Age-associated differences in the cancer molecular landscape

Kasit Chatsirisupachai, Cyril Lagger, and João Pedro de Magalhães

Cancer is an age-related disease, as incidence and mortality for most types of cancer increase with age. However, how molecular alterations in tumors differ among patients of different ages remains poorly understood. Recent studies have shed light on the age-associated molecular landscapes in cancer. Here, we summarize the main findings of these current studies, highlighting major differences in the genomic, transcriptomic, epigenetic, and immunological landscapes between cancer in younger and older patients. Importantly, some cancer driver genes are mutated more frequently in younger or older patients. We discuss the potential roles of aging-related processes in shaping these age-related differences in cancer. We further emphasize the remaining unsolved questions that could provide important insights that will have implications in personalized medicine.

Do cancers differ according to the patient’s age?

Aging involves a progressive deterioration of physiological functions and an increased risk of numerous diseases [1]. In particular, an exponential increase in cancer incidence and mortality rate with age has long been recognized [2,3]. As the aging population continues to rise, a better understanding of the relationship between aging and cancer is critically needed. In addition, disparities between cancers in young and aged patients have also been observed [4]. For instance, breast cancer in younger patients tends to be more aggressive and is associated with poorer survival [5], while the prognosis is worse in older ovarian cancer patients [6]. Several studies have revealed distinct molecular characteristics of tumors in relation to age in various cancer types, such as breast [7,8], prostate [9], and colorectal [10] cancers. These analyses, however, focused on one cancer type and only a few molecular data types at a time. Recently, four independent studies performed pan-cancer analyses to shed light on the age-associated genomic, transcriptomic, and epigenomic patterns [11–14]. The age-related patterns of molecular alterations might suggest differences in the oncogenic mechanisms concerning the patient’s age. Another pan-cancer study focused on age-related markers of immune checkpoint blockade (ICB) and a shift in immune-cell-type abundance with age, which will be crucial for designing immunotherapy strategies [15]. Here, we summarize the major findings from these pan-cancer and cancer-specific studies (Table S1 in the supplemental information online) and discuss potential aging processes that might contribute to these differences in cancer molecular landscape.

Age-related genomic landscape in cancer

Age-related somatic mutation burden in tumors

Increased age is associated with higher somatic mutations (single-nucleotide variants and small insertions/deletions) in most cancer types [11,12,14,16–18], with an estimated increase of 0.077 mutations per megabase per year [12]. The spontaneous deamination of 5-methylcytosine to thymine (C>T) transitions, often referred to as the ‘clock-like’ mutational signature, dominates this age-related increase in mutation load. Furthermore, DNA damage repair signatures are more

Highlights

While the age-related increase in cancer incidence and mortality has been widely recognized, studies of how aging shapes the molecular landscape of tumors have only just begun.

Somatic mutations in cancer driver genes are not uniformly distributed across age. Some driver genes are mutated more often in younger or older patients, as revealed by recent pan-cancer studies.

Age-associated gene expression and epigenetic landscapes in cancer relate to diverse biological processes such as immune-related processes, extracellular matrix organization, and angiogenesis.

Age-related differences in tumor immune landscapes should alter therapeutic responses.

Tissue microenvironment changes with age may have a profound impact on cancer.

1Integrative Genomics of Ageing Group, Institute of Life Course and Medical Sciences, University of Liverpool, Liverpool L7 8TX, UK

*Correspondence:

k.chatsirisupachai@liverpool.ac.uk

(K. Chatsirisupachai) and

jp@senescence.info

(J.P. de Magalhães).
likely to be found in older individuals [12]. The mutational signature related to APOBEC (apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like family) cytidine deaminase activity increases with age in melanoma [12] and prostate cancer [9]. In addition to somatic mutations, **somatic copy-number alterations (SCNAs)** also increase as a function of age in the pan-cancer analysis (Figure 1) [11,12]. Cancer-type-specific analyses revealed a significant positive association between SCNA level and age in a few cancer types, including low-grade glioma, endometrial, ovarian, and prostate cancers [11,12]. However, another study found a positive association between SCNAS and age only in sarcoma [14]. This discrepancy might be due to the use of a 50-year-old cutoff to separate young and old patients [14], in contrast to other studies that used age as a continuous variable in their statistical model [11,12]. Tumors from older individuals tend to accumulate more clonal mutations (i.e., mutations that arise earlier in tumor evolution) [12]. This observation could correspond to an accumulation of somatic mutations with age occurring before carcinogenesis, as recently reported in most noncancerous human tissues [19–21]. Further studies are needed to elucidate how age affects clonal and subclonal mutations in cancer to better understand the impact of age on cancer evolution.

While mutation load increases with age in most cancer types, lung adenocarcinoma and endometrial cancer show an opposite trend. SCNAs also decrease with age in lung adenocarcinoma. The fact that smokers were diagnosed with lung cancer at younger ages in The Cancer Genome Atlas (TCGA) cohort potentially explains the negative association between age and somatic mutation and SCNA in patients with lung cancer [11,12], although other unexplored causes are likely to contribute as well. For endometrial cancer, tumors from younger patients showed a higher proportion of the high **microsatellite instability (MSI-H)** subtype [22]. Furthermore, mutations in DNA polymerase ε (POLE) and polymerase 6 (POLD1) are found more often in younger endometrial cancer patients [11,14,23]. Why the MSI-H and POLE/POLD1 mutation subtypes occur more frequently in younger patients is, however, still unclear.

**How somatic mutations in cancer driver genes differ according to age**

Several cancer types display an age-associated mutational landscape in known **cancer driver genes**. In other words, some driver genes are mutated more often in younger or older individuals (Figure 1). A prominent example of this is a higher frequency of mutations in isocitrate dehydrogenase 1 (IDH1), alpha thalassemia/mental retardation syndrome X-linked gene (ATRX), and tumor protein p53 (TP53) in younger glioma patients. These mutations are associated with the IDH-mutant subtype [11,12,14,24]. One study found that mutations in ATRX are an age-dependent prognostic biomarker for low-grade glioma; such mutations are associated with a poor outcome in younger patients but with better survival in older patients [12]. Conversely, the IDH-wild-type subtype associated with copy-number losses of chromosome 10 (PTEN) and gains of chromosome 7 (EGFR) is higher in older glioma patients [11,14,25]. As another example already mentioned above, younger endometrial cancers are associated with MSI-H and POLE/POLD1 mutation subtypes with a high mutation load. Thus, younger patients contain a higher percentage of somatic mutations in cancer driver genes, including DNA-repair genes, PI3KCA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α), and growth factor signaling pathways [13]. However, older endometrial tumors present a very high SCNA burden in several regions, including regions harboring cancer driver genes [11], and are associated with poorer survival than in younger patients [26].

Breast cancer is potentially the most well-characterized cancer in terms of age-associated subtyping. A favorable prognostic estrogen receptor-positive (ER+) subtype is diagnosed more often in older individuals, while an aggressive human epidermal growth factor receptor 2-positive (HER2+) subtype is more common in younger patients. In the PAM50 subtyping system, younger
women are diagnosed with more biologically aggressive HER2-enriched and basal-like subtypes [27]. Luminal A tumors that have a better prognosis are more common in older women [4]. Regarding somatic mutations, higher cadherin 1 (CDH1) mutations in older patients are observed [7,8,11,13]. The CDH1 mutation is highly enriched in the invasive lobular carcinoma subtype, which is more common in older patients [28]. Mutations in PIK3CA also appear to increase in frequency with age [29,30]. Breast cancer in younger patients is associated with higher TP53, GATA binding protein 3 (GATA3), and AT-rich interaction domain 1A (ARID1A) mutations [7,13,30,31]. Interestingly, a recent report suggests that the age-associated differences in GATA3, ARID1A, and PIK3CA mutations were only found in luminal A but not in other PAM50 subtypes [30].

The identification of age-related driver genes may be clinically relevant. For instance, PIK3CA mutations, which are more common in older patients, correlate with a better treatment outcome in early-stage breast cancer [32]. Next, mutations in GATA3, a gene encoding transcription factor that acts cooperatively with ER and is mutated more frequently in younger patients, could promote tumor cell growth and associate with endocrine resistance [33]. Furthermore, lower GATA3 expression is associated with poor prognosis [34]. However, mutations in GATA3 can be both gain-of-function and loss-of-function [35], and it remains unclear whether GATA3 acts as a tumor suppressor or as an oncogene [36]. Therefore, further studies are required to better clarify biological and clinical implications of GATA3 mutations in younger and older breast cancer patients.

For other cancer types, it has been reported that TP53 and CTNNB1 mutations are more common in younger colorectal cancer patients, while adenomatous polyposis coli (APC), Kirsten rat sarcoma viral oncogene homolog (KRAS), and v-raf murine sarcoma viral oncogene homolog B1 (BRAF) V600 mutations are higher in older patients [10,37,38]. By contrast, BRAF mutations, especially BRAF V600, decrease with age in melanoma [39]. CDH1 mutations, which are higher in older breast cancer patients, decrease with age in stomach cancer [11]. In prostate cancer, structural variation breakpoints were highly enriched near gene regulatory regions such as active enhancers in the early-onset but not late-onset prostate cancer [9].

Overall, somatic mutations in cancer driver genes do not uniformly distribute across age. These age-related somatic mutations appear to be cancer-type specific. In addition, some mutations display opposite trends in different cancers. Typically, mutations in BRAF V600 decline with age in melanoma and increase in colorectal cancer. Mutations in BRAF V600 are an example of age-related mutations that are clinically actionable targets with multiple approved drugs [14]. Additional investigation of age-related driver genes could shed light on the underlying biological differences between tumors from younger and older groups and help improve treatment strategy. In addition, further studies are needed to determine if the effectiveness of targeted drugs differs according to patient’s age [4]. Besides, older patients often present with comorbidities and may have specific therapeutic challenges [40]. In summary, the identification of age-related somatic driver mutations and further investigation of these drivers could have a profound impact in the clinical setting to improve treatment options for patients of different age groups.

Age-associated gene expression, epigenetic, and immunological landscape in cancer
Age-associated gene expression and DNA methylation patterns
Several studies attempted to investigate age-related gene expression in cancer. In breast cancer, an early study reported a higher expression of cell cycle-related genes in tumors from younger than those from older ER+ patients [41]. Recently, another work suggested that age-related differentially expressed genes in breast cancer could partly be controlled by age-related changes in estrogen signaling [42]. Pan-cancer studies reported that the amount of age-associated
differentially expressed genes in cancer varies across tumor types. These genes are partly regulated by age-associated DNA methylation changes [11,13,43]. One study used survival data and the number of differentially expressed genes to classify cancers as age-associated and non-age-associated.

Figure 1. Age-associated differences in the cancer genome. Examples of cancer driver genes that display age-associated patterns in somatic mutations are shown in the figure. Driver genes in blue represent genes that are mutated more frequently in younger patients, while those in red denote genes that are mutated more frequently in older patients. Please note that this is not a comprehensive list of age-related somatic mutations in cancer driver genes. For more complete data, we refer to Table S1 in the online supplemental information online. Figure created with BioRender.com.
associated [13]. Age-associated cancer types include low-grade glioma, lung squamous cell carcinoma, thyroid adenocarcinoma, and cancers of female reproductive organs (breast, ovarian, and endometrial). Notably, tumors from younger patients of age-associated cancers are associated with increased age acceleration as measured by the epigenetic clock. This was not observed in non-age-associated cancers [13]. Nevertheless, the molecular mechanisms behind this observation, and why such a feature is limited to only age-associated cancers, are unclear.

The observed age-related gene expression changes in tumors are associated with numerous biological processes, such as extracellular matrix (ECM) organization, metabolism, development, signaling pathways, and immune-related processes across various cancer types [7,8,11,13,14,43,44]. For instance, the expression of genes from immune-related pathways was lower in younger sarcoma, low-grade glioma, and head and neck cancer [14]. As these results have been derived from bulk RNA sequencing (RNA-seq) analyses, they likely incorporate changes not only from cancer cells themselves but also from the aging tissue microenvironment [45]. The ever-increasing data generated from single-cell RNA-seq (scRNA-seq) hold a great promise to resolve this issue. For example, a recent study in mouse mammary gland revealed age-dependent alterations in cell proportions and gene expression. These changes are potentially associated with pro-tumorigenic microenvironment properties, such as loss of ECM integrity, compromised endothelial barrier, and increased production of proinflammatory cytokines [46]. Yet, to date, the comparison of gene expression between tumors as a function of patient’s age using scRNA-seq is still lacking.

Another critical question is how age-related somatic mutations in cancer driver genes alter age-related transcriptional programs in cancer. Indeed, copy-number alterations usually correlate with the expression of the affected genes [11,12]. However, the precise interplay between age-related omic landscapes in cancer has not been comprehensively examined. We expect recently designed single-cell dual- and tri-omics sequencing methods (e.g., G&T-seq [47], scTrio-seq [48]) or Genotyping of Transcriptomes (GoT) [49] to shed new light on such questions in the near future. For instance, although not in the context of aging, scTrio-seq was able to measure simultaneously the SCNAs, methylome, and transcriptome of individual hepatocellular carcinoma cells and predict malignancy and metastasis potentials of different cell subpopulations [48].

Age-related changes of the immunological landscape in cancer
Aging is associated with a decline in immune system function (immunosenescence) and chronic and persistent inflammation (inflammaging) [50,51]. Immunosenescence is linked with a decrease in immune cell ability to eliminate cancer cells, while inflammaging is associated with carcinogenesis and cancer progression [52,53]. Thymic involution, the shrinkage of the thymus with age, could partly be responsible for immunosenescence, by reducing T cell production and altering T cell antigen receptor (TCR) diversity. Thus, thymic involution is thought to contribute to the rise of cancer incidence with age [54]. Age-related changes in immune cell populations also contribute to a shift of the immune landscape, notably via myeloid-bias differentiation, increase of natural killer cells, decrease of naive T cells, and increase of memory T cells [55].

Immune-related pathways are enriched in age-related differentially expressed genes in several cancers [11,13,14,43]. Although an increasing number of studies use scRNA-seq to explore tumor immune landscape (e.g., [56]), the comparison of immune cell population between cancer from younger and older patients has not been performed. To bridge this gap, a recent study used deconvolution approaches to examine the relationship between age and immune cell proportions in cancer from bulk RNA-seq data [13]. They suggested older age is associated with decreased CD4+ and CD8+ T cells in breast and ovarian cancers and increased M2 macrophages in breast and thyroid cancers. Furthermore, naive B cells decline, while plasma cells increase with age in
breast cancer. Some of these patterns were also discovered by another study [14]. In addition, immune gene signature analysis reported lower transforming growth factor (TGF)-β and elevated interferon (IFN)-γ responses with age, corresponding to a better response in immunotherapy in cancer from older patients [14]. Another recent deconvolution analysis reported a decrease in T cell abundance, together with increased macrophage abundance in tumors from older patients [15]. This study also investigated ICB biomarkers in relation to age across cancer types. Overall, tumors from older patients have a higher mutation burden, increased expression, and decreased promoter methylation of immune checkpoint genes. Therefore, older patients are more likely to benefit from immunotherapy based on these biomarkers. By contrast, a decline in T cell abundance with age might be related to reduced ICB efficiency. Future large-scale studies are needed to shed light on the effects of age-related tumor immune landscape on ICB therapy.

Altogether, recent studies have investigated the age-related tumor immune landscape. Further research using scRNA-seq to compare immune cell population and gene expression between young and old tumors would complement existing studies. The interaction between cancer...
cells and other cell types in the tumor microenvironment, including immune cells, could also be different in patients of different ages. The advent of tools to analyze intercellular communication and spatial transcriptomic is expected to advance our understanding of age-associated immune-cancer crosstalk in tumors [57–59]. Finally, a better understanding of age-related tumor immune infiltration is needed to prioritize cancer patients who will benefit from specific immunotherapy [15,55].

**How may aging processes contribute to age-related features of cancer?**

The studies mentioned above clearly show that age does impact the molecular landscape of cancer. In addition to somatic mutation accumulation with age, tissue microenvironment changes during aging can contribute to cancer progression (Figure 2), as evidenced by mathematical modeling and experimental studies [45,60–63]. Tumor microenvironment may have a profound impact on the cancer genome landscape. For example, a recent study showed an association between breast cancer microenvironment and genomic features [64]. Notably, shifts in ECM organization and angiogenesis might have considerable effects on carcinogenesis and tumor progression [45]. ECM organization-related genes are upregulated with age in normal kidneys but are downregulated with age in clear-cell renal cell carcinoma (ccRCC) [44]. In addition, the expression of angiogenesis-related genes also decreases with age in ccRCC. However, one study found that angiogenesis-related genes are upregulated with age in glioblastoma [65], again highlighting cancer-type-specific gene expression differences with age. It is possible that age-related alterations in the tissue microenvironment might provide different selective advantages for cancer cells containing distinct molecular alterations (Figure 3). This hypothesis is, however, waiting for experimental evidence.

Several aging-related processes might contribute to creating a fertile ground for cancer. For instance, senescent cells release proinflammatory cytokines, chemokines, and growth factors, collectively known as senescence-associated secretory phenotypes (SASPs) [66]. The gene expression signatures of cellular senescence increase with age in various human tissues [67]. Although the SASP has been suggested to promote cancer initiation and progression [66,69], how this process contributes to the progression of cancer cells harboring diverse molecular landscapes is unknown. Likewise, systemic changes in circulating factors during aging, such as hormones, can also influence cancer. A recent study suggested that a majority of age-related differentially expressed genes in breast cancer are potentially regulated by age-dependent estrogen signaling [42]. Another study showed that metabolic alterations with age increase methylmalonic acid (MMA) in blood and promote cancer progression [69]. It remains to be investigated how these aging-related processes affect the cancer molecular landscape in addition to their role in facilitating cancer progression.

**Concluding remarks and future perspectives**

In addition to an increase in cancer incidence and mortality with age, tumors arising from patients of different ages also show distinct characteristics and may relate to age-associated subtypes of cancer. The studies mentioned above relied heavily on only a few large-scale datasets, primarily TCGA [70], Genomics Evidence Neoplasmia Information Exchange (AACR GENIE) [71], and Molecular Taxonomy of Breast Cancer International Consortium (METABRIC) [72] (Table S1 in the supplemental information online). Furthermore, the lack of consistency regarding age cutoffs between studies impairs the reproducibility of the findings. Whereas the meaning of ‘young’ and ‘old’ groups may vary between analyses, other studies choose to analyze age as a continuous variable. Thus, careful consideration should be taken when interpreting these data. Moreover, current datasets usually have limited numbers of samples from extreme age groups, particularly from those 20–30 and 80–90 years old, obscuring the findings of the molecular
alterations specific to these age ranges. While results from the current studies are informative, there is an urgent need for new multi-omic cancer datasets to both validate previous findings and discover novel information.

Current studies have identified the differences in molecular landscape between cancer in younger and older patients. Therefore, the logical next step is to understand why such differences emerge. Indeed, it is also possible that we may still be missing unknown layers of biological and genomic regulation that could be significant in aging and cancer. In addition, several important questions remain to be elucidated (see Outstanding questions). For example, age-dependent metastatic patterns have not been investigated. Novel experimental strategies, such as the use of mouse models of different ages carrying cancer clones with distinct genotypes, and advances in single-cell genomics, spatial omics, and statistical methods, are expected to improve our understanding of the impact of age on the cancer molecular landscape. This knowledge will, ultimately, be helpful to inform treatment strategies for patients of different ages.

Acknowledgments
K.C. is supported by a Mahidol-Liverpool PhD scholarship from Mahidol University, Thailand, and the University of Liverpool, UK. C.L. is grateful for the funding provided by the Human Frontier Science Program (fellowship LT000741/2019-C). J.P.d.M. is grateful for funding from the Wellcome Trust (208375/Z/17/Z) and the Biotechnology and Biological Sciences Research Council (BB/R014949/1).
Supplemental information

Supplemental information associated with this article can be found online at https://doi.org/10.1016/j.trecan.2022.06.007.

References

1. Franceschi, C. et al. (2018) The continuum of aging and age-related diseases: common mechanisms but different rates. Front. Med. (Lausanne) 5, 61
2. Auran, J.R. et al. (2017) The biology of aging and cancer: a brief overview of shared and divergent molecular hallmarks. Aging Dis. 8, 628–642
3. de Magalhaes, J.P. (2013) How ageing processes influence cancer. Nat. Rev. Cancer 13, 357–365
4. van den Hurk, Y. et al. (2021) Is cancer biology different in older patients? Lancet Healthy Longevity 2, e663–e677
5. Anders, C.K. et al. (2008) Young age at diagnosis correlates with worse prognosis and defines a subset of breast cancers with characteristics of minor basal cell carcinoma. J. Clin. Oncol. 26, 3294–3300
6. Maas, H.A. et al. (2005) The influence of age and co-morbidity on treatment and prognosis of ovarian cancer: a population-based study. Gynecol. Oncol. 97, 104–109
7. Li, Z. et al. (2018) Multi-omics profiling of younger Asian breast cancers reveals distinctive molecular signatures. Nat. Commun. 9, 1725
8. Liao, S. et al. (2015) The molecular landscape of premenopausal breast cancer. Breast Cancer Res. 17, 104
9. Gerhauser, C. et al. (2018) Molecular evolution of early-onset prostate cancer identifies molecular risk markers and clinical trajectories. Cancer Cell 34, 996–1011 e8
10. Liao, C.H. et al. (2019) Comprehensive genomic landscapes in early and later onset colorectal cancer. Clin. Cancer Res. 25, 5852–5858
11. Chatsitirapakach, K. et al. (2021) An integrative analysis of the age-associated multi-omic landscape across cancers. Nat. Commun. 12, 2345
12. Li, C.H. et al. (2022) Age influences on the molecular presentation of tumours. Nat. Commun. 13, 208
13. Shah, Y. et al. (2021) Pan-cancer analysis reveals molecular patterns associated with age. CellRep. 37, 11010
14. Lee, W. et al. (2021) Genomic and molecular features distinguish young adult cancer from later-onset cancer. Cell Rep. 37, 110005
15. Erice, R. et al. (2021) Evaluating the impact of age on immune checkpoint therapy biomarkers. Cell Rep. 35, 105693
16. Chalimert, Z.R. et al. (2017) Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. Genome Med. 9, 34
17. Miholland, B. et al. (2015) Age-related somatic mutations in the cancer genome. Oncotarget 6, 24627–24635
18. Alexandrov, L.B. et al. (2015) Clock-like mutational processes in human somatic cells. Nat. Genet. 47, 1402–1407
19. Kalkuchi, N. and Ogawa, S. (2021) Clonal expansion in non-cancer tissues. Nat. Rev. Cancer 21, 239–256
20. Moore, L. et al. (2020) The mutational landscape of normal human endometrial epithelium. Nature 580, 640–646
21. Martincic, I. et al. (2020) Somatic mutant clones colonize the human esophagus with age. Science 362, 911–917
22. Campbell, B.B. et al. (2017) Comprehensive analysis of hypermutation in human cancer. Cell 171, 1042–1056 e10
23. de Magalhaes, J.P. et al. (2018) Somatic mutations in primary and metastatic endometrial cancer reveals distinct patterns of DNA repair defects and shifts during tumor progression. Gynecol. Oncol. 152, 11–19
24. Cencicelli, M. et al. (2018) Molecular profiling reveals biologically discrete subsets and pathways of progression in diffuse glioma. Cell 164, 550–563
25. Kobier, V. et al. (2019) Evolutionary trajectories of IDH-WT glioblastomas reveal a common path of early tumorigenesis instigated years ahead of diagnosis. Cancer Cell 35, 690–704 e12
26. Levine, D.A. and Cancer Genome Atlas Research Network (2013) Integrated genomic characterization of endometrial carcinoma. Nature 497, 67–73
27. Sweeney, C. et al. (2014) Intrinsic subtypes from PAM50 gene expression assay in a population-based breast cancer cohort: differences by age, race, and tumor characteristics. Cancer Epidemiol. Biomark. Prev. 23, 714–724
28. Berger, A.D. et al. (2018) A comprehensive pan-cancer molecular study of gynecologic and breast cancers. Cancer Cell 33, 690–705 e9
29. Mealey, N.E. et al. (2020) Mutational landscape differences between young-onset and older-onset breast cancer patients. BMC Cancer 20, 212
30. Waks, A.G. et al. (2022) Somatic and germline genomic alterations in very young women with breast cancer. Clin. Cancer Res. 28, 2359–2365
31. Azim, H.A., Jr et al. (2015) Genomic aberrations in young and elderly breast cancer patients. BMC Med. 13, 206
32. Zardavas, D. et al. (2018) Tumor P53/CA genotype and prognosis in early-stage breast cancer: a pooled analysis of individual patient data. J. Clin. Oncol. 36, 891–900
33. Adams, A.B. et al. (2014) Breast tumor specific mutation in GATA3 affects physiological mechanisms regulating transcription factor turnover. BMC Cancer 14, 278
34. Meira, R. et al. (2020) Identification of GATA3 as a breast cancer prognostic marker by global gene expression meta-analysis. Cancer Res. 65, 11259–11264
35. Takaku, M. et al. (2018) GATA3 zinc finger 2 mutations reprogram the breast cancer transcriptional network. Nat. Commun. 9, 1059
36. Takaku, M. et al. (2019) GATA3 in breast cancer: tumor suppressor or oncogene? Gene Expr. 16, 163–168
37. Wilner, A.N. et al. (2019) Clinical and molecular characterization of early-onset colorectal cancer. Cancer 125, 2002–2010
38. Berg, M. et al. (2010) DNA sequence profiles of the colorectal cancer critical gene set KRAS- BRAF-PK3CA-PTEN-TP53 related to age at disease onset. PLoS One 5, e13976
39. Bauer, J. et al. (2018) The continuum of aging and age-related diseases: common mechanisms but different rates. Aging Dis. 9, R59
40. Yau, C. et al. (2022) The impact of age on assessment and treatment of breast cancer in older people: you are as old as your oncologist thinks you are. Clin. Oncol. 34, 363–367
41. Yu, C. et al. (2007) Ageing impacts transcripts but not genomes of hormone-dependent breast cancers. Breast Cancer Res. 9, R9
42. Okano, T. et al. (2020) Age-correlated protein and transcript expression in breast cancer and normal breast tissues is dominated by host endocrine effects. Nat. Cancer 1, 518–532
43. Wu, Y. et al. (2019) Comprehensive transcriptome profiling in elderly cancer patients reveals aging-altered immune cells and immune checkpoints. Int. J. Cancer 144, 1657–1663
44. Feulner, L. et al. (2019) Age-related variations in gene expression patterns of renal cell carcinoma. Oncotarget 10, 166–175
45. Fane, M. and Weeraratna, A.T. (2020) How the ageing microenvironment influences tumour progression. Nat. Rev. Cancer 20, 69–106
46. Li, C.M. et al. (2020) Aging-associated alterations in mammary epithelia and stroma revealed by single-cell RNA sequencing. Cell Rep. 33, 108656
47. Macaulay, I.C. et al. (2015) G&T-seq: parallel sequencing of single-cell genomes and transcriptomes. Nat. Methods 12, 519–522

Declaration of interests

J.P. d. M. is an advisor/consultant for the Longevity Vision Fund, NOVOS, YouthBio Therapeutics, and the founder of Magellan Science Ltd, a company providing consulting services in longevity science.

Supplemental information

Supplemental information associated with this article can be found online at https://doi.org/10.1016/j.trecan.2022.06.007.
48. Hou, Y. et al. (2016) Single-cell triple omics sequencing reveals genetic, epigenetic, and transcriptomic heterogeneity in hepatocellular carcinomas. Cell Res. 26, 304–319
49. Nam, A.S. et al. (2019) Somatic mutations and cell identity linked by genotyping of transcriptomes. Nature 571, 355–360
50. Palmer, D. et al. (2021) Ageing transcriptome meta-analysis reveals similarities and differences between key mammalian tissues. Aging (Albany NY) 13, 3313–3341
51. de Magalhães, J.P. et al. (2009) Meta-analysis of age-related gene expression profiles identifies common signatures of aging. Bioinformatics 25, 875–881
52. Leonardi, G.C. et al. (2018) Ageing: from inflammation to cancer. Immun. Ageing 15, 1
53. Pawelec, G. (2017) Immunosenescence and cancer. Biogerontology 18, 717–721
54. Palmer, S. et al. (2018) Thymic involution and rising disease incidence with age. Proc. Natl. Acad. Sci. U. S. A. 115, 1865–1869
55. Berben, L. et al. (2021) Cancer and aging: two tightly interconnected biological processes. Cancers (Basel) 13, 1400
56. Neto, P. et al. (2021) A single-cell tumor immune atlas for precision oncology. Genome Res. 31, 1915–1926
57. Liu, J. et al. (2021) Applications of single-cell omics in tumor immunology. Front. Immunol. 12, 697412
58. Lagger, C. et al. (2021) scAgeCom: a murine atlas of age-related changes in intercellular communication inferred with the package scDiffCom. bioRxiv Published online August 15, 2021. https://doi.org/10.1101/2021.08.13.456238
59. Amingol, E. et al. (2021) Deciphering cell–cell interactions and communication from gene expression. Nat. Rev. Genet. 22, 71–88
60. Lacori, E. et al. (2020) Cancer as a disease of old age: changing mutational and microenvironmental landscapes. Br. J. Cancer 122, 943–952
61. Chatsirisupachai, K. et al. (2019) A human tissue-specific transcriptomic analysis reveals a complex relationship between aging, cancer, and cellular senescence. Aging Cell 18, e13041
62. Rozhok, A. and DeGregori, J. (2019) A generalized theory of age-dependent carcinogenesis. eLife 8, e43960
63. Henry, C.J. et al. (2019) Declining lymphoid progenitor fitness promotes aging-associated leukemogenesis. Proc. Natl. Acad. Sci. U. S. A. 107, 21713–21718
64. Danenberg, E. et al. (2022) Breast tumor microenvironment structures are associated with genomic features and clinical outcome. Nat. Genet. 54, 660–669
65. Bozdag, S. et al. (2013) Age-specific signatures of glioblastoma at the genomic, genetic, and epigenetic levels. PLoS ONE 8, e52982
66. Faget, O.V. et al. (2019) Unmasking senescence: context-dependent effects of SASP in cancer. Nat. Rev. Cancer 19, 439–453
67. Avelar, R.A. et al. (2020) A multidimensional systems biology analysis of cellular senescence in aging and disease. Genome Biol. 21, 91
68. Omer, A. et al. (2020) G3BP1 controls the senescence-associated secretome and its impact on cancer progression. Nat. Commun. 11, 4979
69. Gomes, A.P. et al. (2020) Age-induced accumulation of methylmalonic acid promotes tumour progression. Nature 585, 283–287
70. Cancer Genome Atlas Research Network et al. (2013) The Cancer Genome Atlas Pan-Cancer analysis project. Nat. Genet. 45, 1113–1120
71. AACR Project GENIE Consortium (2017) AACR Project GENIE: powering precision medicine through an international consortium. Cancer Discov. 7, 818–831
72. Curtis, C. et al. (2012) The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. Nature 486, 346–352