-529.
[366] Paschos GK, FitzGerald GA (2017). Circadian Clocks and Metabolism: Implications for Microbiome and Aging. Trends Genet, 33:760-769.
[367] Di Marzo V, Bifulco M, De Petrocellis L (2004). The endocannabinoid system and its therapeutic exploitation. Nat Rev Drug Discov, 3:771-784.
[368] Lowe H, Toyang N, Steele B, Bryant J, Ngwa W (2021). The Endocannabinoid System: A Potential Target for the Treatment of Various Diseases. Int J Mol Sci, 22.
[369] Tudorancea IM, Ciorpac M, Stanciu GD, Caratasu C, Sacarescu A, Ignat B, et al. (2022). The Therapeutic Potential of the Endocannabinoid System in Age-Related Diseases. Biomedicines, 10.
[370] Baban B, Khodadadi H, Salles EL, Costigliola V, Morgan JC, Hess DC, et al. (2021). Inflammaging and Cannabinoids. Ageing Res Rev, 72:101487.
[371] Wang Z, Arnold JC (2024). Cannabinoids and healthy ageing: the potential for extending healthspan and lifespan in preclinical models with an emphasis on Caenorhabditis elegans. Geroscience, 46:5643-5661.
[372] Piyanova A, Lomazzo E, Bindila L, Lerner R, Albayram O, Ruhl T, et al. (2015). Age-related changes in the endocannabinoid system in the mouse hippocampus. Mech Ageing Dev, 150:55-64.
[373] Bilkei-Gorzo A, Racz I, Valverde O, Otto M, Michel K, Sastre M, et al. (2005). Early age-related cognitive impairment in mice lacking cannabinoid CB1 receptors. Proc Natl Acad Sci U S A, 102:15670-15675.
[374] Vasincu A, Rusu RN, Ababei DC, Larion M, Bild W, Stanciu GD, et al. (2022). Endocannabinoid Modulation in Neurodegenerative Diseases: In Pursuit of Certainty. Biology (Basel), 11.
[375] Pyszniak M, Tabarkiewicz J, Luszczki JJ (2016). Endocannabinoid system as a regulator of tumor cell malignancy - biological pathways and clinical significance. Onco Targets Ther, 9:4323-4336.
[376] Faiz MB, Naeem F, Irfan M, Aslam MA, Estevinho LM, Atessahin DA, et al. (2024). Exploring the therapeutic potential of cannabinoids in cancer by modulating signaling pathways and addressing clinical challenges. Discov Oncol, 15:490.
[377] Bakshi HA, Faruck HL, Ravesh Z, Ansari P, Hannan JMA, Hashimoto R, et al. (2022). Therapeutic Potential of Cannabinoids on Tumor Microenvironment: A Molecular Switch in Neoplasia Transformation. Integr Cancer Ther, 21:15347354221096766.
[378] Wittig F, Pannenberg L, Schwarz R, Bekeschus S, Ramer R, Hinz B (2023). Antiangiogenic Action of JZL184 on Endothelial Cells via Inhibition of VEGF Expression in Hypoxic Lung Cancer Cells. Cells, 12.
[379] Iden JA, Raphael-Mizrahi B, Naim A, Kolomansky A, Liron T, Neumann D, et al. (2023). The Anti-Tumorigenic Role of Cannabinoid Receptor 2 in Non-Melanoma Skin Cancer. Int J Mol Sci, 24.
[380] Ferrini ME, Hong S, Stierle A, Stierle D, Stella N, Roberts K, et al. (2017). CB2 receptors regulate natural killer cells that limit allergic airway inflammation in a murine model of asthma. Allergy, 72:937-947.
[381] Aiello A, Farzaneh F, Candore G, Caruso C, Davinelli S, Gambino CM, et al. (2019). Immunosenescence and Its Hallmarks: How to Oppose Aging Strategically? A Review of Potential Options for Therapeutic Intervention. Front Immunol, 10:2247.
[382] Xiang W, Shi R, Kang X, Zhang X, Chen P, Zhang L, et al. (2018). Monoacylglycerol lipase regulates cannabinoid receptor 2-dependent macrophage activation and cancer progression. Nat Commun, 9:2574.
[383] Almogi-Hazan O, Or R (2020). Cannabis, the Endocannabinoid System and Immunity-the Journey from the Bedside to the Bench and Back. Int J Mol Sci, 21.
[384] Odamaki T, Kato K, Sugahara H, Hashikura N, Takahashi S, Xiao JZ, et al. (2016). Age-related changes in gut microbiota composition from newborn to centenarian: a cross-sectional study. BMC Microbiol, 16:90.
[385] Ling Z, Liu X, Cheng Y, Yan X, Wu S (2022). Gut microbiota and aging. Crit Rev Food Sci Nutr, 62:3509-3534.
[386] Wu Y, Zhuang J, Zhang Q, Zhao X, Chen G, Han S, et al. (2023). Aging characteristics of colorectal cancer based on gut microbiota. Cancer Med, 12:17822-17834.

[387] Kandalai S, Li H, Zhang N, Peng H, Zheng Q (2023). The human microbiome and cancer: a diagnostic and therapeutic perspective. Cancer Biol Ther, 24:2240084.
[388] de Martel C, Georges D, Bray F, Ferlay J, Clifford GM (2020). Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. Lancet Glob Health, 8:e180-e190.
[389] Ghosh TS, Shanahan F, O'Toole PW (2022). The gut microbiome as a modulator of healthy ageing. Nat Rev Gastroenterol Hepatol, 19:565-584.
[390] DeJong EN, Surette MG, Bowdish DME (2020). The Gut Microbiota and Unhealthy Aging: Disentangling Cause from Consequence. Cell Host Microbe, 28:180-189.
[391] Johansson A, Ho NP, Takizawa H (2025). Microbiome and Hemato-immune Aging. Exp Hematol, 141:104685.
[392] Mancabelli L, Milani C, De Biase R, Bocchio F, Fontana F, Lugli GA, et al. (2024). Taxonomic and metabolic development of the human gut microbiome across life stages: a worldwide metagenomic investigation. mSystems, 9:e0129423.
[393] Zhang S, Zeng B, Chen Y, Yang M, Kong F, Wei L, et al. (2021). Gut microbiota in healthy and unhealthy long-living people. Gene, 779:145510.
[394] Ye C, Li Z, Ye C, Yuan L, Wu K, Zhu C (2024). Association between Gut Microbiota and Biological Aging: A Two-Sample Mendelian Randomization Study. Microorganisms, 12.
[395] Jian X, Zhu Y, Ouyang J, Wang Y, Lei Q, Xia J, et al. (2020). Alterations of gut microbiome accelerate multiple myeloma progression by increasing the relative abundances of nitrogen-recycling bacteria. Microbiome, 8:74.
[396] Liu F, Li J, Guan Y, Lou Y, Chen H, Xu M, et al. (2019). Dysbiosis of the Gut Microbiome is associated with Tumor Biomarkers in Lung Cancer. Int J Biol Sci, 15:2381-2392.
[397] Priya S, Burns MB, Ward T, Mars RAT, Adamowicz B, Lock EF, et al. (2022). Identification of shared and disease-specific host gene-microbiome associations across human diseases using multi-omic integration. Nat Microbiol, 7:780-795.
[398] Yu D, Yang J, Jin M, Zhou B, Shi L, Zhao L, et al. (2021). Fecal Streptococcus Alteration Is Associated with Gastric Cancer Occurrence and Liver Metastasis. mBio, 12:e0299421.
[399] Connor MG, Camarasa TMN, Patey E, Rasid O, Barrio L, Weight CM, et al. (2021). The histone demethylase KDM6B fine-tunes the host response to Streptococcus pneumoniae. Nat Microbiol, 6:257-269.
[400] Wei Z, Yang B, Tang T, Xiao Z, Ye F, Li X, et al. (2023). Gut microbiota and risk of five common cancers: A univariable and multivariable Mendelian randomization study. Cancer Med, 12:10393-10405.
[401] Wang Y, Wan X, Wu X, Zhang C, Liu J, Hou S (2021). Eubacterium rectale contributes to colorectal cancer initiation via promoting colitis. Gut Pathog, 13:2.
[402] Ma M, Zheng Z, Li J, He Y, Kang W, Ye X (2024). Association between the gut microbiota, inflammatory factors, and colorectal cancer: evidence from Mendelian randomization analysis. Front Microbiol, 15:1309111.
[403] Liu X, Dong Q (2024). Associations between gut microbiota and three prostate diseases: a bidirectional two-sample Mendelian randomization study. Sci Rep, 14:4019.
[404] Li J, Gao X, Sun X, Li H, Wei J, Lv L, et al. (2024). Investigating the causal role of the gut microbiota in esophageal cancer and its subtypes: a two-sample Mendelian randomization study. BMC Cancer, 24:416.
[405] Otsuka K, Isobe J, Asai Y, Nakano T, Hattori K, Ariyoshi T, et al. (2024). Butyricimonas is a key gut microbiome component for predicting postoperative recurrence of esophageal cancer. Cancer Immunol Immunother, 73:23.
[406] Hurria A, Togawa K, Mohile SG, Owusu C, Klepin HD, Gross CP, et al. (2011). Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. J Clin Oncol, 29:3457-3465.
[407] Pitkala KH, Strandberg TE (2022). Clinical trials in older people. Age Ageing, 51.
[408] Bumanlag IM, Jaoude JA, Rooney MK, Taniguchi CM, Ludmir EB (2022). Exclusion of Older Adults from Cancer Clinical Trials: Review of the Literature and Future Recommendations. Semin Radiat Oncol, 32:125-134.
[409] Habr D, McRoy L, Papadimitrakopoulou VA (2021). Age Is Just a Number: Considerations for Older Adults in Cancer Clinical Trials. J Natl Cancer Inst, 113:1460-1464.
[410] Mohile SG, Dale W, Somerfield MR, Schonberg MA, Boyd CM, Burhenn PS, et al. (2018). Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology. J Clin Oncol, 36:2326-2347.
[411] Jebanesan N, Alibhai SMH, Santa Mina D, Jones J, Legacy N, Freeman L, et al. (2025). Supporting older adults with cancer and their support person through geriatric assessment and remote exercise and education: The SOAR study protocol. J Geriatr Oncol, 16:102194.
[412] FDA (2022). Inclusion of Older Adults in Cancer Clinical Trials - Guidance for Industry. Available at https://www.fda.gov/media/156616/download.
[413] Available at https://clinicaltrials.gov/search?cond=Cancer&term=aging&viewType=Card&aggFilters=ages:older. Accessed on July 2, 2025.
[414] Fusco D, Ferrini A, Pasqualetti G, Giannotti C, Cesari M, Laudisio A, et al. (2021). Comprehensive geriatric assessment in older adults with cancer: Recommendations by the Italian Society of Geriatrics and Gerontology (SIGG). Eur J Clin Invest, 51:e13347.
[415] Hamaker M, Lund C, Te Molder M, Soubeyran P, Wildiers H, van Huis L, et al. (2022). Geriatric assessment in the management of older patients with cancer - A systematic review (update). J Geriatr Oncol, 13:761-777.

[416] Paredero-Perez I, Jimenez-Fonseca P, Cano JM, Arrazubi V, Carmona-Bayonas A, Covela-Rua M, et al. (2024). State of the scientific evidence and recommendations for the management of older patients with gastric cancer. J Geriatr Oncol, 15:101657.

[417] Dale W, Klepin HD, Williams GR, Alibhai SMH, Bergerot C, Brintzenhofeszoc K, et al. (2023). Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Systemic Cancer Therapy: ASCO Guideline Update. J Clin Oncol, 41:4293-4312.

[418] Rostoft S, O'Donovan A, Soubeyran P, Alibhai SMH, Hamaker ME (2021). Geriatric Assessment and Management in Cancer. J Clin Oncol, 39:2058-2067.

[419] Hernandez Torres C, Hsu T (2017). Comprehensive Geriatric Assessment in the Older Adult with Cancer: A Review. Eur Urol Focus, 3:330-339.

[420] Overcash J, Ford N, Kress E, Ubbing C, Williams N (2019). Comprehensive Geriatric Assessment as a Versatile Tool to Enhance the Care of the Older Person Diagnosed with Cancer. Geriatrics (Basel), 4.

[421] Hurria A, Mohile S, Gajra A, Klepin H, Muss H, Chapman A, et al. (2016). Validation of a Prediction Tool for Chemotherapy Toxicity in Older Adults With Cancer. J Clin Oncol, 34:2366-2371.

[422] Extermann M, Boler I, Reich RR, Lyman GH, Brown RH, DeFelice J, et al. (2012). Predicting the risk of chemotherapy toxicity in older patients: the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score. Cancer, 118:3377-3386.

[423] Lewis A, Reed M, Walde N, Voutsadakis IA (2023). An evaluation of the Index4 tool for chemotherapy toxicity prediction in cancer patients older than 70 years old. Sci Rep, 13:1082.

[424] Magnuson A, Sedrak MS, Gross CP, Tew WP, Klepin HD, Wildes TM, et al. (2021). Development and Validation of a Risk Tool for Predicting Severe Toxicity in Older Adults Receiving Chemotherapy for Early-Stage Breast Cancer. J Clin Oncol, 39:608-618.

[425] Mahmoud AM, Biello F, Maggiora PM, Bruna R, Burrafato G, Cappelli M, et al. (2021). A randomized clinical study on the impact of Comprehensive Geriatric Assessment (CGA) based interventions on the quality of life of elderly, frail, onco-hematologic patients candidate to anticancer therapy: protocol of the ONCO-Aging study. BMC Geriatr, 21:320.

[426] Puts MTE, Hsu T, Mariano C, Monette J, Brennenstuhl S, Pitters E, et al. (2019). Clinical and Cost-effectiveness of a Comprehensive geriatric assessment and management for Canadian elders with Cancer-the 5C study: a study protocol for a randomised controlled phase III trial. BMJ Open, 9:e024485.

[427] Gonzalez Serrano A, Laurent M, Barnay T, Martinez-Tapia C, Audureau E, Boudou-Rouquette P, et al. (2022). A Two-Step Frailty Assessment Strategy in Older Patients With Solid Tumors: A Decision Curve Analysis. J Clin Oncol:JCO2201118.

[428] Disalvo D, Moth E, Soo WK, Garcia MV, Blinman P, Steer C, et al. (2023). The effect of comprehensive geriatric assessment on care received, treatment completion, toxicity, cancer-related and geriatric assessment outcomes, and quality of life for older adults receiving systemic anti-cancer treatment: A systematic review. J Geriatr Oncol, 14:101585.

[429] Li D, Sun CL, Kim H, Soto-Perez-de-Celis E, Chung V, Koczywas M, et al. (2021). Geriatric Assessment-Driven Intervention (GAIN) on Chemotherapy-Related Toxic Effects in Older Adults With Cancer: A Randomized Clinical Trial. JAMA Oncol, 7:e214158.

[430] Mohile SG, Mohamed MR, Xu H, Culakova E, Loh KP, Magnuson A, et al. (2021). Evaluation of geriatric assessment and management on the toxic effects of cancer treatment (GAP70+): a cluster-randomised study. Lancet, 398:1894-1904.

[431] Presley CJ, Mohamed MR, Culakova E, Flannery M, Vibhakar PH, Hoyd R, et al. (2022). A Geriatric Assessment Intervention to Reduce Treatment Toxicity Among Older Adults With Advanced Lung Cancer: A Subgroup Analysis From a Cluster Randomized Controlled Trial. Front Oncol, 12:835582.

[432] Available at https://clinicaltrials.gov/search?cond=Cancer&term=aging&aggFilters=ages:older&intr=Comprehensive%20geriatric%20assessment%20%5C(CGA%5C). Accessed on July 2, 2025.

[433] Cabrera Chien L, Sun CL, Kim H, Uranga C, Soto-Perez-de-Celis E, Burhenn P, et al. (2025). Geriatric Assessment-driven INterventions among Hospitalized older adults with cancer (GAIN-HOSP), a prospective pilot study. J Geriatr Oncol, 16:102063.

[434] Lynch KA, Merdjanoff A, Wilson D, Chiarello L, Hay J, Mao JJ (2022). "Moving Forward": Older Adult Motivations for Group-Based Physical Activity After Cancer Treatment. Int J Behav Med, 29:286-298.

[435] Cao A, Ferrucci LM, Caan BJ, Irwin ML (2022). Effect of Exercise on Sarcopenia among Cancer Survivors: A Systematic Review. Cancers (Basel), 14.

[436] Fournier B, Nicolas-Virelizier E, Russo C, Perol O, Millet GY, Maire A, et al. (2021). Individualised physical activity programme in patients over 65 years with haematological malignancies (OCAPI): protocol for a single-arm feasibility trial. BMJ Open, 11:e046409.

[437] Adeline F, Hugo PR, Rene M, Tamas F, Eleonor R, Michel P (2021). Effects of a mixed exercise program on cancer related-fatigue and health-related quality of life in oncogeriatric patients: A feasibility study. J Geriatr Oncol, 12:915-921.

[438] Soones T, Ombres R, Escalante C (2022). An update on cancer-related fatigue in older adults: A narrative review. J Geriatr Oncol, 13:125-131.

[439] Sun J, Ge L, Cao C, Yao W, Wang X (2023). Effects of resistance exercise in elderly cancer patients. Afr Health Sci, 23:298-304.

[440] Kemerich JAP, Giongo CLM, Pivetta HMF (2024). Effects of Physical Exercise in Older Patients with Cancer: Literature Integrative Review. Rev. Bras. Cancerol. [Internet], 70:e-154514

[441] Giallauria F, Testa C, Cuomo G, Di Lorenzo A, Venturini E, Lauretani F, et al. (2023). Exercise Training in Elderly Cancer Patients: A Systematic Review. Cancers (Basel), 15.

[442] Ferrara MC, Zambom-Ferraresi F, Castillo A, Delgado M, Galbete A, Arrazubi V, et al. (2025). Effects of an individualised exercise program in hospitalised older adults with cancer: A randomised clinical trial. J Nutr Health Aging, 29:100424.

[443] Guo S, Han W, Wang P, Wang X, Fang X (2022). Effects of exercise on chemotherapy-induced peripheral neuropathy in cancer patients: a systematic review and meta-analysis. J Cancer Surviv.

[444] Lopez-Garzon M, Cantarero-Villanueva I, Postigo-Martin P, Gonzalez-Santos A, Lozano-Lozano M, Galiano-Castillo N (2022). Can Physical Exercise Prevent Chemotherapy-Induced Peripheral Neuropathy in Patients With Cancer? A Systematic Review and Meta-analysis. Arch Phys Med Rehabil, 103:2197-2208.

[445] Mizrahi D, Lai JKL, Wareing H, Ren Y, Li T, Swain CTV, et al. (2024). Effect of exercise interventions on hospital length of stay and admissions during cancer treatment: a systematic review and meta-analysis. Br J Sports Med, 58:97-109.

[446] Brown JC, Brighton E, Campbell N, McCleary NJ, Abrams TA, Cleary JM, et al. (2022). Physical activity in older adults with metastatic gastrointestinal cancer: a pilot and feasibility study. BMJ Open Sport Exerc Med, 8:e001353.

[447] Thomsen SN, Lahart IM, Thomsen LM, Fridh MK, Larsen A, Mau-Sorensen M, et al. (2023). Harms of exercise training in patients with cancer undergoing systemic treatment: a systematic review and meta-analysis of published and unpublished controlled trials. EClinicalMedicine, 59:101937.

[448] Tiffon C (2018). The Impact of Nutrition and Environmental Epigenetics on Human Health and Disease. Int J Mol Sci, 19.

[449] Blasiak J, Chojnacki J, Pawlowska E, Szczepanska J, Chojnacki C (2020). Nutrition in Cancer Therapy in the Elderly-An Epigenetic Connection? Nutrients, 12.

[450] Presley CJ, Dotan E, Soto-Perez-de-Celis E, Jatoi A, Mohile SG, Won E, et al. (2016). Gaps in nutritional research among older adults with cancer. J Geriatr Oncol, 7:281-292.

[451] Manson JE, Aragaki AK, Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, et al. (2017). Menopausal Hormone Therapy and Long-term All-Cause and Cause-Specific Mortality: The Women's Health Initiative Randomized Trials. JAMA, 318:927-938.

[452] Manson JE, Bassuk SS, Kaunitz AM, Pinkerton JV (2020). The Women's Health Initiative trials of menopausal hormone therapy: lessons learned. Menopause, 27:918-928.

[453] Pan K, Aragaki AK, Neuhouser ML, Simon MS, Luo J, Caan B, et al. (2019). Low-fat dietary pattern and breast cancer mortality by metabolic syndrome degree: Secondary analyses of the Women's Health Initiative (WHI) Dietary Modification randomized trial. 37:1539-1539.

[454] Wooten SV, Wolf JS, Jr., Mendoza D, Bartholomew JB, Stanforth PR, Stanforth D, et al. (2022). The Impact of a Multimodal Sport Science-Based Prehabilitation Program on Clinical Outcomes in Abdominal Cancer Patients: A Cohort Study. Am Surg, 88:2302-2308.

[455] Klepin HD, Tooze JA, Bitting RL, Davis B, Pleasant K, Melo AC, et al. (2023). Study design and methods for the pilot study of muscadine grape extract supplement to improve fatigue among older adult cancer survivors (FOCUS) trial. J Geriatr Oncol, 14:101478.

[456] Klepin HD, Tooze JA, Davis B, Velasquez De Kamm M, Melo AM, Bitting RL, et al. (2025). Pilot study of a muscadine grape extract supplement to decrease fatigue among older cancer survivors. 43:12057-12057.

[457] Available at https://clinicaltrials.gov/search?cond=Cancer&term=aging&intr=Dietary%20supplement&aggFilters=ages:older. Accessed on july 2, 2025.

[458] Vettori JC, da-Silva LG, Pfrimer K, Jordao AA, Louzada-Junior P, Moriguti JC, et al. (2022). Effect of chocolate on older patients with cancer in palliative care: a randomised controlled study. BMC Palliat Care, 21:5.

[459] Prentice RL, Caan B, Chlebowski RT, Patterson R, Kuller LH, Ockene JK, et al. (2006). Low-fat dietary pattern and risk of invasive breast cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. JAMA, 295:629-642.

[460] Chlebowski RT, Aragaki AK, Anderson GL, Thomson CA, Manson JE, Simon MS, et al. (2017). Low-Fat Dietary Pattern and Breast Cancer Mortality in the Women's Health Initiative Randomized Controlled Trial. J Clin Oncol, 35:2919-2926.

[461] Balasubramanian P, Howell PR, Anderson RM (2017). Aging and Caloric Restriction Research: A Biological Perspective With Translational Potential. EBioMedicine, 21:37-44.

[462] Waziry R, Ryan CP, Corcoran DL, Huffman KM, Kobor MS, Kothari M, et al. (2023). Effect of long-term caloric restriction on DNA methylation measures of biological aging in healthy adults from the CALERIE trial. Nat Aging, 3:248-257.

[463] Pomatto-Watson LCD, Bodogai M, Bosompra O, Kato J, Wong S, Carpenter M, et al. (2021). Daily caloric restriction limits tumor growth more effectively than caloric cycling regardless of dietary composition. Nat Commun, 12:6201.

[464] Caffa I, Spagnolo V, Vernieri C, Valdemarin F, Becherini P, Wei M, et al. (2020). Fasting-mimicking diet and hormone therapy induce breast cancer regression. Nature, 583:620-624.

[465] de Groot S, Pijl H, van der Hoeven JJM, Kroep JR (2019). Effects of short-term fasting on cancer treatment. J Exp Clin Cancer Res, 38:209.

[466] Longo VD, Anderson RM (2022). Nutrition, longevity and disease: From molecular mechanisms to interventions. Cell, 185:1455-1470.

[467] Nencioni A, Caffa I, Cortellino S, Longo VD (2018). Fasting and cancer: molecular mechanisms and clinical application. Nat Rev Cancer, 18:707-719.
[468] Castellano I, Gallo F, Durelli P, Monge T, Fadda M, Metovic J, et al. (2023). Impact of Caloric Restriction in Breast Cancer Patients Treated with Neoadjuvant Chemotherapy: A Prospective Case Control Study. Nutrients, 15.
[469] Pifferi F, Aujard F (2019). Caloric restriction, longevity and aging: Recent contributions from human and non-human primate studies. Prog Neuropsychopharmacol Biol Psychiatry, 95:109702.
[470] Rothschild J, Hoddy KK, Jambazian P, Varady KA (2014). Time-restricted feeding and risk of metabolic disease: a review of human and animal studies. Nutr Rev, 72:308-318.
[471] Patterson RE, Sears DD (2017). Metabolic Effects of Intermittent Fasting. Annu Rev Nutr, 37:371-393.
[472] Johnstone A (2015). Fasting for weight loss: an effective strategy or latest dieting trend? Int J Obes (Lond), 39:727-733.
[473] Regmi P, Heilbronn LK (2020). Time-Restricted Eating: Benefits, Mechanisms, and Challenges in Translation. iScience, 23:101161.
[474] O'Connor SG, Boyd P, Bailey CP, Shams-White MM, Agurs-Collins T, Hall K, et al. (2021). Perspective: Time-Restricted Eating Compared with Caloric Restriction: Potential Facilitators and Barriers of Long-Term Weight Loss Maintenance. Adv Nutr, 12:325-333.
[475] Anton SD, Lee SA, Donahoo WT, McLaren C, Manini T, Leeuwenburgh C, et al. (2019). The Effects of Time Restricted Feeding on Overweight, Older Adults: A Pilot Study. Nutrients, 11.
[476] Martens CR, Rossman MJ, Mazzo MR, Jankowski LR, Nagy EE, Denman BA, et al. (2020). Short-term time-restricted feeding is safe and feasible in non-obese healthy midlife and older adults. Geroscience, 42:667-686.
[477] Stringer EJ, Cloke RWG, Van der Meer L, Murphy RA, Macpherson NA, Lum JJ (2024). The Clinical Impact of Time-restricted Eating on Cancer: A Systematic Review. Nutr Rev.
[478] Zhang Z, Zhao H, Tao Z, Jiang M, Pu J (2024). A National Study Exploring the Association between Fasting Duration and Mortality among the Elderly. Nutrients, 16.
[479] Ezzati A, Tamargo JA, Golberg L, Haub MD, Anton SD (2025). The Effects of Time-Restricted Eating on Inflammation and Oxidative Stress in Overweight Older Adults: A Pilot Study. Nutrients, 17.
[480] Czerwinska-Ledwig O, Nowak-Zaleska A, Zychowska M, Meyza K, Palka T, Dzidek A, et al. (2024). The Positive Effects of Training and Time-Restricted Eating in Gut Microbiota Biodiversity in Patients with Multiple Myeloma. Nutrients, 17.
[481] Madeo F, Carmona-Gutierrez D, Hofer SJ, Kroemer G (2019). Caloric Restriction Mimetics against Age-Associated Disease: Targets, Mechanisms, and Therapeutic Potential. Cell Metab, 29:592-610.
[482] Hofer SJ, Davinelli S, Bergmann M, Scapagnini G, Madeo F (2021). Caloric Restriction Mimetics in Nutrition and Clinical Trials. Front Nutr, 8:717343.
[483] Jafari M, Macho-Gonzalez A, Diaz A, Lindenau K, Santiago-Fernandez O, Zeng M, et al. (2024). Calorie restriction and calorie-restriction mimetics activate chaperone-mediated autophagy. Proc Natl Acad Sci U S A, 121:e2317945121.
[484] Eriau E, Paillet J, Kroemer G, Pol JG (2021). Metabolic Reprogramming by Reduced Calorie Intake or Pharmacological Caloric Restriction Mimetics for Improved Cancer Immunotherapy. Cancers (Basel), 13.
[485] Bouamar H, Broome LE, Lathrop KI, Jatoi I, Brenner AJ, Nazarullah A, et al. (2023). mTOR inhibition abrogates human mammary stem cells and early breast cancer progression markers. Breast Cancer Res, 25:131.
[486] Luis C, Maduro AT, Pereira P, Mendes JJ, Soares R, Ramalho R (2022). Nutritional senolytics and senomorphics: Implications to immune cells metabolism and aging - from theory to practice. Front Nutr, 9:958563.
[487] Partridge L, Fuentealba M, Kennedy BK (2020). The quest to slow ageing through drug discovery. Nat Rev Drug Discov, 19:513-532.
[488] Zhang L, Pitcher LE, Prahalad V, Niedernhofer LJ, Robbins PD (2023). Targeting cellular senescence with senotherapeutics: senolytics and senomorphics. FEBS J, 290:1362-1383.
[489] Baker DJ, Wijshake T, Tchkonia T, LeBrasseur NK, Childs BG, van de Sluis B, et al. (2011). Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders. Nature, 479:232-236.
[490] Childs BG, Durik M, Baker DJ, van Deursen JM (2015). Cellular senescence in aging and age-related disease: from mechanisms to therapy. Nat Med, 21:1424-1435.
[491] Wang C, Hao X, Zhang R (2022). Targeting cellular senescence to combat cancer and ageing. Mol Oncol, 16:3319-3332.
[492] Schmitt CA, Wang B, Demaria M (2022). Senescence and cancer - role and therapeutic opportunities. Nat Rev Clin Oncol, 19:619-636.
[493] Collado M, Serrano M (2010). Senescence in tumours: evidence from mice and humans. Nat Rev Cancer, 10:51-57.
[494] Amor C, Feucht J, Leibold J, Ho YJ, Zhu C, Alonso-Curbelo D, et al. (2020). Senolytic CAR T cells reverse senescence-associated pathologies. Nature, 583:127-132.
[495] Zhu Y, Tchkonia T, Pirtskhalava T, Gower AC, Ding H, Giorgadze N, et al. (2015). The Achilles' heel of senescent cells: from transcriptome to senolytic drugs. Aging Cell, 14:644-658.
[496] Lelarge V, Capelle R, Oger F, Mathieu T, Le Calve B (2024). Senolytics: from pharmacological inhibitors to immunotherapies, a promising future for patients' treatment. NPJ Aging, 10:12.
[497] Chaib S, Tchkonia T, Kirkland JL (2022). Cellular senescence and senolytics: the path to the clinic. Nat

Med, 28:1556-1568.
[498] Kang C (2019). Senolytics and Senostatics: A Two-Pronged Approach to Target Cellular Senescence for Delaying Aging and Age-Related Diseases. Mol Cells, 42:821-827.
[499] Suda M, Paul KH, Tripathi U, Minamino T, Tchkonia T, Kirkland JL (2024). Targeting Cell Senescence and Senolytics: Novel Interventions for Age-Related Endocrine Dysfunction. Endocr Rev, 45:655-675.
[500] Short S, Fielder E, Miwa S, von Zglinicki T (2019). Senolytics and senostatics as adjuvant tumour therapy. EBioMedicine, 41:683-692.
[501] Fielder E, Wan T, Alimohammadiha G, Ishaq A, Low E, Weigand BM, et al. (2022). Short senolytic or senostatic interventions rescue progression of radiation-induced frailty and premature ageing in mice. Elife, 11.
[502] Bitting RL, Tooze JA, Isom S, Petty WJ, Grant SC, Desnoyers RJ, et al. (2021). Phase I Study of Muscadine Grape Extract for Patients With Advanced Cancer. Am J Clin Oncol, 44:239-246.
[503] Bischoff-Ferrari HA, Freystatter G, Vellas B, Dawson-Hughes B, Kressig RW, Kanis JA, et al. (2022). Effects of vitamin D, omega-3 fatty acids, and a simple home strength exercise program on fall prevention: the DO-HEALTH randomized clinical trial. Am J Clin Nutr, 115:1311-1321.
[504] Bischoff-Ferrari HA, Vellas B, Rizzoli R, Kressig RW, da Silva JAP, Blauth M, et al. (2020). Effect of Vitamin D Supplementation, Omega-3 Fatty Acid Supplementation, or a Strength-Training Exercise Program on Clinical Outcomes in Older Adults: The DO-HEALTH Randomized Clinical Trial. JAMA, 324:1855-1868.
[505] Gagesch M, Wieczorek M, Vellas B, Kressig RW, Rizzoli R, Kanis J, et al. (2023). Effects of Vitamin D, Omega-3 Fatty Acids and a Home Exercise Program on Prevention of Pre-Frailty in Older Adults: The DO-HEALTH Randomized Clinical Trial. J Frailty Aging, 12:71-77.
[506] Bischoff-Ferrari HA, Gangler S, Wieczorek M, Belsky DW, Ryan J, Kressig RW, et al. (2025). Individual and additive effects of vitamin D, omega-3 and exercise on DNA methylation clocks of biological aging in older adults from the DO-HEALTH trial. Nat Aging, 5:376-385.
[507] Sierra F (2016). The Emergence of Geroscience as an Interdisciplinary Approach to the Enhancement of Health Span and Life Span. Cold Spring Harb Perspect Med, 6:a025163.
[508] Liu N, Wu J, Deng E, Zhong J, Wei B, Cai T, et al. 2024. Reversing Immunosenescence with Senolytics to Enhance Tumor Immunotherapy.
[509] De-Leon-Covarrubias UE, Perez-Trujillo JJ, Villa-Cedillo SA, Martinez-Perez AG, Montes-de-Oca-Saucedo CR, Loera-Arias MJ, et al. (2024). Unlocking the Potential: Caloric Restriction, Caloric Restriction Mimetics, and Their Impact on Cancer Prevention and Treatment. Metabolites, 14.
[510] Acosta-Rodriguez VA, Rijo-Ferreira F, Green CB, Takahashi JS (2021). Importance of circadian timing for aging and longevity. Nat Commun, 12:2862.
[511] Ruben MD, Wu G, Smith DF, Schmidt RE, Francey LJ, Lee YY, et al. (2018). A database of tissue-specific rhythmically expressed human genes has potential applications in circadian medicine. Sci Transl Med, 10.
[512] Sulli G, Manoogian ENC, Taub PR, Panda S (2018). Training the Circadian Clock, Clocking the Drugs, and Drugging the Clock to Prevent, Manage, and Treat Chronic Diseases. Trends Pharmacol Sci, 39:812-827.
[513] Available at https://clinicaltrials.gov/search?cond=Cancer&term=chronotherapy. Accessed on July 2, 2025.
[514] Available at https://clinicaltrials.gov/search?cond=Cancer&term=Circadian%20Dysregulation. Accessed on July 2, 2025.
[515] Available at https://clinicaltrials.gov/search?cond=Cancer&term=circadian%20genes%20dysregulation. Accessed on July 2, 2025.
[516] Available at https://clinicaltrials.gov/search?cond=Aging&term=circadian%20dysregulation. Accessed on July 2, 2025.
[517] Damato AR, Katumba RGN, Luo J, Atluri H, Talcott GR, Govindan A, et al. (2022). A randomized feasibility study evaluating temozolomide circadian medicine in patients with glioma. Neurooncol Pract, 9:193-200.
[518] Savard MF, Ibrahim M, Saunders D, Pond GR, Ng TL, Awan AA, et al. (2025). A pragmatic, multicenter, randomized trial comparing morning versus evening dosing of adjuvant endocrine therapy (REaCT-CHRONO Study). NPJ Breast Cancer, 11:49.
[519] Levi FA, Boige V, Hebbar M, Smith D, Lepere C, Focan C, et al. (2016). Conversion to resection of liver metastases from colorectal cancer with hepatic artery infusion of combined chemotherapy and systemic cetuximab in multicenter trial OPTILIV. Ann Oncol, 27:267-274.
[520] Karaboué A, Collon T, Pavese I, Bodiguel V, Cucherousset J, Zakine E, et al. (2022). Time-Dependent Efficacy of Checkpoint Inhibitor Nivolumab: Results from a Pilot Study in Patients with Metastatic Non-Small-Cell Lung Cancer. Cancers (Basel), 14.
[521] Qian DC, Kleber T, Brammer B, Xu KM, Switchenko JM, Janopaul-Naylor JR, et al. (2021). Effect of immunotherapy time-of-day infusion on overall survival among patients with advanced melanoma in the USA (MEMOIR): a propensity score-matched analysis of a single-centre, longitudinal study. The Lancet Oncology, 22:1777-1786.
[522] Bermudez-Guzman L, Blanco-Saborio A, Ramirez-Zamora J, Lovo E (2021). The Time for Chronotherapy in Radiation Oncology. Front Oncol, 11:687672.
[523] Bjarnason GA, Mackenzie RG, Nabid A, Hodson ID, El-Sayed S, Grimard L, et al. (2009). Comparison of toxicity associated with early morning versus late

afternoon radiotherapy in patients with head-and-neck cancer: a prospective randomized trial of the National Cancer Institute of Canada Clinical Trials Group (HN3). Int J Radiat Oncol Biol Phys, 73:166-172.

[524] Goyal M, Shukla P, Gupta D, Bisht SS, Dhawan A, Gupta S, et al. (2009). Oral mucositis in morning vs. evening irradiated patients: a randomised prospective study. Int J Radiat Biol, 85:504-509.

[525] Shukla P, Gupta D, Bisht SS, Pant MC, Bhatt ML, Gupta R, et al. (2010). Circadian variation in radiation-induced intestinal mucositis in patients with cervical carcinoma. Cancer, 116:2031-2035.

[526] Altucci L, Rots MG (2016). Epigenetic drugs: from chemistry via biology to medicine and back. Clin Epigenetics, 8:56.

[527] Miranda Furtado CL, Dos Santos Luciano MC, Silva Santos RD, Furtado GP, Moraes MO, Pessoa C (2019). Epidrugs: targeting epigenetic marks in cancer treatment. Epigenetics, 14:1164-1176.

[528] Farani MR, Sarlak M, Gholami A, Azaraian M, Binabaj MM, Kakavandi S, et al. (2023). Epigenetic drugs as new emerging therapeutics: What is the scale's orientation of application and challenges? Pathol Res Pract, 248:154688.

[529] Guo R, Li J, Hu J, Fu Q, Yan Y, Xu S, et al. (2023). Combination of epidrugs with immune checkpoint inhibitors in cancer immunotherapy: From theory to therapy. Int Immunopharmacol, 120:110417.

[530] Sharma S, Bhonde R (2023). Epigenetic Modifiers as Game Changers for Healthy Aging. Rejuvenation Res, 26:88-104.

[531] Available at https://clinicaltrials.gov/search?cond=Cancer&term=epigenetic%20drugs. Accessed on July 2, 2025.

[532] Mondal P, Natesh J, Penta D, Meeran SM (2022). Progress and promises of epigenetic drugs and epigenetic diets in cancer prevention and therapy: A clinical update. Semin Cancer Biol, 83:503-522.

[533] Suraweera A, O'Byrne KJ, Richard DJ (2025). Epigenetic drugs in cancer therapy. Cancer Metastasis Rev, 44:37.

[534] Moreno V, Vieito M, Sepulveda JM, Galvao V, Hernandez-Guerrero T, Doger B, et al. (2023). BET inhibitor trotabresib in heavily pretreated patients with solid tumors and diffuse large B-cell lymphomas. Nat Commun, 14:1359.

[535] Candelaria M, Gallardo-Rincon D, Arce C, Cetina L, Aguilar-Ponce JL, Arrieta O, et al. (2007). A phase II study of epigenetic therapy with hydralazine and magnesium valproate to overcome chemotherapy resistance in refractory solid tumors. Ann Oncol, 18:1529-1538.

[536] Coronel J, Cetina L, Pacheco I, Trejo-Becerril C, González-Fierro A, de la Cruz-Hernandez E, et al. (2011). A double-blind, placebo-controlled, randomized phase III trial of chemotherapy plus epigenetic therapy with hydralazine valproate for advanced cervical cancer. Preliminary results. Medical Oncology, 28:540-546.

[537] Lübbert M, Schmoor C, Berg T, Kruszewski M, Schittenhelm MM, Götze K, et al. (2022). Phase I Study of the LSD1 Inhibitor Tranylcypromine (TCP) in Combination with All-Trans Retinoic Acid (ATRA) and Low-Dose Cytarabine (LDAC) in Elderly, Medically Non-Fit Patients with AML or High-Risk MDS (TRANSATRA trial). Blood, 140:9087-9088.

[538] Im A, Quann K, Agha M, Raptis A, Redner RL, Hou JZ, et al. (2024). Phase 2 study of epigenetic priming with decitabine followed by cytarabine for acute myeloid leukemia in older patients. Am J Hematol, 99:380-386.

[539] Alalhareth IS, Alyami SM, Alshareef AH, Ajeibi AO, Al Munjem MF, Elfifi AA, et al. (2025). Cellular Epigenetic Targets and Epidrugs in Breast Cancer Therapy: Mechanisms, Challenges, and Future Perspectives. Pharmaceuticals (Basel), 18.

[540] Terranova-Barberio M, Pawlowska N, Dhawan M, Moasser M, Chien AJ, Melisko ME, et al. (2020). Exhausted T cell signature predicts immunotherapy response in ER-positive breast cancer. Nat Commun, 11:3584.

[541] Joerger M, Diem S, Wyss N, Koster KL, Besse L, Hess D, et al. (2025). Open-label nonrandomized phase IB study to characterize the safety and recommended dose of tinostamustine in combination with nivolumab in patients with advanced melanoma (ENIgMA). Melanoma Res, 35:252-258.

[542] Feng K, Liu Y, Wang C, Nie J, Xia Y, Jiang J, et al. (2023). Phase I study of the bifunctional anti-PD-L1/TGF-βRII agent SHR-1701 combined with SHR2554, an EZH2 inhibitor, in patients with previously treated advanced lymphoma and solid tumors. J Clin Oncol., 41:2507-2507.

[543] Song Y, Jin Z, Li Z-M, Liu Y, Li L, He C, et al. (2024). Enhancer of Zeste Homolog 2 Inhibitor SHR2554 in Relapsed or Refractory Peripheral T-cell Lymphoma: Data from the First-in-Human Phase I Study. Clinical Cancer Research, 30:1248-1255.

[544] Troyer J, Tanco K (2024). Review of the Use of Medicinal Cannabis Products in Palliative Care. Cancers (Basel), 16.

[545] Available at https://clinicaltrials.gov/search?cond=Cancer&term=cannabinoids. Accessed on July 2, 2025.

[546] Available at https://clinicaltrials.gov/search?cond=Aging&term=cannabinoids. Accessed on July 2, 2025.

[547] Myint ZW, St Clair WH, Strup SE, Yan D, Li N, Allison DB, et al. (2023). A Phase I Dose Escalation and Expansion Study of Epidiolex (Cannabidiol) in Patients with Biochemically Recurrent Prostate Cancer. Cancers (Basel), 15.

[548] Twelves C, Sabel M, Checketts D, Miller S, Tayo B, Jove M, et al. (2021). A phase 1b randomised, placebo-controlled trial of nabiximols cannabinoid oromucosal spray with temozolomide in patients with recurrent glioblastoma. Br J Cancer, 124:1379-1387.

[549] Ramer R, Hinz B (2025). Effect of cannabinoids on the efficacy and side effects of anticancer therapeutic strategies - Current status of preclinical and clinical

research. Pharmacol Ther, 270:108851.
[550] Bouchahda M, Ulusakarya A, Thirot-Bidault A, Attari A, Bossevot R, Tuligenga R, et al. (2023). Multicentre, interventional, single-arm study protocol of telemonitored circadian rhythms and patient-reported outcomes for improving mFOLFIRINOX safety in patients with pancreatic cancer (MultiDom, NCT04263948). BMJ Open, 13:e069973.
[551] Nouriani B, Zeitzer JM, Palesh OG, Koopman C, Aldridge-Gerry A, Neri E, et al. (2023). Assessment of sleep and circadian rhythms of endocrine and immune function among women With advanced breast cancer. 4:71-85.
[552] Walton RG, Dungan CM, Long DE, Tuggle SC, Kosmac K, Peck BD, et al. (2019). Metformin blunts muscle hypertrophy in response to progressive resistance exercise training in older adults: A randomized, double-blind, placebo-controlled, multicenter trial: The MASTERS trial. Aging Cell, 18:e13039.
[553] Reitz KM, Seymour CW, Vates J, Quintana M, Viele K, Detry M, et al. (2020). Strategies to Promote ResiliencY (SPRY): a randomised embedded multifactorial adaptative platform (REMAP) clinical trial protocol to study interventions to improve recovery after surgery in high-risk patients. BMJ Open, 10:e037690.
[554] Siddiqa A, Wang Y, Thapa M, Martin DE, Cadar AN, Bartley JM, et al. (2023). A pilot metabolomic study of drug interaction with the immune response to seasonal influenza vaccination. NPJ Vaccines, 8:92.
[555] de Kreutzenberg SV, Ceolotto G, Cattelan A, Pagnin E, Mazzucato M, Garagnani P, et al. (2015). Metformin improves putative longevity effectors in peripheral mononuclear cells from subjects with prediabetes. A randomized controlled trial. Nutr Metab Cardiovasc Dis, 25:686-693.
[556] Kumari S, Bubak MT, Schoenberg HM, Davidyan A, Elliehausen CJ, Kuhn KG, et al. (2022). Antecedent Metabolic Health and Metformin (ANTHEM) Aging Study: Rationale and Study Design for a Randomized Controlled Trial. J Gerontol A Biol Sci Med Sci, 77:2373-2377.
[557] McKenzie AI, Mahmassani ZS, Petrocelli JJ, de Hart N, Fix DK, Ferrara PJ, et al. (2022). Short-term exposure to a clinical dose of metformin increases skeletal muscle mitochondrial H(2)O(2) emission and production in healthy, older adults: A randomized controlled trial. Exp Gerontol, 163:111804.
[558] Petrocelli JJ, McKenzie AI, de Hart N, Reidy PT, Mahmassani ZS, Keeble AR, et al. (2023). Disuse-induced muscle fibrosis, cellular senescence, and senescence-associated secretory phenotype in older adults are alleviated during re-ambulation with metformin pre-treatment. Aging Cell, 22:e13936.
[559] Heisey HD, Kunik ME, Qualls C, Segoviano-Escobar MB, Villareal DT (2022). Truncal Fat and Frailty Are Important Predictors of Cognitive Performance among Aging Adults with Obesity. J Nutr Health Aging, 26:425-429.
[560] Valerie Sia JE, Lai X, Mak WY, Wu X, Zhang F, Cui C, et al. (2024). Aging-Related CYP3A Functional Changes in Chinese Older Patients: New Findings from Model-Based Assessment of Amlodipine. Clin Pharmacol Ther, 116:858-865.
[561] Kraig E, Linehan LA, Liang H, Romo TQ, Liu Q, Wu Y, et al. (2018). A randomized control trial to establish the feasibility and safety of rapamycin treatment in an older human cohort: Immunological, physical performance, and cognitive effects. Exp Gerontol, 105:53-69.
[562] Moel M, Harinath G, Lee V, Nyquist A, Morgan SL, Isman A, et al. (2025). Influence of rapamycin on safety and healthspan metrics after one year: PEARL trial results. Aging (Albany NY), 17.
[563] Singh M, Jensen MD, Lerman A, Kushwaha S, Rihal CS, Gersh BJ, et al. (2016). Effect of Low-Dose Rapamycin on Senescence Markers and Physical Functioning in Older Adults with Coronary Artery Disease: Results of a Pilot Study. J Frailty Aging, 5:204-207.
[564] Dickinson JM, Drummond MJ, Fry CS, Gundermann DM, Walker DK, Timmerman KL, et al. (2013). Rapamycin does not affect post-absorptive protein metabolism in human skeletal muscle. Metabolism, 62:144-151.
[565] Layne AS, Krehbiel LM, Mankowski RT, Anton SD, Leeuwenburgh C, Pahor M, et al. (2017). Resveratrol and exercise to treat functional limitations in late life: design of a randomized controlled trial. Contemp Clin Trials Commun, 6:58-63.
[566] Pastor RF, Iermoli RH, Saporito-Magriña CM, Pastor I, Pastor E, Manfredi Carabetti Z, et al. (2024). Reversal of epigenetic age and body composition improvement in consumers of resveratrol-enriched wine. 9:159-168.
[567] Muscari A, Forti P, Brizi M, Magalotti D, Capelli E, Poti S, et al. (2023). Can We Slow Down Biological Age Progression? Study Protocol for the proBNPage Reduction (PBAR) Randomized, Double-Blind, Placebo-Controlled Trial (Effects of 4 "Anti-Aging" Food Supplements in Healthy Older Adults). Clin Interv Aging, 18:1813-1825.
[568] Yoshino J, Conte C, Fontana L, Mittendorfer B, Imai S, Schechtman KB, et al. (2012). Resveratrol supplementation does not improve metabolic function in nonobese women with normal glucose tolerance. Cell Metab, 16:658-664.
[569] Anton SD, Embry C, Marsiske M, Lu X, Doss H, Leeuwenburgh C, et al. (2014). Safety and metabolic outcomes of resveratrol supplementation in older adults: results of a twelve-week, placebo-controlled pilot study. Exp Gerontol, 57:181-187.
[570] Kulzow N, Witte AV, Kerti L, Grittner U, Schuchardt JP, Hahn A, et al. (2016). Impact of Omega-3 Fatty Acid Supplementation on Memory Functions in Healthy Older Adults. J Alzheimers Dis, 51:713-725.
[571] Xue M, Weickert MO, Qureshi S, Kandala NB, Anwar A, Waldron M, et al. (2016). Improved Glycemic Control and Vascular Function in Overweight and

Obese Subjects by Glyoxalase 1 Inducer Formulation. Diabetes, 65:2282-2294.

[572] Moran C, Scotto di Palumbo A, Bramham J, Moran A, Rooney B, De Vito G, et al. (2018). Effects of a Six-Month Multi-Ingredient Nutrition Supplement Intervention of Omega-3 Polyunsaturated Fatty Acids, vitamin D, Resveratrol, and Whey Protein on Cognitive Function in Older Adults: A Randomised, Double-Blind, Controlled Trial. J Prev Alzheimers Dis, 5:175-183.

[573] Kooshyar MM, Mozafari PM, Amirchaghmaghi M, Pakfetrat A, Karoos P, Mohasel MR, et al. (2017). A Randomized Placebo- Controlled Double Blind Clinical Trial of Quercetin in the Prevention and Treatment of Chemotherapy-Induced Oral Mucositis. J Clin Diagn Res, 11:ZC46-ZC50.

[574] Henning SM, Wang P, Lee RP, Trang A, Husari G, Yang J, et al. (2020). Prospective randomized trial evaluating blood and prostate tissue concentrations of green tea polyphenols and quercetin in men with prostate cancer. Food Funct, 11:4114-4122.

[575] Zwicker JI, Schlechter BL, Stopa JD, Liebman HA, Aggarwal A, Puligandla M, et al. (2019). Targeting protein disulfide isomerase with the flavonoid isoquercetin to improve hypercoagulability in advanced cancer. JCI Insight, 4.

[576] Redorta JP, Sanguedolce F, Pardo GS, Romancik M, Vittori G, Minervini A, et al. (2021). Multicentre International Study for the Prevention with iAluRil of Radio-induced Cystitis (MISTIC): A Randomised Controlled Study. Eur Urol Open Sci, 26:45-54.

[577] Ji J, Bae M, Wong FL, Crespi CM, Yee LD, Sedrak MS (2024). A phase II randomized double-blind placebo-controlled study of fisetin to improve physical function in frail older breast cancer survivors (TROFFi). J. Clin. Oncol., 42:TPS1645-TPS1645.

[578] Ji J, Lipsyc-Sharf M, Zektser Y, Ness KK, Abdou Y, Manohar P, et al. (2025). A phase II randomized placebo-controlled study of fisetin and exercise to mitigate chemotherapy-related functional decline in postmenopausal women with early breast cancer (PROFFi). J Clin Oncol, 43:TPS12148-TPS12148.

[579] Lee E, Carreras-Gallo N, Lopez L, Turner L, Lin A, Mendez TL, et al. (2024). Exploring the effects of Dasatinib, Quercetin, and Fisetin on DNA methylation clocks: a longitudinal study on senolytic interventions. Aging (Albany NY), 16:3088-3106.

[580] Millar CL, Iloputaife I, Baldyga K, Kuo J, Tchkonia T, Kirkland JL, et al. (2023). Rationale and Design of STAMINA: Senolytics To Alleviate Mobility Issues and Neurological Impairments in Aging, A Geroscience Feasibility Study. Transl Med Aging, 7:109-117.

[581] Millar CL, Iloputaife I, Baldyga K, Norling AM, Boulougoura A, Vichos T, et al. (2025). A pilot study of senolytics to improve cognition and mobility in older adults at risk for Alzheimer’s disease. eBioMedicine, 113.

[582] Schweiger A, Diniz B, Nicol G, Schweiger J, Dasklakis-Perez AE, Lenze EJ (2024). Protocol for a pilot clinical trial of the senolytic drug combination Dasatinib Plus Quercetin to mitigate age-related health and cognitive decline in mental disorders. F1000Res, 13:1072.

[583] Murphy R, Chander G, Martinez M, Ward C, Khan SR, Naik M, et al. (2023). Study protocol of LANTana: a phase Ib study to investigate epigenetic modification of somatostatin receptor-2 with ASTX727 to improve therapeutic outcome with [177Lu]Lu-DOTA-TATE in patients with metastatic neuroendocrine tumours, UK. BMJ Open, 13:e075221.

[584] O'Sullivan Coyne G, Chen AP, Kummar S, Meehan RS, Collins J, Zlott J, et al. (2016). 269 - Phase I trial of oral 5-fluoro-2′-deoxycytidine with oral tetrahydrouridine in patients with advanced solid tumors. European Journal of Cancer, 69:S90.

[585] Moreno V, Sepulveda JM, Vieito M, Hernandez-Guerrero T, Doger B, Saavedra O, et al. (2020). Phase I study of CC-90010, a reversible, oral BET inhibitor in patients with advanced solid tumors and relapsed/refractory non-Hodgkin's lymphoma. Ann Oncol, 31:780-788.

[586] Siveke JT, Sinn M, Dorman K, Siegler GM, Seufferlein T, Trojan J, et al. (2024). 1525P Nab-paclitaxel/gemcitabine with or without epigenetic targeting followed by consolidating immune targeting with durvalumab and lenalidomide in patients with advanced pancreatic ductal adenocarcinoma: Results from the SEPION/AIO-PAK-0118 phase I/II study. Annals of Oncology, 35:S931.

[587] Frenel JS, Cartron PF, Gourmelon C, Campion L, Aumont M, Augereau P, et al. (2020). 370MO FOLAGLI: A phase I study of folinic acid combined with temozolomide and radiotherapy to modulate MGMT gene promoter methylation in newly diagnosed MGMT non-methytated glioblastoma. Annals of Oncology, 31:S400.

[588] Campone M, Gianni L, Cortes J, Beck T, Miller J, Chen P, et al. (2016). Phase II trial of CC-486, a DNA methyltransferase inhibitor, in combination with fulvestrant in postmenopausal women with ER+, HER2- metastatic breast cancer who have progressed on an aromatase inhibitor (AI). J Clin Oncol., 34:TPS616-TPS616.

[589] Zhu X-Z, Jin X, Zhang H-Y-L, Liu X, Zhou Y-F, Chen Y-Y, et al. (2024). Abstract PO1-15-07: Subtyping-directed precision treatment refines traditional one-size-fits-all therapy in HR+/HER2- breast cancer: a sub-study of the MULAN umbrella trial. Cancer Research, 84:PO1-15-07-PO11-15-07.

[590] Arce C, Perez-Plasencia C, Gonzalez-Fierro A, de la Cruz-Hernandez E, Revilla-Vazquez A, Chavez-Blanco A, et al. (2006). A proof-of-principle study of epigenetic therapy added to neoadjuvant doxorubicin cyclophosphamide for locally advanced breast cancer. PLoS One, 1:e98.

[591] Hawkes EA, Phillips T, Budde LE, Santoro A, Saba NS, Roncolato F, et al. (2021). Avelumab in Combination Regimens for Relapsed/Refractory DLBCL: Results from the Phase Ib JAVELIN DLBCL

Study. Target Oncol, 16:761-771.

[592] Levy BP, Giaccone G, Besse B, Felip E, Garassino MC, Domine Gomez M, et al. (2019). Randomised phase 2 study of pembrolizumab plus CC-486 versus pembrolizumab plus placebo in patients with previously treated advanced non-small cell lung cancer. Eur J Cancer, 108:120-128.

[593] Halpern AB, Buckley SA, Othus M, Huebner EM, Orlowski KF, Scott BL, et al. (2016). Mitoxantrone, Etoposide, and Cytarabine (MEC) Following Epigenetic Priming with Decitabine in Adults with Relapsed/Refractory Acute Myeloid Leukemia (AML) or High-Risk Myelodysplastic Syndrome (MDS): Final Results from a Phase 1/2 Study. Blood, 128:1064.

[594] Nguyen J, O'Sullivan Coyne GH, Takebe N, Naqash AR, Mukherjee J, Bruns A, et al. (2021). Phase I trial of 5-aza-4'-thio-2'-deoxycytidine (Aza-TdC) in patients with advanced solid tumors. J Clin Oncol., 39:3088-3088.

[595] Luke JJ, Fakih M, Schneider C, Chiorean EG, Bendell J, Kristeleit R, et al. (2023). Phase I/II sequencing study of azacitidine, epacadostat, and pembrolizumab in advanced solid tumors. Br J Cancer, 128:2227-2235.

[596] Xia C, Leon-Ferre R, Laux D, Deutsch J, Smith BJ, Frees M, et al. (2014). Treatment of resistant metastatic melanoma using sequential epigenetic therapy (decitabine and panobinostat) combined with chemotherapy (temozolomide). Cancer Chemother Pharmacol, 74:691-697.

[597] Skorupan N, Ahmad MI, Steinberg SM, Trepel JB, Cridebring D, Han H, et al. (2022). A phase II trial of the super-enhancer inhibitor Minnelide in advanced refractory adenosquamous carcinoma of the pancreas. Future Oncol, 18:2475-2481.

[598] Zhang Z, Garzotto M, Davis EW, 2nd, Mori M, Stoller WA, Farris PE, et al. (2020). Sulforaphane Bioavailability and Chemopreventive Activity in Men Presenting for Biopsy of the Prostate Gland: A Randomized Controlled Trial. Nutr Cancer, 72:74-87.

[599] Augustin LS, Libra M, Crispo A, Grimaldi M, De Laurentiis M, Rinaldo M, et al. (2017). Low glycemic index diet, exercise and vitamin D to reduce breast cancer recurrence (DEDiCa): design of a clinical trial. BMC Cancer, 17:69.

[600] Morgensztern D, Cobo M, Ponce Aix S, Postmus PE, Lewanski CR, Bennouna J, et al. (2018). ABOUND.2L+: A randomized phase 2 study of nanoparticle albumin-bound paclitaxel with or without CC-486 as second-line treatment for advanced nonsquamous non-small cell lung cancer (NSCLC). Cancer, 124:4667-4675.

[601] Gao XN, Su YF, Li MY, Jing Y, Wang J, Xu L, et al. (2023). Single-center phase 2 study of PD-1 inhibitor combined with DNA hypomethylation agent + CAG regimen in patients with relapsed/refractory acute myeloid leukemia. Cancer Immunol Immunother, 72:2769-2782.

[602] Rodriguez-Rivera II, Wu TH, Ciotti R, Senapedis W, Sullivan K, Gao JZ, et al. (2023). A phase 1/2 open-label study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary antitumor activity of OTX-2002 as a single agent and in combination with standard of care in patients with hepatocellular carcinoma and other solid tumor types known for association with the MYC oncogene (MYCHELANGELO I). J Clin Oncol., 41:TPS627-TPS627.

[603] Hunault-Berger M, Maillard N, Himberlin C, Recher C, Schmidt-Tanguy A, Choufi B, et al. (2017). Maintenance therapy with alternating azacitidine and lenalidomide in elderly fit patients with poor prognosis acute myeloid leukemia: a phase II multicentre FILO trial. Blood Cancer Journal, 7:e568-e568.

[604] Li Y, Zeng R, He Y, Wang C, Xia C, Wang Z, et al. (2024). A Prospective Phase II Clinical Trial Using Chidamide, Tislelizumab, and Pegaspargase (CTP regimen) in Combination with Radiotherapy As First-Line Treatment in High-Risk Stages I and II of Extranodal NK/T-Cell Lymphoma. Blood, 144:6394.

[605] Celorrio San Miguel AM, Cacharro LM, Santamaría G, Garrosa M, Celorrio San Miguel M, Roche E, et al. (2025). Adjuvant melatonin therapy during exercise prescription in breast cancer survivors on physical and anthropometric parameters, quality of life, and hormonal response. A randomized controlled trial. Volume 7 - 2025.

[606] Marseglia A, Xu W, Fratiglioni L, Fabbri C, Berendsen AAM, Bialecka-Debek A, et al. (2018). Effect of the NU-AGE Diet on Cognitive Functioning in Older Adults: A Randomized Controlled Trial. Front Physiol, 9:349.