# Is cancer biology different in older patients?

*Yannick Van Herck*, Annelies Feyaerts*, Shabbir Alibhai, Demetris Papamichael, Lore Decoster, Yentl Lambrechts, Michael Pinchuk, Oliver Bechter, Jaime Herrera-Caceres, Frédéric Bibeau, Christine Desmedt, Sigrid Hatse, Hans Wildiers*

**Roughly 50% of cancer cases occur in people aged 65 years or older. Older people are often diagnosed at a later stage and might receive less (intensive) treatment, which might affect the outcome. In addition, an older age might be associated with biological differences in tumour and microenvironment behaviour, a domain that has been poorly studied so far. In this narrative Review of published literature, we explored the reported differences in tumour biology according to age in five major cancer types: breast, colorectal, prostate, lung, and melanoma. Our literature search uncovered clear differences in tumour histology and subtype distribution in older people compared with younger patients, as well as age-specific patterns of tumour mutations and other molecular alterations. Several studies also indicate notable changes in tumour-infiltrating immune cells in tumours of older versus younger people, although this research is still in its infancy. More research is needed and might lead to a better understanding of the biology of ageing in relation to malignancy. This knowledge could provide new perspectives for more personalised cancer treatments, eventually improving the global outcomes of older patients with cancer.**

*Lancet Healthy Longev* 2021; 2: e663–677

*Joint first authorship

**Laboratory of Experimental Oncology** (Y V Herck MD, Y Lambrechts, O Bechter MD, S Hatse PhD, Prof H Wildiers PhD) **and Laboratory for Translational Breast Cancer Research** (C Desmedt PhD), **Department of Oncology, Katholieke Universiteit Leuven, Leuven, Belgium; Department of General Medical Oncology, University Hospitals Leuven, Leuven Cancer Institute, Leuven, Belgium** (Y V Herck, A Feyaerts MD, Y Lambrechts, M Pinchuk, O Bechter, S Hatse, Prof H Wildiers)**; Department of Medicine, Princess Margaret Cancer Centre** (Prof S Alibhai MD) **and Department of Surgical Oncology (Urological Oncology)** (J Herrera-Caceres MD), **University Health Network & University of Toronto, Toronto, Canada; Department of Medical Oncology, Bank of Cyprus Oncology Centre, Nicosia, Cyprus** (D Papamichael MBBS); **Department of Medical Oncology, Vrije Universiteit Brussel, University Hospitals Brussels, Brussels, Belgium** (L Decoster MD)**; Department of Pathology, Caen University Hospital, University of Caen Normandie, Caen, France** (F Bibeau MD)

Correspondence to:
Prof Hans Wildiers, Laboratory of Experimental Oncology, Department of Oncology, Katholieke Universiteit Leuven, Leuven 3000, Belgium
**hans.wildiers@uzleuven.be**

## Introduction

Because of an ongoing increase in global life expectancy[1–3] combined with a disproportionately high incidence of most cancer types in older adults,[4,5] cancer care for older patients has attracted increasing attention. Geriatric oncology can be considered a specific expertise within clinical oncology,[6] but since most cancers occur in older people, it is important that all oncologists and health-care workers are aware of the particularities within this domain. Geriatric oncology presents unique age-specific challenges, including competing health and socio-economic factors, but also age-related changes in tumour biology that might have an effect on screening, diagnosis, treatment, and outcome.

Most of the research done within the field of geriatric oncology has highlighted differences in tumour-extrinsic features between older and young age groups and their impact on treatment effectiveness and outcome. Host-specific factors such as functional disability,[7] polypharmacy,[8–11] malnutrition,[12–14] sarcopenia,[15–21] cognitive impairment,[22–26] age-related pharmacological differences in the metabolism of anticancer drugs,[27–29] systemic metabolic changes,[30] depression,[31,32] and chemotherapy dose adaptation[33,34] have all been reported to affect the disease course in older individuals. In addition, ageism (ie, discrimination based on perceived or actual chronological age) is an invisible and insidious social occurrence that exists in many dimensions within cancer care.[35] Conversely, surprisingly little attention has been given as to whether tumour-intrinsic features, such as histopathological presentation or molecular profile, differ according to age group and how these differences could potentially influence cancer care.

To bridge this knowledge gap, we did an in-depth literature review to gather existing evidence concerning tumour biological differences according to age. We chose to focus on five of the most common tumour types in older people according to the Surveillance, Epidemiology, and End Results programme database:[36] breast, lung, prostate, colorectal, and melanoma. A working group of international experts, with expertise in both one of the five tumour domains and in geriatric oncology, was established. For each tumour type, the dedicated experts did a tailored literature search, focusing on well-known disease-specific characteristics with prognostic or clinical relevance, or both. Importantly, only the tumour characteristics of newly diagnosed, untreated tumours were considered, to avoid the effect of previous treatment. It was also decided upfront that the focus should only be on differences in tumour biology, and not on differences in prognosis or treatment response, because differences in these responses might have multiple causes other than the differences in tumour biology. The literature search thus principally covered age-related differences in the key aspects of tumour biology (ie, histology, subtype, and molecular markers). In addition, specific attention was also given to age-related remodelling of the tumour microenvironment (stroma or immune infiltrate) for each of the five subtypes.

## Breast cancer

Breast cancer is the most common cancer in women worldwide with a mean age at diagnosis of 62 years.[37] The major clinical, histopathological, and tumour biology characteristics according to age are summarised in figure 1 and the panel.

### Age-related differences in histology

Older adults present with slightly less high-grade tumours than younger adults.[38–40] The proportion of the invasive ductal carcinoma subtype (the most common subtype, officially referred to as invasive breast carcinoma of no special type and accounting for approximately 70% of breast cancers) was shown to consistently decline with increasing age in the studies included, whereas the data on the invasive lobular subtype (accounting for approximately 15% of breast cancers) are inconsistent in terms of changing proportion with age.[38–42] The rare mucinous histological subtype is only slightly more frequent (approximately 1%) in older people.[38,39] Hormone

**Breast cancer**

**Age-related differences in histology and subtypes**

| | Reference | Age group | n | Grade I (%) | Grade II (%) | Grade III (%) | Grade IV (%) | Unknown (%) |
|---|---|---|---|---|---|---|---|---|
| High grade tumours↓ | Schonberg et al (2010)[38] | 67–69 | 7437 | **18·6** | **39·4** | **26·4** | **2·0** | **13·6** |
| | | 85–89 | 4707 | **18·7** | **38·7** | **25·4** | **1·9** | **15·7** |
| | Lodi et al (2017)[39] | 70–79 | 2858 | **19·8** | **47·1** | **25·5** | .. | **7·6** |
| | | ≥80 | 1472 | **23·2** | **45·0** | **21·5** | .. | **10·4** |
| | Malik et al (2013)[40] | <71 | 2065 | 15·0 | 41·0 | 31·0 | .. | 12·0 |
| | | ≥71 | 382 | 17·0 | 54·0 | 22·0 | .. | 8·1 |

| | Reference | Age group | n | IDC (%) | ILC (%) | Mucinous (%) | Unknown (%) |
|---|---|---|---|---|---|---|---|
| IDC↓<br>ILC*<br>Mucinous↑ | Schonberg et al (2010)[38] | 67–69 | 7437 | **79·1** | **8·0** | **3·5** | **9·4** |
| | | 85–89 | 4707 | **77·4** | **6·9** | **5·5** | **10·2** |
| | Lodi et al (2017)[39] | 70–79 | 59 850 | **66·8** | **10·0** | **3·7** | **19·5** |
| | | ≥80 | 34 220 | **61·5** | **6·9** | **4·3** | **27·3** |
| | Malik et al (2013)[40] | <71 | 2065 | **68·0** | 7·9 | .. | 24·1 |
| | | ≥71 | 382 | **69·0** | 12·0 | .. | 19·0 |
| | Wang et al (2018)[41] | <39 | 75 | **90·7** | **0·0** | .. | **9·3** |
| | | 40–59 | 487 | **73·5** | **17·3** | .. | **9·2** |
| | | >60 | 494 | **66·2** | **23·7** | .. | **10·1** |
| | Azim et al (2015)[42] | ≤45 | 125 | **93·0** | **7·0** | .. | |
| | | 46–49 | 486 | **76·0** | **24·0** | .. | |
| | | ≥70 | 169 | **71·0** | **29·0** | .. | |

| | Reference | Age group | n | ER+ (%) | PR+ (%) | HER2+ (%) |
|---|---|---|---|---|---|---|
| Immunohistochemistry:<br>ER↑<br>PR↑<br>HER2 ↓ | Schonberg et al (2010)[38] | 67–69 | 7437 | **81·8** | **56·6** | |
| | | 85–89 | 4707 | **86·1** | **53·4** | |
| | Lodi et al (2017)[39] | 70–79 | 1928 | .. | **67·3** | |
| | | ≥80 | 785 | .. | **72·7** | |
| | Malik et al (2013)[40] | <71 | 2065 | **77·0** | .. | |
| | | ≥71 | 382 | **86·0** | .. | |
| | Wang et al (2018)[41] | <39 | 75 | **71·8** | **63·4** | 21·9 |
| | | 40–59 | 487 | **72·1** | **63·0** | 20·6 |
| | | >60 | 494 | **82·0** | **70·8** | 23·0 |
| | Anderson et al (2011)[43] | 30–34 | .. | 55·9 | .. | |
| | | 80–84 | .. | 85·1 | .. | |
| | De Munck et al (2011)[44] | <40 | 785 | .. | .. | 22·0 |
| | | >70 | 3738 | .. | .. | 10·0 |

**Age-related differences in molecular markers**

| | Reference | Age group | n | Luminal A (%) | Luminal B (%) | HER2+ (%) | Basal (%) | Healthy (%) |
|---|---|---|---|---|---|---|---|---|
| PAM50 subtypes:<br>Luminal A↑,<br>Luminal B ↑†,<br>HER2↓ , Basal ↓ | Azim et al (2015)[42] | ≤45 | 125 | 35·0 | 33·0 | 12·0 | 20·0 | .. |
| | | 46–69 | 486 | 41·0 | 29·0 | 12·0 | 18·0 | .. |
| | | ≥70 | 169 | 41·0 | 38·0 | 7·0 | 14·0 | .. |
| | Jenkins et al (2014)[45] | 21–39 | 335 | **18·0** | **12·0** | 15·0 | **44·0** | 11·0 |
| | | 70–93 | 802 | **39·0** | **32·0** | 11·0 | **9·0** | 9·0 |
| | De Kruijf et al (2014)[46] | <65 | 361 | **42·6** | **20·0** | **17·4** | **20·2** | .. |
| | | ≥65 | 189 | **53·4** | **23·0** | **14·3** | **14·2** | .. |
| | Mealey et al (2020)[47] | ≤40 | 78 | 50·0 | 23·0 | 4·0 | **22·0** | 1·0 |
| | | >40 | 774 | 50·8 | 21·2 | 8·5 | **16·7** | 2·8 |
| | | >60 | 372 | 59·0 | 20·0 | 7·0 | **12·0** | 2·0 |

| | Reference | Age group | n | *TP53* (%) | *PIK3CA* (%) | *GATA3* (%) | *MLL3* (%) | *CDH1* (%) | *MAP3K1* (%) | *MAP2K4* (%) | *AKT1* (%) | *NF1* (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Mutations:<br>*TP53*↓<br>*PIK3CA*↑†<br>*GATA3*↓<br>*MLL3*↑<br>*CDH1*↑<br>*MAP3K1*↑<br>*MAP2K4*†<br>*AKT1*↓†<br>*NF1*† | Wang et al (2018)[41] | <39 | 75 | **31·9** | **26·1** | **24·6** | **4·3** | **1·5** | **2·9** | .. | .. | .. |
| | | 40–59 | 487 | **41·5** | **30·9** | **15·3** | **7·0** | **12·2** | **6·5** | .. | .. | .. |
| | | >60 | 494 | **29·1** | **36·9** | **9·4** | **12·8** | **19·3** | **11·5** | .. | .. | .. |
| | Azim et al (2015)[42] | ≤45 | 118 | .. | .. | **15·2** | .. | .. | .. | .. | .. | .. |
| | | 46–49 | 449 | .. | .. | **8·2** | .. | .. | .. | .. | .. | .. |
| | | ≥70 | 155 | .. | .. | **9·0** | .. | .. | .. | .. | .. | .. |
| | Mealey et al (2020)[47] | ≤40 | 78 | 34·0 | **24·0** | **22·0** | .. | **4·0** | **3·0** | 4·0 | 4·0 | 7·0 |
| | | >40 | 774 | 33·6 | **35·7** | **12·9** | .. | **17·9** | **11·3** | 5·6 | 3·4 | 10·2 |
| | | >60 | 372 | 28·6 | **37·4** | **10·8** | .. | **20·6** | **14·2** | 5·6 | 3·0 | 12·3 |
| | Selenica et al (2020)[48] | <65 | 926 | **34·0** | .. | .. | .. | .. | .. | **4·0** | **6·0/5·0‡** | **6·0** |
| | | ≥65 | 608 | **23·0** | .. | .. | .. | .. | .. | **0·4** | **2·0/1·0‡** | **2·0** |
| | Kalinsky et al (2009)[49] | <50 | 160 | .. | **19·0** | .. | .. | .. | .. | .. | .. | .. |
| | | 50–69 | 304 | .. | **57·0** | .. | .. | .. | .. | .. | .. | .. |
| | | ≥70 | 126 | .. | **24·0** | .. | .. | .. | .. | .. | .. | .. |

***Figure 1:*** **Differences in breast cancer biology according to age**

Arrow pointing down indicates that all data point to a decrease with age. Arrow pointing up indicates that all data point to an increase with age. ER=oestrogen receptor. IDC=invasive ductal carcinoma. ILC=invasive lobular carcinoma. PAM50=Prediction Analysis of Microarray 50 gene expression profiles. PR=progesterone receptor. *There are no clear age differences. †Data are not perfectly consistent. ‡Two independent cohorts. Bold values indicate statistically significant difference between the young and old group in each study (p<0·05).

***Panel*: Summary of the most important age-related differences in cancer biology for breast cancer, lung cancer, prostate cancer, melanoma, and colorectal cancer**

**Breast cancer**

- Older age is associated with slightly fewer high-grade tumours, fewer triple-negative breast cancer and HER2+ subtypes, and more luminal tumours than a younger age, but all subtypes occur in all age categories
- The tumour mutational landscape differs with age; for example, fewer *TP53* and more *PIK3CA* mutations occur in the older breast cancer population than the younger population
- Age-dependent changes in systemic and peritumoral immunity have been reported but require further research in different breast cancer subtypes

**Lung cancer**

- Clear histological (more frequent squamous cell carcinoma) and molecular (increased tumour mutational burden; different *EGFR* mutation subtypes; and less prevalent *ALK*, *ROS1*, and *RET* rearrangement) differences seem to emerge with increasing age that could potentially affect lung cancer treatment
- The expression of PD-1 and PD-L1 does not seem to differ between age groups, yet more research is needed for an in-depth characterisation of the tumour microenvironment to highlight differences between older and younger patients

**Prostate cancer**

- Prostate cancer in older men generally seems to behave more aggressively, established from the higher Gleason grade, higher D'Amico risk group, more frequent luminal B subtype, more prevalent intraductal carcinoma of prostate architecture, higher p53 positivity, and more tumours with a high-risk Decipher score
- Older age hampers the interpretation of serum prostate-specific antigen, hence the use of age-based references or alternative biomarkers (including the PCA3 score and the four kallikreins score) is suggested
- Our literature search yielded no relevant studies evaluating age-related differences in immunological features

**Melanoma**

- Melanoma in older people typically presents with more frequent adverse prognostic histological characteristics and signs of cumulative sun exposure (increased Breslow thickness, more ulceration, higher mitotic rate, more head and neck location, and more nodular malignant melanoma and lentigo maligna melanoma subtypes)
- At the molecular level, increasing age is associated with an increased frequency of *NRAS* mutations and decreased frequency of *BRAF* mutations, suggestive of divergent age-dependent pathways for melanoma development
- Little is known about age-specific differences in the composition of the tumour microenvironment, despite the wide use of the immune checkpoint blockade as a systemic therapeutic approach in melanoma

**Colorectal cancer**

- Colorectal cancer in older patients has marked biological differences compared with younger patients with the disease. At an older age, there is a higher incidence of right-sided tumours, and serrated polyps are more likely to be implicated in carcinogenesis, rather than the conventional adenoma-carcinoma pathway
- At the molecular level, there is a higher prevalence of CpG island methylator phenotype-high tumours, microsatellite instability phenotype, and *BRAF* mutations, that might have profound therapeutic implications in view of the increasing use of targeted approaches and immunotherapy
- The prognostic effect of an immunoscore appears to be independent of age

receptor state (oestrogen receptor and progesterone receptor) is the best studied biological characteristic in breast cancer. Oestrogen or progesterone receptors, or both, are expressed in approximately 80% of breast tumours and positivity for these receptors is associated with a better prognosis and response to antihormonal therapy. Oestrogen and progesterone receptor expression increases progressively with increasing age, but is also notably affected by the menopausal state, which presumably accounts for the greatest difference in oestrogen and progesterone receptor positivity between younger (<35 years) and older (>65 years) adults.[38,40,41,43,50] Tumours in older adults are slightly less likely to be positive for HER2,[41,44,51] which is overexpressed in approximately 15% of breast cancers. HER2+ tumours are associated with aggressive behaviour; however, they are responsive to anti-HER2 therapies, such as trastuzumab.[52]

Some studies evaluated specific biomarkers in the triple negative (ie, oestrogen receptor, progesterone receptor, and HER2 negative) breast cancer subset (not shown). Triple-negative breast cancer occurs much less with increasing age, and if it occurs, the biology of the tumour is more favourable in older groups with less invasive ductal carcinoma and a higher presence of rare subtypes such as triple negative apocrine or lobular carcinoma.[45,53,54]

Triple-negative tumours in older women have lower amounts of the well known proliferation marker Ki67, compared with tumours in younger women (<70 years): in one study 52·0% in the older group versus 12·3% in the younger group had Ki67 expression levels of less than 10%.[55] Furthermore, tumours in older women more often show a normal p53 protein expression compared with tumours in younger women (55·6% *vs* 44·6%, respectively).[55] The p53 protein is produced by *TP53*, a well-known tumour suppressor gene, and its

overexpression is associated with a poor prognosis. Triple-negative breast cancer in older women also tends to express BCL-2[55] more frequently (ie, 79·3% in older *vs* 43·5% in younger women), an anti-apoptotic gene that can cause cancer development by impeding cell death.[56]

### Age-related differences in molecular markers

When looking at the distribution of intrinsic molecular subtypes identified by the gene expression profiling test Prediction Analysis of Microarray 50 gene expression profiles (PAM50), which is based on the mRNA expression of 50 genes, luminal A and B tumours (both oestrogen receptor positive HER2 negative tumours, but with a low differentiation grade for luminal A and a high grade for luminal B) are more common in women aged 70 years or older, compared with younger women.[42,45–47] The HER2-enriched subtype (independent of oestrogen receptor status) declines slightly with age,[42,45,46] whereas for the basal-like signature, a more prominent age-related decrease is consistently reported in all studies.[45–47]

When evaluating tumour driver mutations in primary breast cancer according to age, mutated *TP53*, *AKT1* (targetable with *AKT* inhibitors), *GATA3*, and *MAP2K4* were less frequently found in older people (>65 years) than younger people,[41,42,47,48,57–60] although some data were conflicting. In contrast, other tumour mutations occur more frequently in older individuals, such as *PIK3CA* (targetable with *PIK3CA* inhibitors), *MLL3*, *CDH1*, and *MAP3K1* mutations.[41,42,47–49,57,61–65] As such, the proportion of patients that qualify for the targeted treatment of a specific molecular alteration is determined by age, although it still needs to be investigated whether the effectiveness differs according to age.

**Lung cancer**

**Age-related differences in histology and subtypes**

SCC↑ Adenocarcinoma↓* SCLC*†

| Reference | Age group | n | SCC (%) | Adenocarcinoma (%) | SCLC (%) | Other (%) |
|---|---|---|---|---|---|---|
| Giroux et al (2012)[73] | <70 | 101 | **10·9** | **57·4** | **13·8** | **17·9** |
| | ≥70 | 92 | **27·2** | **39·1** | **13·0** | **20·7** |
| Zhong et al (2018)[74] | <40 | 272 | **5·9** | **72·8** | **2·2** | **19·1** |
| | >60 | 167 | **29·3** | **53·9** | **12·0** | **4·8** |

Differentiation*†

| Reference | Age group | n | Poor differentiation (%) |
|---|---|---|---|
| Zhong et al (2018)[74] | <40 | 272 | **35·3** |
| | >60 | 167 | **56·3** |
| Goodgame et al (2009)[75] | <70 | 429 | **31·0** |
| | ≥70 | 286 | **37·1** |
| Sterlacci et al (2012)[76] | <70 | 283 | 53·7 |
| | ≥70 | 100 | 50·0 |

**Age-related differences in molecular markers**

EGFR mutations Exon 19 deletion↓ L85R↑

| Reference | Age group | n | Exon 19 deletion (%) | L85R (%) | Other (%) | Wild type (%) |
|---|---|---|---|---|---|---|
| Zhong et al (2018)[74] | <40 | 272 | **30·4** | **8·7** | **2·2** | **58·7** |
| | >60 | 167 | **14·0** | **21·1** | **8·8** | **56·1** |

*KRAS* mutations↑* *BRAF* mutations*†

| Reference | Age group | n | *KRAS* mutation (%) | *BRAF* mutation (%) |
|---|---|---|---|---|
| Sacher et al (2016)[77] | 40-49 | 210 | **13·3** | .. |
| | ≥70 | 479 | **27·3** | .. |
| | 40-49 | 195 | .. | 0·5 |
| | ≥70 | 414 | .. | 2·2 |
| Tsao et al (2012)[78] | ≤70 | 200 | 15·8 | 1·4 |
| | >70 | 55 | 3·7 | 0·9 |
| Dong et al (2016)[79] | 40-49 | 74 | 1·4 | .. |
| | ≥60 | 149 | 4·6 | .. |
| Boldrini et al (2018)[80] | <50 | 44 | 29·5 | .. |
| | >50 | 44 | 47·7 | .. |

*ALK*r↓ *RET*r↓ *ROS1*r↓†

| Reference | Age group | n | ALKr (%) | RETr (%) | ROS1r (%) |
|---|---|---|---|---|---|
| Sacher et al (2016)[77] | 40-49 | 203 | **12·8** | .. | .. |
| | ≥70 | 439 | **0·9** | .. | .. |
| | 40-49 | 154 | .. | .. | 1·9 |
| | ≥70 | 344 | .. | .. | 1·4 |
| Dong et al (2016)[79] | 40-49 | 74 | **14·9** | **5·4** | .. |
| | ≥60 | 149 | **3·4** | **0·0** | .. |
| Ye et al (2014)[81] | <40 | 36 | 5·6 | 2·8 | .. |
| | ≥40 | 87 | 4·6 | 1·1 | .. |

*PDL1*+† *PD1*+†

| Reference | Age group | n | PDL1+ (%) | PD1+ (%) |
|---|---|---|---|---|
| Velcheti et al (2013)[82] | <70 | 327 | 26·9‡ | .. |
| | ≥70 | 125 | 32·0‡ | .. |
| Lin et al (2015)[83] | ≤65 | 40 | 55·0§ | 32·5 |
| | >65 | 16 | 50·0§ | 31·3 |

***Figure 2:*** **Differences in lung cancer biology according to age**
Arrow pointing down indicates that all data point to a decrease with age. Arrow pointing up indicates that all data point to an increase with age. ALKr=anaplastic lymphoma kinase relocation. EGFR=epidermal growth factor receptor. RETr=RET rearrangement. ROS1r=ROS1 rearrangement. SCC=squamous cell carcinoma. SCLC=small cell lung cancer. *Data are not perfectly consistent. †There are no clear age differences. ‡Only tumor PD-L1 expression. §Both tumour and immune PD-L1 expression. Bold values indicate a statistically significant difference between the young and old group in each study (p<0·05).

### Immunological features and their association with age

The detection of stromal tumour-infiltrating lymphocytes, assessed on routine haematoxylin and eosin-stained slides, has emerged as a robust prognostic and predictive biomarker in patients with breast cancer.[66,67] An increase in stromal tumour-infiltrating lymphocyte has predicted a response to neoadjuvant chemotherapy in all molecular subtypes assessed, but was also associated with a benefit in overall survival for both triple-negative breast cancer and HER2-positive breast cancer.[68] With increasing age, a decrease in stromal tumour-infiltrating lymphocyte percentage is observed both for patients with breast cancer in general[68] and with triple negative breast cancer specifically.[69] Notably, in oestrogen receptor-positive and HER2-negative tumours, higher stromal tumour-infiltrating lymphocyte amounts are only associated with a younger age in invasive lobular carcinoma but not in invasive ductal carcinoma tumours.[70] In addition, age-dependent changes in systemic and peritumoral immunity have been reported in luminal B subtype tumours.[71] An age-related decrease was observed for total lymphocytic tumoral infiltration, with an altered immune constitution (decreased densities of CD3+, CD5+, and especially the cytotoxic CD8+ cells).[71]

## Lung cancer

Lung cancer mainly affects older adults and is often not amenable for curative treatment at diagnosis, and is therefore a notable cause of death in this age group. The mean age at diagnosis is 71 years.[72] The main age-related tumour biology characteristics are summarised in figure 2 and the panel.

### Age-related differences in histology

In general, older adults with non-small cell lung cancer (NSCLC) are more frequently diagnosed with squamous cell carcinoma (SCC) and less frequently with adeno-carcinoma,[73,74] whereas data on the age distribution of

small cell carcinomas are not conclusive.[73] Adenocarcinoma and SCC have different outcomes in lung cancer, with significantly higher stage-specific 5-year overall survival rates for adenocarcinoma compared with SCC. Furthermore, there is insufficient data supporting a variation in the differentiation grade between age groups, although a trend towards poorer tumour differentiation at an older age has been reported.[74–76]

### Age-related differences in molecular markers

The tumour mutational burden (total number of somatic mutations) increases with age.[84] Moreover, in non-squamous NSCLC, broad molecular screening is currently the standard of care because of the availability of targeted therapies. For example, *EGFR* mutations are present in 14–38% of patients with NSCLC and are associated with a favourable outcome.[85,86] Remarkably, the specific tumour genomic *EGFR* alteration differs depending on age. Although exon 21 L858R mutations occur more frequently in the older population, exon 19 deletions are more frequent within younger patients.[74] Noticeably, sensitivity to *EGFR* tyrosine-kinase inhibitors, such as first-generation gefitinib, depends on the underlying mutation subtype with significantly longer progression-free survival and overall survival with exon 19 deletion compared with L858R mutation.[87]

*KRAS* mutations are frequent in NSCLC (20–40%), tend to be associated with a worse outcome,[86,88] and are more prevalent in the older population, although reported age-dependent differences are not consistent.[77–80,89,90] However, this variation in mutational frequency can probably largely be explained by differences in the study population, as *KRAS* mutations are typically present in smokers and those with non-squamous NSCLC. The presence of *BRAF* mutations, targetable by *BRAF* inhibitors, is rare and do not clearly differ by age, although the specific *BRAF* V600E mutation might be more prevalent in older people (compared with melanoma).[77–79,91] In contrast, *ALK, ROS1,* and *RET* rearrangements, all targetable proto-oncogenes with tyrosine-kinase activity, are most prevalent within the younger age category of 40–49 years.[77,79,81,92–96] Finally, for other clinically relevant molecular alterations, such as the *MET* exon 14 skipping mutation that occurs in 3–4% of NSCLC[97] and is also targetable,[98,99] no clear age-related differences have been reported.

### Immunological features and their association with age

The expression of the immune checkpoints PD-1 and PD-L1 does not seem to change notably with age.[82,83,100] Some data suggest an increased PD-1 expression with older age on the surface of T cells, pointing to exhaustion. This finding is in line with the lower T cell activity observed in the older population. Myeloid-derived suppressor cells, a heterogeneous population of immature myeloid cells that can express PD-L1 on their surface, are reported to play a role in lung cancer immune evasion and disease progression by accumulating in the tumour microenvironment, thereby suppressing immune function by inhibiting the activation and proliferation of T cells.[101,102] A possible role of myeloid-derived suppressor cells in the age-related susceptibility of lung cancer has been proposed in ageing mice, yet needs to be confirmed in humans.[103]

## Prostate cancer

Prostate cancer is the second most commonly diagnosed cancer and the fifth leading cause of cancer death among men worldwide.[104] 60% of patients are aged 65 years and older at diagnosis, and cancer deaths in men aged 70 years and older are expected to almost double between 2018 and 2030.[105] An overview of the age-specific differences in prostate tumour biology can be found in figure 3 and the panel.

**Prostate cancer**

**Age-related differences in histology and subtypes**

Gleason grade↑

| Reference | Age group | n | Gleason Score ≥7 (%) |
|---|---|---|---|
| Pettersson et al (2018)[106] | 55–69 | 55 478 | **47·4** |
| | 70–79 | 43 427 | **65·9** |
| | ≥80 | 22 487 | **81·0** |

D'Amico risk group↑

| Reference | Age group | n | High Risk (%) |
|---|---|---|---|
| Zhang et al (2013)[107] | <65 | 22 914 | **11·0** |
| | 65–74 | 29 680 | **14·8** |
| | ≥75 | 17 751 | **26·3** |

IDC-P↑

| Reference | Age group | n | IDC-P positive (%) |
|---|---|---|---|
| Dinerman et al (2017)[108] | <50 | 9 896 | **0·12** |
| | 50–74 | 146 756 | **0·15** |
| | ≥75 | 3 125 | **0·38** |

**Age-related differences in molecular and serological markers**

Serum PSA↑

| Reference | Age group | n | PSA ≥4 in Gleason ≤6 in T1cN0M0 (%) | PSA ≥4 in Gleason 7 in T1cN0M0 (%) | PSA ≥4 in Gleason ≥8 in T1cN0M0 (%) |
|---|---|---|---|---|---|
| Zhang et al (2013)[107] | <60 | 8120 | **85·0** | - | .. |
| | 60–69 | 16 826 | **90·7** | - | .. |
| | ≥70 | 16 654 | **91·9** | - | .. |
| Zhang et al (2013)[107] | <60 | 2785 | .. | **91·3** | .. |
| | 60–69 | 7284 | .. | **93·8** | .. |
| | ≥70 | 11 525 | .. | **93·4** | .. |
| Zhang et al (2013)[107] | <60 | 605 | .. | .. | 95·5 |
| | 60–69 | 1952 | .. | .. | 94·1 |
| | ≥70 | 4598 | .. | .. | 94·0 |

Somatic mutations: Decipher↑ p53↑ AR↓* ESR1↑* ESR2↑* *ERG:TMPRSS2*↓

| Reference | Age group | n | High Decipher risk group (%) |
|---|---|---|---|
| Goldberg et al (2020)[109] | <65 | 3393 | **27·9** |
| | 65–74 | 4294 | **33·8** |
| | ≥75 | 1747 | **44·9** |

| Reference | Age group | n | p53 positive (%) |
|---|---|---|---|
| Calvocoressi et al (2018)[110] | <70 | 373 | **24·4** |
| | 70–79 | 535 | **25·1** |
| | ≥80 | 63 | **44·3** |

| Reference | Age group | n | High AR expression (%) | High ESR1 expression (%) | High ESR2 expression (%) |
|---|---|---|---|---|---|
| Jędroszka et al (2017)[111] | ≤50 | 35 | **65·7** | **31·4** | **31·4** |
| | 51–70 | 425 | **45·6** | **8·5** | **57·2** |
| | >70 | 37 | **45·9** | **32·4** | **43·2** |

| Reference | Age group | n | ERG positive (%) |
|---|---|---|---|
| Schaefer et al (2013)[112] | <61 | 530 | **59·4** |
| | ≥62 | 509 | **45·6** |

***Figure 3:*** **Differences in prostate cancer biology according to age**
Arrow pointing down indicates that all data point to a decrease with age. Arrow pointing up indicates that all data point to an increase with age. AR=androgen receptor. ESR1=oestrogen receptor 1. ESR2=oestrogen receptor 2. IDC P=intraductal carcinoma of the prostate. PSA=prostate-specific antigen. *Data are not perfectly consistent. Bold values indicate a statistically significant difference between the young and old group in each study (p<0·05). For the D'Amico risk group, high-risk disease was defined as a prostate-specific antigen of 20 ng/mL or more or a Gleason grade of 8 or more, or both. Decipher refers to the Decipher genomic classifier.

### Age-related differences in histology

Most prostate cancers develop in the peripheral zone of the prostate, which does not show a significant increase in volume with age (unlike the transitional zone, which increases in size as men get older).[113] Older patients have a higher Gleason grade[106] (the higher grade, the more aggressive the tumour) and D'Amico[107] risk classification (a risk score incorporating stage, Gleason Grade, and prostate-specific antigen) at diagnosis. Furthermore, the presence of some tumour characteristics has been associated with a poor prognosis. For example, intraductal carcinoma of the prostate, a pathological entity characterised by carcinoma cells growing or extending into the prostatic ducts or acini, or both, which results in a more locally advanced disease and a higher risk of biochemical recurrence after definitive treatment using prostatectomy or brachytherapy.[114] Intraductal carcinoma of the prostate architecture is also associated with older age, being more common in patients older than 70 years, albeit still rare (<1% of prostate cancers).[108,115]

### Age-related differences in molecular and serological markers

Screening for prostate-specific antigen has been the subject of much controversy over many years.[105,116] Patient age might be one of the main factors influencing the sensitivity and specificity of prostate-specific antigen in predicting a positive biopsy,[117] and the use of an age-based reference standard has been suggested. In older men, a prostate-specific antigen higher than or equal to 4 nmol/L is frequently associated with a prostate cancer with a Gleason score of 6 or more (with less than 6 now not considered to be a cancer), and not necessarily a more aggressive tumour requiring a radical treatment.[107] The International Society of Uro-Pathologists (ISUP) grade is a new histological grading system for prostate cancer that has largely replaced the conventional Gleason score. A cancer with an ISUP grade of 2 or more is more likely to leak prostate-specific antigen into the blood than ISUP grade 1 cancer; therefore, resulting in higher amounts of prostate-specific antigen. This process is why higher amounts of prostate-specific antigen are related to the presence of higher ISUP grade prostate cancer, and both seem to happen more in older men.[118] The interpretation of prostate-specific antigen amounts with age is confounded by the fact that there is an enlargement of the prostate gland with age, and both benign and malignant prostate cells produce prostate-specific antigen, and for this reason, the prostate-specific antigen dynamics (eg, prostate-specific antigen doubling time and prostate-specific antigen velocity) can provide information complementary to an individual prostate-specific antigen measurement.

PCA3 is a urine biomarker that can improve the detection of prostate cancer. Since age was the strongest independent predictor of PCA3 score, the use of an age-adjusted PCA3 score has also been suggested.[119] Data also showed that PCA3 score increases with age and that age-specific PCA3-score interpretation leads to a higher diagnostic accuracy.[120] Another promising marker is the 4K score, a panel of four kallikreins measured in blood. This score has also improved the ability to predict lethal prostate cancer, mainly for men older than 69 years.[121]

The PAM50 classifier divides prostate cancer on a molecular basis into luminal A, luminal B, and basal subtypes, with luminal B being associated with worst prognosis, followed by basal subtype, whereas luminal A tumours have a better prognosis.[122] The prevalence of the adverse phenotype luminal B increases with age in patients with ISUP grade 1 and 2 (<60 years, 22·7% in ISUP grade 1 and 40·2% in ISUP grade 2 *vs* ≥80 years, 29·7% in ISUP grade 1 and 49·1% in ISUP grade 2), reflecting a more aggressive behaviour even of low ISUP grade tumours in older patients. On the contrary, no differences between age groups can be found in ISUP grade 3–5 tumours.[109]

The Decipher genomic classifier is a gene expression profiling test including 22 mRNA. Higher scores are an independent predictor for the development of metastatic disease, regardless of Gleason score and other disease characteristics. Older age was consistently associated with a high-risk Decipher score, even in patients with an ISUP grade of 1,[109] reflecting the more aggressive behaviour of prostate tumours in older people. Tumours in older men also have significantly more p53 immunoreactivity (the abnormal protein produced by the mutant *TP53* gene is more stable and tends to accumulate in the nucleus, which allows for detection via an immunohistochemical stain) and high micro-vessel density than younger men,[110] again suggesting that tumours are biologically more aggressive in older men. Also, the epithelial-to-mesenchymal transition gene expression profile seems to differ notably between ages,[111] with older individuals having a higher downregulation of transcription factors and mesenchymal markers as well as the overexpression of adhesion factors that are associated with a more aggressive and invasive phenotype, independent of Gleason score. In parallel, there is also a change in hormone receptor expression dominance with age, shifting from a predominant expression of androgen receptor in younger patients, to predominantly oestrogen receptors 1 and 2 in older patients. Several investigators suggest that this shift might be caused by the occurrence of andropause in the oldest age group. On the other hand, the *TMPRSS2:ERG* gene fusion, leading to overexpression of *ERG*, is frequently encountered in prostate cancer and has been associated with metastatic disease.[123] *ERG*-positive prostate tumours are more common in younger patients,[112] and a meta-analysis[124] showed that the prevalence of *TMPRSS2:ERG* fusion was more common in young men (<65 years) with prostate cancer.

## Melanoma

With a median age of 65 years at diagnosis and as the fifth most common malignancy with age-adjusted

incidence rates rising on average by 1·5% per year (in the period 2008–2017),[125] melanoma represents a substantial tumour burden in the older population. Melanoma in the older adult typically presents with both distinct histopathological features and molecular differences compared with melanoma in younger people, suggesting that different biological mechanisms are causing melanoma development and growth (figure 4 and panel).

## Age-related differences in histology

Compared with younger patients, older patients typically present with a higher frequency of adverse prognostic histological markers, with a greater mean Breslow

**Melanoma**

**Age-related differences in histology and subtypes**

| | Reference | Age group | n | ≤1·00 mm (%) | 1·01–2·00 mm (%) | 2·01–4·00 mm (%) | >4·00 mm (%) | Unknown (%) |
|---|---|---|---|---|---|---|---|---|
| Breslow thickness ↑ | Schuurman et al (2020)[126] | <70 | 42 474 | **58·1** | **22·1** | **11·3** | **5·2** | **3·3** |
| | | 70–79 | 9004 | **46·5** | **20·6** | **17·4** | **11·6** | **3·9** |
| | | 80–89 | 4372 | **35·0** | **18·5** | **21·4** | **19·4** | **5·7** |
| | | ≥90 | 696 | **22·8** | **13·5** | **24·1** | **32·0** | **7·6** |
| | Weiss et al (2016)[127] | ≤ 45 | 28 316 | **76·9** | **13·6** | **5·9** | **3·6** | .. |
| | | 46–65 | 60 322 | **73·2** | **14·5** | **7·4** | **4·9** | .. |
| | | >65 | 60 923 | **64·7** | **15·3** | **11·3** | **8·7** | .. |

| | Reference | Age group | n | Present (%) |
|---|---|---|---|---|
| Ulceration ↑ | Weiss et al (2016)[127] | ≤ 45 | 28 181 | **8·1** |
| | | 46–65 | 60 083 | **10·8** |
| | | >65 | 61 150 | **17·0** |
| | Ciocan et al (2013)[128] | <70 | 1134 | **12·4** |
| | | ≥70 | 487 | **20·9** |

| | Reference | Age group | n | Mitotic figures per mm² |
|---|---|---|---|---|
| Mitotic rate ↑ | Macdonald et al (2011)[129] | <70 | 373 | **2·7** |
| | | ≥70 | 237 | **3·6** |
| | Shen et al (2014)[130] | <50 | 469 | **2·0** |
| | | 50–70 | 623 | **2·7** |
| | | >70 | 408 | **4·0** |

| | Reference | Age group | n | Head and neck (%) | Trunk (%) | Extremities (%) | Unknown (%) |
|---|---|---|---|---|---|---|---|
| Location of the primary tumour: Head and neck ↑ Trunk ↓ Extremities* | Schuurman et al (2020)[126] | <70 | 42 474 | **9·5** | **42·0** | **48·4** | **0·1** |
| | | 70–79 | 9004 | **19·9** | **33·1** | **46·8** | **0·2** |
| | | 80–89 | 4372 | **32·6** | **21·5** | **45·6** | **0·3** |
| | | ≥90 | 696 | **45·3** | **13·9** | **40·4** | **0·4** |
| | Ciocan et al (2013)[128] | <70 | 1134 | **8·7** | **41·5** | **49·8** | .. |
| | | ≥70 | 487 | **29·4** | **28·6** | **42·0** | .. |
| | Cavanaugh-Hussey et al (2015)[131] | <60 | 82 348 | **11·7** | **44·0** | **40·7** | **3·6** |
| | | 60–79 | 61 363 | **24·1** | **30·7** | **39·2** | **6·0** |
| | | ≥80 | 23 102 | **35·8** | **20·5** | **36·3** | **7·4** |

| | Reference | Age group | n | SSMM (%) | NMM (%) | LMM (%) | Other or unspecified (%) |
|---|---|---|---|---|---|---|---|
| Histological subtypes: SSMM ↓ NMM ↑ LMM ↑ | Schuurman et al (2020)[126] | <70 | 42 474 | **72·8** | **10·4** | **2·3** | **14·6** |
| | | 70–79 | 9004 | **59·6** | **15·6** | **8·9** | **15·9** |
| | | 80–89 | 4372 | **46·5** | **20·5** | **13·9** | **19·1** |
| | | ≥90 | 696 | **32·9** | **26·9** | **15·5** | **18·8** |
| | Ciocan et al (2013)[129] | <70 | 1134 | **77·4** | **11·0** | **2·0** | **9·6** |
| | | ≥70 | 487 | **55·9** | **21·8** | **10·7** | **11·6** |
| | Cavanaugh-Hussey et al (2015)[131] | <60 | 73 348 | **34·2** | **5·3** | .. | **60·5** |
| | | 60–79 | 62 363 | **25·2** | **6·8** | .. | **68·0** |
| | | ≥80 | 23 102 | **18·5** | **10·3** | .. | **71·2** |

**Age-related differences in molecular markers**

| | Reference | Age group | n | *BRAF* mutation (%) | V600E† (%) | V600K† (%) | non V600† (%) |
|---|---|---|---|---|---|---|---|
| *BRAF* mutations: Overall ↓ V600 ↓ Non V600E ↑ | Bauer et al (2011)[132] | ≤ 45 | 118 | **67·8** | .. | .. | .. |
| | | 46–70 | 278 | **47·8** | .. | .. | .. |
| | | >70 | 144 | **31·9** | .. | .. | .. |
| | Menzies et al (2011)[133] | ≤50 | 86 | **66·3** | **84·2** | **8·8** | **7·0** |
| | | 51–70 | 161 | **45·3** | **69·9** | **26·0** | **4·1** |
| | | >70 | 65 | **21·5** | **50·0** | **21·4** | **28·6** |
| | Devitt et al (2011)[134] | <60 | 161 | **51·6** | .. | .. | .. |
| | | ≥60 | 88 | **33·0** | .. | .. | .. |

| | Reference | Age group | n | *NRAS* mutation |
|---|---|---|---|---|
| *NRAS* mutations ↑ | Devitt et al (2011)[134] | <60 | 161 | 13·7 |
| | | ≥60 | 88 | 15·9 |
| | Thomas et al (2015)[135] | <50 | 299 | **8·4** |
| | | 50–69 | 355 | **15·2** |
| | | ≥70 | 240 | **17·9** |
| | Heppt et al (2017)[136] | <50 | 52 | 17·3 |
| | | 50–69 | 90 | 25·6 |
| | | ≥70 | 70 | 30·0 |

***Figure 4:*** **Differences in melanoma biology according to age**

Arrow pointing down indicates that all data point to a decrease with age. Arrow pointing up indicates that all data point to an increase with age. LMM=lentigo maligna melanoma. NMM=nodular malignant melanoma. SSMM=superficial spreading malignant melanoma. *There are no clear age differences. Bold values indicate a statistically significant difference between the young and old group in each study (p<0·05). †Indicates % compared with total *BRAF* mutations.

tumour thickness,[126,127,129] higher frequency of ulceration,[127,128] and a higher mitotic index.[129,130] This difference could partly be explained by a delay in diagnosis because of difficulties in self-skin examination (eg, visual impairment and physical limitations), the absence of a partner for a home examination,[128] or simply by physical impairments, practical issues, or both, making doctor visits more difficult. It could also be because of the clinical presentation of the lesion making self-diagnosis more difficult. The nodular melanoma subtype, for example, often does not have the classic asymmetry, border irregularity, colour variation, and diameter of more than 6 mm criteria, hence making this lesion more difficult to detect to the untrained eye.[137,138] In addition, melanoma in the older adult is more often associated with clinical signs of chronic, cumulative sun exposure (photoaging), such as solar elastosis.[139,140] Therefore, it is not surprising that older patients preferentially develop primary melanoma in habitually sun-exposed areas, such as the head and neck, face, and dorsal-distal side of the extremities.[126,128,131] Notably, several studies indicate that melanoma located on the scalp is associated with a higher incidence of brain metastases[141,142] and represents an independent predictor for worse melanoma-specific survival.[143,144]

When comparing the distribution of the histopathological subtypes in different age groups, it is notable that nodular melanoma, an aggressive subtype with a disproportionally high case-fatality rate compared with the incidence rate,[145] is more frequent in the older patient. In contrast, superficial spreading melanoma, the most common subtype in young patients, is less frequent at an older age.[126,128,131] Lentigo maligna melanoma, a lentigo maligna that invades the dermis, can be considered the classic subtype associated with chronic sun-damage and is, unsurprisingly, more frequent at an older age.[126,128]

### Age-related differences in molecular markers

*BRAF* mutation is a molecular hallmark in approximately 50% of primary melanomas. This mutation does not influence the disease-free interval after the primary diagnosis, yet it shows a trend towards a poorer outcome in stage 4 disease.[146–148] Notably, the prevalence of *BRAF* mutation is inversely proportional to age and solar elastosis.[132] Younger patients with metastatic melanoma have a high prevalence of *BRAF* mutations with a predominance of the V600E genotype.[132–134] In contrast, older patients have a lower prevalence of *BRAF* mutations overall, but within the group of *BRAF* alterations there is a higher proportion of non-V600E genotypes, predominantly V600K.[132–134] Furthermore, an increased frequency of the *NRAS* mutation is observed with increasing age and is associated with a worse outcome.[134,136,149] *NRAS*-targeted therapies are still in the stage of clinical trials, but *MEK* inhibition has been used in clinical trials[150] and *NRAS*-mutated melanoma might have an increased benefit from immune-based therapies compared with other genetic subtypes.[151]

### Immunological features and their association with age

The immune system plays a role in controlling tumour growth in melanoma. Ageing of the immune system is believed to cause an absence of immune surveillance, hence facilitating melanoma development and growth. However, little is known about the differences in the composition of the tumour environment between young and old patients. The presence or absence of a lymphocytic infiltrate in the vertical growth phase of a primary melanoma is needed to predict patient outcomes in terms of lymph node metastasis, disease recurrence, and melanoma-specific survival.[152–154] The lymphocytic infiltrate is defined as brisk, that is, that there is diffuse infiltration of lymphocytes in the entire invasive component or across the entire base of the vertical growth phase, or non-brisk, that is, that there is focal infiltration of lymphocytes. Notably, no significant differences between different age groups (eg, a brisk infiltration pattern in 15·5% of patients <50 years *vs* 12·8% in patients aged 70 years or older) were reported in the literature.[129,135]

## Colorectal cancer

Patients with colorectal cancer are diagnosed at a median age of around 70 years. In the UK and France, approximately 45% of cases are identified in patients aged older than 75 years,[155–158] with the age group with the highest incidence being 85–89 years. An overview of the age-specific differences in colorectal cancer biology can be found in figure 5 and the panel.

### Age-related differences in histology

Colorectal cancer typically arises from genetic mutations and epigenetic modifications affecting different molecular pathways. Depending on the germline and somatic mutation burden, many different mechanisms are involved, making this a complex and heterogeneous disease. Approximately 80% of sporadic colorectal cancer follows the so-called conventional adenoma-carcinoma pathway, whereby the mechanisms of epithelial renewal are disrupted either through exogenous (eg, diet, smoking, alcohol, or obesity) or endogenous (eg, chronic inflammation or oxidative stress) factors.[175] In this setting, adenomatous polyps can evolve into dysplastic lesions and eventually lead to the development of colorectal cancer. The molecular pathway involved is the chromosomal instability pathway, which is characterised by deletions, insertions, and a loss of heterozygosity. The most important genes involved are *APC*, *TP53*, and *DCC*.[176,177] For the other approximately 20% of colorectal cancer cases, an alternative pathway for colorectal cancer carcinogenesis exists, which appears to be more common in older patients. Implicated in this pathway are so-called serrated polyps (traditional serrated adenomas or sessile serrated lesion).[178] These polyps are more likely to be found in the right colon, have a higher malignant potential, and are rarely present with mutations in the *APC* gene.[179] In addition, their natural course is less

predictable and time to malignant transformation can be quite short. Older patients have a higher incidence of right-sided tumours, reaching approximately 50% in patients over 80 years.[159,160,180] In this age group, women have a more than 10% higher incidence than men for right-sided tumours. Biologically, right-sided tumours show a particular appearance, with mucosal microbiota being characterised almost universally by invasive bacterial aggregates.[181] Generally, they are associated with a worse prognosis in the metastatic disease setting as compared with left-sided tumours.[182] The histological grading of colorectal cancer, including the degree of tumour differentiation, does not change with age.[161,162] Similarly, the histological subtype generally does not differ notably between young and older patients, with equally prevalent adenocarcinoma and signet ring cell carcinoma; but with the exception of mucinous adenocarcinoma, which is more common in the older patient.[163] Nonetheless, adenocarcinoma is by far the most prevalent subtype in all age groups.[163]

## Age-related differences in molecular markers

As stated earlier, serrated polyps are more likely to be encountered in older patients. There are two main molecular mechanisms implicated in the malignant transformation from benign serrated polyps to colorectal cancer: CpG island methylator phenotype (CIMP) and microsatellite instability (MSI). The CIMP pathway is based on epigenetic instability and is characterised by the hypermethylation of several gene promoter regions, such as hMLH1, which is abundant in CpG islands. MSI results from the defective mismatch repair mechanism leading to a predisposition to mutations and drives one of the key mechanisms of oncogenesis in colorectal cancer. CIMP-high tumours have a distinct clinical and molecular profile. They are mostly associated with a right-sided colon location, poor histological differentiation, the presence of *BRAF* mutations, and an older age.[164–166] CIMP can exist with or without MSI, but 70–80% of MSI tumours can be attributed to CIMP.[165,183–185] Therefore, it is unsurprising that there is a high prevalence of the MSI phenotype and *BRAF* mutations in older patients with colorectal cancer, especially those older than 75 years.[164,165,167–171] MSI tumours are more common in women, although there is no clear sex difference for the *BRAF* mutation.[186] The overall incidence of *BRAF* mutations in colorectal cancer is 10–15%, but as already mentioned, it appears to be higher in older patients. The presence of *BRAF* mutations without MSI results in a worse prognosis in a metastatic setting.[187] However, phase 3 trials have shown a benefit for the combination of *BRAF* and *EGFR* (and *MEK*) inhibitors as a second and subsequent line of treatment for patients with metastatic colorectal cancer.[188]

*KRAS* mutations, associated with a poor prognosis in patients with colorectal cancer,[172] are also common in right-sided tumours and age-specific differences might also exist, but are not clearly documented in the

**Colorectal cancer**

**Age-related differences in histology and subtypes**

Tumour sidedness: Right colon↑ Left colon* Rectum↓

| Reference | Age group | n | Right colon (%) | Left colon (%) | Rectum (%) |
|---|---|---|---|---|---|
| Yang et al (2018)[159] | <60 | 78105 | **34·8** | **33·3** | **31·9** |
| | 60–69 | 64942 | **45·2** | **29·9** | **31·9** |
| | ≥70 | 127343 | **59·0** | **24·6** | **31·9** |
| Kotake et al (2015)[160] | ≤64 | 18620 | **23·0** | **31·0** | **31·9** |
| | 64–79 | 18518 | **32·7** | **32·2** | **31·9** |
| | ≥80 | 3713 | **43·0** | **27·6** | **31·9** |

Differentiation* (grade)

| Reference | Age group | n | Grade 1 (%) | Grade 2 (%) | Grade 3 (%) | Grade 4 (%) |
|---|---|---|---|---|---|---|
| Patel et al (2013)[161] | ≤64 | 8925 | **8·8** | **69·6** | **20·9** | **0·6** |
| | 65–79 | 13761 | **8·8** | **69·1** | **21·4** | **0·7** |
| | ≥80 | 8220 | **8·1** | **67·6** | **23·4** | **0·8** |
| Derwinger et al (2010)[162] | <53 | 226 | 5·0 | 61·3 | 24·7 | 9·0 |
| | 53–84 | 1770 | 5·4 | 69·4 | 19·6 | 5·6 |
| | ≥85 | 224 | 5·1 | 66·0 | 24·7 | 4·2 |

Histological subtypes: Adenocarcinoma and SRCC* MAC↑

| Reference | Age group | n | Adenocarcinoma (%) | MAC (%) | SRCC (%) |
|---|---|---|---|---|---|
| Wu et al (2019)[163] | <60 | 111818 | **91·6** | **7·1** | **1·3** |
| | 60–74 | 141249 | **91·5** | **7·5** | **1·0** |
| | ≥75 | 131929 | **89·6** | **9·4** | **1·0** |

**Age-related differences in molecular markers**

CIMP↑

| Reference | Age group | n | CIMP high or positive (%) |
|---|---|---|---|
| Vedeld et al (2017)[164] | <60 | 193 | **10·9** |
| | 60–74 | 430 | **18·6** |
| | ≥75 | 490 | **21·2** |
| Barault et al (2008)[165] | ≤65 | 156 | **5·8** |
| | 66–75 | 184 | **14·1** |
| | >75 | 242 | **25·6** |
| Jia et al (2016)[166] | ≤65 | 501 | **10·2** |
| | 66–75 | 456 | **12·1** |
| | >75 | 428 | **19·4** |

MSI↑ (dMMR)

| Reference | Age group | n | MSI (dMMR) (%) |
|---|---|---|---|
| Vedeld et al (2017)[164] | <60 | 193 | **11·9** |
| | 60–74 | 430 | **14·7** |
| | ≥75 | 490 | **19·2** |
| Barault et al (2008)[165] | ≤65 | 154 | **3·9** |
| | 66–75 | 183 | **10·9** |
| | >75 | 242 | **22·7** |
| Bläker et al (2019)[167] | <65 | 642 | **10·3** |
| | 65–74 | 698 | **8·7** |
| | ≥75 | 655 | **15·0** |
| Aasebø et al (2019)[168] | ≤75 | 383 | 5·5 |
| | >75 | 200 | 9·5 |
| Aparicio et al (2014)[169] | <75 | 482 | **10·8** |
| | ≥75 | 272 | **19·5** |

*BRAF* mutations↑

| Reference | Age group | n | *BRAF* mutation (%) |
|---|---|---|---|
| Bläker et al (2019)[167] | <65 | 642 | **4·8** |
| | 65–74 | 698 | **6·6** |
| | ≥75 | 655 | **12·5** |
| Sorbye et al (2015)[170] | <60 | 106 | 17·9 |
| | 60–75 | 190 | 20·0 |
| | >75 | 150 | 23·3 |
| Phipps et al (2012)[171] | <60 | 955 | **6·3** |
| | 60–69 | 619 | **17·0** |
| | ≥70 | 406 | **20·2** |

*KRAS* mutations*†

| Reference | Age group | n | *KRAS* mutation (%) |
|---|---|---|---|
| Dai et al (2020)[172] | <60 | 3,821 | **39·4** |
| | 60–79 | 4,171 | **41·7** |
| | ≥80 | 991 | **37·2** |
| Farina-Sarasqueta et al (2010)[173] | <60 | 72 | 26·4 |
| | 60–72 | 146 | 34·9 |
| | ≥73 | 73 | 41·1 |
| Berg et al (2010)[174] | <50 | 45 | 28·9 |
| | 51–70 | 67 | 29·9 |
| | >70 | 69 | 34·8 |

***Figure 5:*** **Differences in colorectal cancer biology according to age**
Arrow pointing down indicates that all data point to a decrease with age. Arrow pointing up indicates that all data point to an increase with age. *There are no clear age differences. †Data are not perfectly consistent. Bold values indicate statistically significant difference between the young and old group in each study (p<0·05). CIMP=CpG island methylator phenotype. dMMR=deficient mismatch repair. MAC=mucinous adenocarcinoma. MSI=microsatellite instability. SRCC=signet ring cell carcinoma.

### Search strategy and selection criteria

For this narrative Review, the references were identified through searches of PubMed with the search terms "aging", "older patients", "elderly", "breast cancer", "melanoma", "lung cancer", "colorectal cancer", and "prostate cancer", published at the latest by May, 2021 . Articles were also identified through searches of the authors' own files. Further references were extracted by manually searching the bibliographies of all selected articles. We only included articles in English that were published in peer-reviewed journals. Epidemiological data was also retrieved from different cancer registries, including the Surveillance, Epidemiology, and End Results programme of the National Cancer Institute, the French Network of Cancer Registries of the Institut National du Cancer, and the National Cancer Registration and Analysis Service of Public Health England. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review.

literature.[172–174] This absence of documentation might partly be because most studies looking at *KRAS* incidence are retrospective, quite often based on previously done clinical trials and therefore have a bias for younger age groups. Intriguingly, the *KRAS* Q61K mutation is associated with older, female patients and is rarely found in rectal tumours.[186,189] The molecular characteristics described earlier might have profound implications for everyday clinical practice, especially in this older age group.[190–192]

### Immunological features and their association with age

In colon cancer, there is a strong correlation both between immune cell infiltrates or adaptive immune reactions in the tumour and the invasive margin, and the time to recurrence and overall survival. Consensus immunoscore is a scoring system that relates to CD3+ and cytotoxic CD8+ T-lymphocytes densities within the tumour and the invasive margin.[193] Multivariate analysis from a large validation of the consensus immunoscore for the prognostic effect of colon cancer showed that the association between the immunoscore and the time to recurrence was independent of age, sex, tumour and node stage, and MSI status.[194] However, the role of the immunoscore in the management of colorectal cancer needs more investigation to better define its effect on the need, type, and duration of adjuvant therapies.[195]

## Conclusion

Ageing clearly affects tumour biology. In this Review, we focused mainly on age-related biological characteristics at the first diagnosis of cancer, which are truly inherent to the tumour and unaffected by previous treatment or by different treatment approaches according to age. We did not analyse the effect of age on treatment response or survival, which is beyond the scope of this Review. Moreover, there might be many reasons other than tumour biology as to why response or survival are different in older people, including differences in treatment choice, drug pharmacokinetics and pharmacodynamics, the competing risk of mortality, and comorbidities, etc. The publications selected for this Review are the ones considered most relevant by the authors; most of them are highly specialised in one of the five specific tumour types considered, as well as in geriatric oncology as a whole. We did not do a systemic review, as this would have been impossible; nearly every biomarker in every tumour type would need a separate systematic review.

Our review reveals biological differences in all five common cancer types that were evaluated. In breast cancer, tumours are in general more indolent with a lower grade, more luminal subtype, and more oestrogen receptor positivity. Subtypes also differ in lung cancer, with a higher proportion of the SCC (with its poor prognosis) compared with the adenocarcinoma subtype at an older age. Likewise, prostate cancer and melanoma seem more aggressive at higher age, as indicated by a higher Gleason or ISUP grade and D'Amico risk group in prostate cancer, and increased Breslow thickness, ulceration, and mitotic rate in melanoma. In addition, for melanoma, clear age-related differences exist in tumour location and histological subtype. In colorectal cancer, right colon tumours (which are prognostically less favourable) increase with age, whereas rectal cancer decreases.

Studies reporting on molecular alterations according to age show clear differences in specific tumour mutations or other molecular markers. This finding might have notable consequences regarding treatment (eg, targeted therapies) for the different tumour types. Mutational signatures are also expected to alter with increasing age, but there are hardly any data available. It has been shown that tumours from older patients present with an overall increase in genomic instability, somatic copy-number alterations, and somatic mutations, along with age-related global transcriptomic changes, partly regulated by age-associated DNA methylation changes.[196]

The investigation of the peri-tumour or intra-tumour immune environment according to age is still undeveloped. Exploratory studies in older patients with cancer show marked differences in the abundance and composition of the immune infiltrate. More research is needed and might lead to a better understanding of the immune landscape in older patients with cancer, and consequently more potential for targeted (immunotherapy) interventions according to age.

One notable limitation of this Review that might affect the results to some extent is the heterogeneity in the population included in the different studies. However, this variety would primarily explain the differences in frequency observed throughout the studies, but consistency in the direction of the observed differences

(increase or decrease) in several studies is most likely reflecting an underlying age-related biological process. In addition, the selection of the five most prevalent cancer types within this Review is on the basis of the Surveillance, Epidemiology, and End Results programme database, which is mostly representative of the epidemiology of cancer in a so-called Anglo-European, high-income country, whereas other countries or regions might have different cancer issues (eg, cervical and head and neck cancer in India).

To conclude, although most tumour subtypes and molecular alterations seem to be present in all age categories, there are clear shifts in the distribution of these characteristics with increasing age. The biological explanation as to why some subtypes and alternations are more frequent in older people has yet to be elucidated. Cumulative DNA damage with increasing age and immunosenescence might play a role, but are insufficient to explain all the observations summarised in this Review. A better understanding of these biological processes is needed and might help to better understand cancer biology globally, and as such improve personalised cancer care in both young and old people with cancer.

#### Contributors

YVH, AF, and HW contributed to the conceptualisation and design of the study. YVH and HW provided supervision of the study. SA, DP, LD, YL, MP, OB, JH-C, FB, CD, and SH contributed to the literature search and data collection. All authors contributed to the literature review, data collection, and assembly of the data. YVH, AF, and HW wrote the original draft of the manuscript, and all authors reviewed and edited the manuscript. All authors gave final approval of the manuscript and agreed with the decision to submit for publication.

#### Declaration of interests

HW's institution (Department of General Medical Oncology, University Hospitals Leuven, Leuven Cancer Institute, Leuven, Belgium) received financial compensation for advisory board and lecture fees from AbbVie, ARIEZ, AstraZeneca, AstraZeneca Ireland, Biocartes, Congress Care, Daiichi Sankyo, Eisai, Immutep, Federaal Kenniscentrum Voor de Gezondheidszorg, Lilly, Merck Sharp & Dohme, Novartis, ORION Corporation, Pfizer, PSI CRO AG, Puma Biotech, Roche, Sirtex, The Planning Shop, and Aptitude Health; and an unrestricted research grant from Roche. LD's institution received research grants from Boehringer Ingelheim; financial compensation for advisory board and lecture fees from AstraZeneca, Bristol Myers Squibb, Merck Sharp & Dohme, and Roche; and travel support from AstraZeneca, Merck Sharp & Dohme, and Roche. FB received financial compensation for advisory boards and lecture fees from Bayer, Bristol Myers Squibb, GlaxoSmithKline, Merck, and Merck Sharp & Dohme; a research grant from Sanofi; and travel support from Bristol Myers Squibb, GlaxoSmithKline, and Merck Sharp & Dohme. All other authors declare no competing interests.

#### Acknowledgments

HW is a recipient of the Fonds voor Wetenschappelijk Onderzoek – Vlaanderen (funds from The Research Foundation – Flanders).

#### References

1 Kontis V, Bennett JE, Mathers CD, Li G, Foreman K, Ezzati M. Future life expectancy in 35 industrialised countries: projections with a Bayesian model ensemble. *Lancet* 2017; **389:** 1323–35.

2 Abbafati C, Machado DB, Cislaghi B, et al. 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* 2020; **396:** 1160–203.

3 Foreman KJ, Marquez N, Dolgert A, et al. 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* 2018; **392:** 2052–90.

4 Pilleron S, Sarfati D, Janssen-Heijnen M, et al. Global cancer incidence in older adults, 2012 and 2035: a population-based study. *Int J Cancer* 2019; **144:** 49–58.

5 DeSantis CE, Miller KD, Dale W, et al. Cancer statistics for adults aged 85 years and older, 2019. *CA Cancer J Clin* 2019; **69:** 452–67.

6 SIOG. International Society of Geriatric Oncology. 2015. http://www.siog.org (accessed April 15, 2021).

7 Soto-Perez-de-Celis E, Sun CL, Tew WP, et al. Association between patient-reported hearing and visual impairments and functional, psychological, and cognitive status among older adults with cancer. *Cancer* 2018; **124:** 3249–56.

8 Sharma M, Loh KP, Nightingale G, Mohile SG, Holmes HM. Polypharmacy and potentially inappropriate medication use in geriatric oncology. *J Geriatr Oncol* 2016; **7:** 346–53.

9 Nightingale G, Hajjar E, Swartz K, Andrel-Sendecki J, Chapman A. Evaluation of a pharmacist-led medication assessment used to identify prevalence of and associations with polypharmacy and potentially inappropriate medication use among ambulatory senior adults with cancer. *J Clin Oncol* 2015; **33:** 1453–59.

10 Mohile SG, Fan L, Reeve E, et al. Association of cancer with geriatric syndromes in older Medicare beneficiaries. *J Clin Oncol* 2011; **29:** 1458–64.

11 Mohamed MR, Ramsdale E, Loh KP, et al. Associations of polypharmacy and inappropriate medications with adverse outcomes in older adults with cancer: a systematic review and meta-analysis. *Oncologist* 2020; **25:** e94–108.

12 Zhang X, Tang T, Pang L, et al. Malnutrition and overall survival in older adults with cancer: a systematic review and meta-analysis. *J Geriatr Oncol* 2019; **10:** 874–83.

13 Zhang X, Pang L, Sharma SV, Li R, Nyitray AG, Edwards BJ. Malnutrition and overall survival in older patients with cancer. *Clin Nutr* 2020; **40:** 966–77.

14 Bullock AF, Greenley SL, McKenzie GAG, Paton LW, Johnson MJ. Relationship between markers of malnutrition and clinical outcomes in older adults with cancer: systematic review, narrative synthesis and meta-analysis. *Eur J Clin Nutr* 2020; **74:** 1519–35.

15 Dunne RF, Loh KP, Williams GR, Jatoi A, Mustian KM, Mohile SG. Cachexia and sarcopenia in older adults with cancer: a comprehensive review. *Cancers (Basel)* 2019; **11:** E1861.

16 Williams GR, Rier HN, McDonald A, Shachar SS. Sarcopenia & aging in cancer. *J Geriatr Oncol* 2019; **10:** 374–77.

17 Wang B, Thapa S, Zhou T, et al. Cancer-related fatigue and biochemical parameters among cancer patients with different stages of sarcopenia. *Support Care Cancer* 2020; **28:** 581–88.

18 Williams GR, Chen Y, Kenzik KM, et al. Assessment of sarcopenia measures, survival, and disability in older adults before and after diagnosis with cancer. *JAMA Netw Open* 2020; **3:** e204783.

19 Ligibel JA, Schmitz KH, Berger NA. Sarcopenia in aging, obesity, and cancer. *Transl Cancer Res* 2020; **9:** 5760–71.

20 Oflazoglu U, Alacacioglu A, Varol U, et al. Prevalence and related factors of sarcopenia in newly diagnosed cancer patients. *Support Care Cancer* 2020; **28:** 837–43.

21 Zhang XM, Dou QL, Zeng Y, Yang Y, Cheng ASK, Zhang WW. Sarcopenia as a predictor of mortality in women with breast cancer: a meta-analysis and systematic review. *BMC Cancer* 2020; **20:** 172.

22 Pergolotti M, Battisti NML, Padgett L, et al. Embracing the complexity: older adults with cancer-related cognitive decline-a young International Society of Geriatric Oncology position paper. *J Geriatr Oncol* 2020; **11:** 237–43.

23 Jayani RV, Magnuson AM, Sun CL, et al. Association between a cognitive screening test and severe chemotherapy toxicity in older adults with cancer. *J Geriatr Oncol* 2020; **11:** 284–89.

24 Aparicio T, Jouve JL, Teillet L, et al. Geriatric factors predict chemotherapy feasibility: ancillary results of FFCD 2001-02 phase III study in first-line chemotherapy for metastatic colorectal cancer in elderly patients. *J Clin Oncol* 2013; **31:** 1464–70.

25 Extermann M, Boler I, Reich RR, et al. Predicting the risk of chemotherapy toxicity in older patients: the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score. *Cancer* 2012; **118:** 3377–86.

26 Gurney J, Sarfati D, Stanley J. The impact of patient comorbidity on cancer stage at diagnosis. *Br J Cancer* 2015; **113:** 1375–80.

27 Wildiers H, de Glas NA. Anticancer drugs are not well tolerated in all older patients with cancer. *Lancet Healthy Longev* 2020; **1:** e43–47.

28 Hurria A, Lichtman SM. Clinical pharmacology of cancer therapies in older adults. *Br J Cancer* 2008; **98:** 517–22.

29 Nightingale G, Schwartz R, Kachur E, et al. Clinical pharmacology of oncology agents in older adults: a comprehensive review of how chronologic and functional age can influence treatment-related effects. *J Geriatr Oncol* 2019; **10:** 4–30.

30 Gomes AP, Ilter D, Low V, et al. Age-induced accumulation of methylmalonic acid promotes tumour progression. *Nature* 2020; **585:** 283–87.

31 Gu D, Morgan RO, Li R, Weber ES, Shen C. Association between depression and healthcare expenditures among elderly cancer patients. *BMC Psychiatry* 2020; **20:** 131.

32 Wang X, Wang N, Zhong L, et al. Prognostic value of depression and anxiety on breast cancer recurrence and mortality: a systematic review and meta-analysis of 282,203 patients. *Mol Psychiatry* 2020; **25:** 3186–97.

33 Gajra A, Klepin HD, Feng T, et al. Predictors of chemotherapy dose reduction at first cycle in patients age 65 years and older with solid tumors. *J Geriatr Oncol* 2015; **6:** 133–40.

34 Wildiers H. Mastering chemotherapy dose reduction in elderly cancer patients. *Eur J Cancer* 2007; **43:** 2235–41.

35 Kagan SH. Ageism in cancer care. *Semin Oncol Nurs* 2008; **24:** 246–53.

36 National Cancer Institute. Cancer stat facts: cancer of any site. 2020. https://seer.cancer.gov/statfacts/html/all.html (accessed April 20, 2021).

37 Bidoli E, Virdone S, Hamdi-Cherif M, et al. Worldwide age at onset of female breast cancer: a 25-year population-based cancer registry study. *Sci Rep* 2019; **9:** 14111.

38 Schonberg MA, Marcantonio ER, Li D, Silliman RA, Ngo L, McCarthy EP. Breast cancer among the oldest old: tumor characteristics, treatment choices, and survival. *J Clin Oncol* 2010; **28:** 2038–45.

39 Lodi M, Scheer L, Reix N, et al. Breast cancer in elderly women and altered clinico-pathological characteristics: a systematic review. *Breast Cancer Res Treat* 2017; **166:** 657–68.

40 Malik MK, Tartter PI, Belfer R. Undertreated breast cancer in the elderly. *J Cancer Epidemiol* 2013; **2013:** 893104.

41 Wang MX, Ren JT, Tang LY, Ren ZF. Molecular features in young *vs* elderly breast cancer patients and the impacts on survival disparities by age at diagnosis. *Cancer Med* 2018; **7:** 3269–77.

42 Azim HA Jr, Nguyen B, Brohée S, Zoppoli G, Sotiriou C. Genomic aberrations in young and elderly breast cancer patients. *BMC Med* 2015; **13:** 266.

43 Anderson WF, Katki HA, Rosenberg PS. Incidence of breast cancer in the United States: current and future trends. *J Natl Cancer Inst* 2011; **103:** 1397–402.

44 de Munck L, Schaapveld M, Siesling S, et al. Implementation of trastuzumab in conjunction with adjuvant chemotherapy in the treatment of non-metastatic breast cancer in the Netherlands. *Breast Cancer Res Treat* 2011; **129:** 229–33.

45 Jenkins EO, Deal AM, Anders CK, et al. Age-specific changes in intrinsic breast cancer subtypes: a focus on older women. *Oncologist* 2014; **19:** 1076–83.

46 de Kruijf EM, Bastiaannet E, Rubertá F, et al. Comparison of frequencies and prognostic effect of molecular subtypes between young and elderly breast cancer patients. *Mol Oncol* 2014; **8:** 1014–25.

47 Mealey NE, O'Sullivan DE, Pader J, et al. Mutational landscape differences between young-onset and older-onset breast cancer patients. *BMC Cancer* 2020; **20:** 212.

48 Selenica P, Pareja F, Tadros A, et al. Genomic landscape of breast cancer occurring in elderly individuals. 2019 San Antonio Breast Cancer Symposium; San Antonio, TX; Dec 10–14, 2019 (abstr P4–05–08).

49 Kalinsky K, Jacks LM, Heguy A, et al. PIK3CA mutation associates with improved outcome in breast cancer. *Clin Cancer Res* 2009; **15:** 5049–59.

50 Biganzoli L, Wildiers H, Oakman C, et al. Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). *Lancet Oncol* 2012; **13:** e148–60.

51 Gennari R, Curigliano G, Rotmensz N, et al. Breast carcinoma in elderly women: features of disease presentation, choice of local and systemic treatments compared with younger postmenopasual patients. *Cancer* 2004; **101:** 1302–10.

52 Pinto AC, Ades F, de Azambuja E, Piccart-Gebhart M. Trastuzumab for patients with HER2 positive breast cancer: delivery, duration and combination therapies. *Breast* 2013; **22** (suppl 2)**:** S152–55.

53 Aapro M, Wildiers H. Triple-negative breast cancer in the older population. *Ann Oncol* 2012; **23** (suppl 6)**:** vi52–55.

54 Dreyer G, Vandorpe T, Smeets A, et al. Triple negative breast cancer: clinical characteristics in the different histological subtypes. *Breast* 2013; **22:** 761–66.

55 Syed BM, Green AR, Nolan CC, Morgan DAL, Ellis IO, Cheung KL. Biological characteristics and clinical outcome of triple negative primary breast cancer in older women – comparison with their younger counterparts. *PLoS One* 2014; **9:** e100573.

56 Bouchalova K, Svoboda M, Kharaishvili G, et al. *BCL2* is an independent predictor of outcome in basal-like triple-negative breast cancers treated with adjuvant anthracycline-based chemotherapy. *Tumour Biol* 2015; **36:** 4243–52.

57 Yang SX, Polley E, Lipkowitz S. New insights on PI3K/AKT pathway alterations and clinical outcomes in breast cancer. *Cancer Treat Rev* 2016; **45:** 87–96.

58 Liu S, Huang J, Zhang Y, Liu Y, Zuo S, Li R. *MAP2K4* interacts with Vimentin to activate the PI3K/AKT pathway and promotes breast cancer pathogenesis. *Aging (Albany NY)* 2019; **11:** 10697–710.

59 Guo Y, Yu P, Liu Z, et al. Prognostic and clinicopathological value of GATA binding protein 3 in breast cancer: a systematic review and meta-analysis. *PLoS One* 2017; **12:** e0174843.

60 Mehra R, Varambally S, Ding L, et al. Identification of GATA3 as a breast cancer prognostic marker by global gene expression meta-analysis. *Cancer Res* 2005; **65:** 11259–64.

61 Pham TT, Angus SP, Johnson GL. *MAP3K1*: genomic alterations in cancer and function in promoting cell survival or apoptosis. *Genes Cancer* 2013; **4:** 419–26.

62 Maani N, Westergard S, Yang J, et al. NF1 patients receiving breast cancer screening: Insights from the Ontario high risk breast screening program. *Cancers (Basel)* 2019; **11:** E707.

63 Corso G, Veronesi P, Sacchini V, Galimberti V. Prognosis and outcome in CDH1-mutant lobular breast cancer. *Eur J Cancer Prev* 2018; **27:** 237–38.

64 Shenoy S. *CDH1* (E-cadherin) mutation and gastric cancer: genetics, molecular mechanisms and guidelines for management. *Cancer Manag Res* 2019; **11:** 10477–86.

65 Rabello DA, de Moura CA, de Andrade RV, Motoyama AB, Silva FP. Altered expression of MLL methyltransferase family genes in breast cancer. *Int J Oncol* 2013; **43:** 653–60.

66 Hudeček J, Voorwerk L, van Seijen M, et al. Application of a risk-management framework for integration of stromal tumor-infiltrating lymphocytes in clinical trials. *NPJ Breast Cancer* 2020; **6:** 15.

67 Adams S, Gray RJ, Demaria S, et al. Prognostic value of tumor-infiltrating lymphocytes in triple-negative breast cancers from two phase III randomized adjuvant breast cancer trials: ECOG 2197 and ECOG 1199. *J Clin Oncol* 2014; **32:** 2959–66.

68 Denkert C, von Minckwitz G, Darb-Esfahani S, et al. Tumour-infiltrating lymphocytes and prognosis in different subtypes of breast cancer: a pooled analysis of 3771 patients treated with neoadjuvant therapy. *Lancet Oncol* 2018; **19:** 40–50.

69 Loi S, Drubay D, Adams S, et al. Tumor-infiltrating lymphocytes and prognosis: a pooled individual patient analysis of early-stage triple-negative breast cancers. *J Clin Oncol* 2019; **37:** 559–69.

70 Desmedt C, Salgado R, Fornili M, et al. Immune infiltration in invasive lobular breast cancer. *J Natl Cancer Inst* 2018; **110:** 768–76.

71 Berben L, Floris G, Kenis C, et al. Age-related remodelling of the blood immunological portrait and the local tumor immune response in patients with luminal breast cancer. *Clin Transl Immunology* 2020; **9:** e1184.

72 National Cancer Institute. SEER Cancer Statistics Review (CSR) 1975-2018. April 15, 2021. https://seer.cancer.gov/csr/1975_2018/ (accessed April 26, 2021)

73 Giroux Leprieur E, Labrune S, Giraud V, Gendry T, Cobarzan D, Chinet T. Delay between the initial symptoms, the diagnosis and the onset of specific treatment in elderly patients with lung cancer. *Clin Lung Cancer* 2012; **13:** 363–68. .

74 Zhong W, Zhao J, Huang K, Zhang J, Chen Z. Comparison of clinicopathological and molecular features between young and old patients with lung cancer. *Int J Clin Exp Pathol* 2018; **11:** 1031–35.

75 Goodgame B, Viswanathan A, Zoole J, et al. Risk of recurrence of resected stage I non-small cell lung cancer in elderly patients as compared with younger patients. *J Thorac Oncol* 2009; **4:** 1370–74.

76 Sterlacci W, Stockinger R, Schmid T, et al. The elderly patient with surgically resected non-small cell lung cancer–a distinct situation? *Exp Gerontol* 2012; **47:** 237–42.

77 Sacher AG, Dahlberg SE, Heng J, Mach S, Jänne PA, Oxnard GR. Association between younger age and targetable genomic alterations and prognosis in non-small-cell lung cancer. *JAMA Oncol* 2016; **2:** 313–20.

78 Tsao AS, Liu S, Lee JJ, et al. Clinical outcomes and biomarker profiles of elderly pretreated NSCLC patients from the BATTLE trial. *J Thorac Oncol* 2012; **7:** 1645–52.

79 Dong YU, Ren W, Qi J, et al. *EGFR, ALK, RET, KRAS* and *BRAF* alterations in never-smokers with non-small cell lung cancer. *Oncol Lett* 2016; **11:** 2371–78.

80 Boldrini L, Giordano M, Lucchi M, Melfi F, Fontanini G. Expression profiling and microRNA regulation of the LKB1 pathway in young and aged lung adenocarcinoma patients. *Biomed Rep* 2018; **9:** 198–205.

81 Ye T, Pan Y, Wang R, et al. Analysis of the molecular and clinicopathologic features of surgically resected lung adenocarcinoma in patients under 40 years old. *J Thorac Dis* 2014; **6:** 1396–402.

82 Velcheti V, Schalper KA, Carvajal DE, et al. Programmed death ligand-1 expression in non-small cell lung cancer. *Lab Invest* 2014; **94:** 107–16.

83 Lin C, Chen X, Li M, et al. Programmed death-ligand 1 expression predicts tyrosine kinase inhibitor response and better prognosis in a cohort of patients with epidermal growth factor receptor mutation-positive lung adenocarcinoma. *Clin Lung Cancer* 2015; **16:** e25–35.

84 Perrotta F, Rocco D, Vitiello F, et al. Immune checkpoint blockade for advanced NSCLC: a new landscape for elderly patients. *Int J Mol Sci* 2019; **20:** E2258.

85 Zhang YL, Yuan JQ, Wang KF, et al. The prevalence of *EGFR* mutation in patients with non-small cell lung cancer: a systematic review and meta-analysis. *Oncotarget* 2016; **7:** 78985–93.

86 Eberhard DA, Johnson BE, Amler LC, et al. Mutations in the epidermal growth factor receptor and in *KRAS* are predictive and prognostic indicators in patients with non-small-cell lung cancer treated with chemotherapy alone and in combination with erlotinib. *J Clin Oncol* 2005; **23:** 5900–09.

87 Choi YW, Jeon SY, Jeong GS, et al. EGFR exon 19 deletion is associated with favorable overall survival after first-line gefitinib therapy in advanced non-small cell lung cancer patients. *Am J Clin Oncol* 2018; **41:** 385–90.

88 Lohinai Z, Klikovits T, Moldvay J, et al. KRAS-mutation incidence and prognostic value are metastatic site-specific in lung adenocarcinoma: poor prognosis in patients with KRAS mutation and bone metastasis. *Sci Rep* 2017; **7:** 39721.

89 Awad MM, Oxnard GR, Jackman DM, et al. *MET* exon 14 mutations in non-small-cell lung cancer are associated with advanced age and stage-dependent MET genomic amplification and c-Met overexpression. *J Clin Oncol* 2016; **34:** 721–30.

90 Giordano M, Boldrini L, Servadio A, et al. Differential microRNA expression profiles between young and old lung adenocarcinoma patients. *Am J Transl Res* 2018; **10:** 892–900.

91 Paik PK, Arcila ME, Fara M, et al. Clinical characteristics of patients with lung adenocarcinomas harboring *BRAF* mutations. *J Clin Oncol* 2011; **29:** 2046–51.

92 Bergethon K, Shaw AT, Ou SHI, et al. *ROS1* rearrangements define a unique molecular class of lung cancers. *J Clin Oncol* 2012; **30:** 863–70.

93 Shaw AT, Ou S-HI, Bang Y-J, et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. *N Engl J Med* 2014; **371:** 1963–71.

94 Peters S, Camidge DR, Shaw AT, et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *N Engl J Med* 2017; **377:** 829–38.

95 Solomon BJ, Mok T, Kim D-W, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N Engl J Med* 2014; **371:** 2167–77.

96 Mazières J, Zalcman G, Crinò L, et al. Crizotinib therapy for advanced lung adenocarcinoma and a ROS1 rearrangement: results from the EUROS1 cohort. *J Clin Oncol* 2015; **33:** 992–99.

97 Vuong HG, Ho ATN, Altibi AMA, Nakazawa T, Katoh R, Kondo T. Clinicopathological implications of MET exon 14 mutations in non-small cell lung cancer–a systematic review and meta-analysis. *Lung Cancer* 2018; **123:** 76–82.

98 Paik PK, Felip E, Veillon R, et al. Tepotinib in non-small-cell lung cancer with *MET* exon 14 skipping mutations. *N Engl J Med* 2020; **383:** 931–43.

99 Wolf J, Seto T, Han J-Y, et al. Capmatinib in *MET* exon 14-mutated or *MET*-amplified non-small-cell lung cancer. *N Engl J Med* 2020; **383:** 944–57.

100 Brody R, Zhang Y, Ballas M, et al. PD-L1 expression in advanced NSCLC: insights into risk stratification and treatment selection from a systematic literature review. *Lung Cancer* 2017; **112:** 200–15.

101 Srivastava MK, Andersson Å, Zhu L, et al. Myeloid suppressor cells and immune modulation in lung cancer. *Immunotherapy* 2012; **4:** 291–304.

102 Ortiz ML, Lu L, Ramachandran I, Gabrilovich DI. Myeloid-derived suppressor cells in the development of lung cancer. *Cancer Immunol Res* 2014; **2:** 50–58.

103 Chen S, Liu H, Su N, Zhang G, Wang L. Myeloid-derived suppressor cells promote age-related increase of lung cancer growth via B7-H1. *Exp Gerontol* 2015; **61:** 84–91.

104 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68:** 394–424.

105 Boyle HJ, Alibhai S, Decoster L, et al. Updated recommendations of the International Society of Geriatric Oncology on prostate cancer management in older patients. *Eur J Cancer* 2019; **116:** 116–36.

106 Pettersson A, Robinson D, Garmo H, Holmberg L, Stattin P. Age at diagnosis and prostate cancer treatment and prognosis: a population-based cohort study. *Ann Oncol* 2018; **29:** 377–85.

107 Zhang H, Messing EM, Travis LB, et al. Age and racial differences among PSA-detected (AJCC stage T1cN0M0) prostate cancer in the U.S.: a population-based study of 70,345 men. *Front Oncol* 2013; **3:** 312.

108 Dinerman BF, Khani F, Golan R, et al. Population-based study of the incidence and survival for intraductal carcinoma of the prostate. *Urol Oncol* 2017; **35:** 673.e9–14.

109 Goldberg H, Spratt D, Chandrasekar T, et al. Clinical-genomic characterization unveils more aggressive disease features in elderly prostate cancer patients with low-grade disease. *Eur Urol Focus* 2020; published online March 7. https://doi.org/10.1016/j.euf.2020.02.008.

110 Calvocoressi L, Uchio E, Ko J, Radhakrishnan K, Aslan M, Concato J. Prostate cancer aggressiveness and age: impact of p53, BCL-2 and microvessel density. *J Investig Med* 2018; **66:** 1142–46.

111 Jędroszka D, Orzechowska M, Hamouz R, Górniak K, Bednarek AK. Markers of epithelial-to-mesenchymal transition reflect tumor biology according to patient age and Gleason score in prostate cancer. *PLoS One* 2017; **12:** e0188842.

112 Schaefer G, Mosquera JM, Ramoner R, et al. Distinct ERG rearrangement prevalence in prostate cancer: higher frequency in young age and in low PSA prostate cancer. *Prostate Cancer Prostatic Dis* 2013; **16:** 132–38.

113 Matsugasumi T, Fujihara A, Ushijima S, et al. Morphometric analysis of prostate zonal anatomy using magnetic resonance imaging: impact on age-related changes in patients in Japan and the USA. *BJU Int* 2017; **120:** 497–504.

114 Dinerman BF, Bernstein AN, Khani F, Hu JC. Intraductal carcinoma of the prostate: a risk for rapid recurrence. *Urology* 2017; **105:** e1–2.

115 Hollemans E, Verhoef EI, Bangma CH, et al. Large cribriform growth pattern identifies ISUP grade 2 prostate cancer at high risk for recurrence and metastasis. *Mod Pathol* 2019; **32:** 139–46.

116 Fenton JJ, Weyrich MS, Durbin S, Liu Y, Bang H, Melnikow J. Prostate-specific antigen-based screening for prostate cancer evidence report and systematic review for the us preventive services task force. *JAMA* 2018; **319:** 1914–31.

117 Sun WG, Liang CZ, Zheng QC, Hu XW, Li ZZ, Wu P. Influence of age on seven putative prostate tumor markers: a cohort study in Chinese men. *Asian J Androl* 2017; **19:** 463–67.

118 Palsdottir T, Nordström T, Aly M, et al. Are Prostate specific-antigen (PSA) and age associated with the risk of ISUP grade 1 prostate cancer? Results from 72 996 individual biopsy cores in 6 083 men from the Stockholm3 study. *PLoS One* 2019; **14:** e0218280.

119 Klatte T, Waldert M, de Martino M, Schatzl G, Mannhalter C, Remzi M. Age-specific PCA3 score reference values for diagnosis of prostate cancer. *World J Urol* 2012; **30:** 405–10.

120 Hennenlotter J, Neumann T, Alperowitz S, et al. Age-adapted prostate cancer gene 3 score interpretation - suggestions for clinical use. *Clin Lab* 2020; **66**.

121 Vertosick EA, Häggström C, Sjoberg DD, et al. Prespecified 4-Kallikrein marker model at age 50 or 60 for early detection of lethal prostate cancer in a large population based cohort of asymptomatic men followed for 20 years. *J Urol* 2020; **204:** 281–88.

122 Zhao SG, Chang SL, Erho N, et al. Associations of luminal and basal subtyping of prostate cancer with prognosis and response to androgen deprivation therapy. *JAMA Oncol* 2017; **3:** 1663–72.

123 García-Perdomo HA, Chaves MJ, Osorio JC, Sanchez A. Association between TMPRSS2:ERG fusion gene and the prostate cancer: systematic review and meta-analysis. *Cent European J Urol* 2018; **71:** 410–19.

124 Song C, Chen H. Predictive significance of *TMRPSS2-ERG* fusion in prostate cancer: a meta-analysis. *Cancer Cell Int* 2018; **18:** 177.

125 SEER. Cancer stat facts: melanoma of the skin. 2020. https://seer.cancer.gov/statfacts/html/melan.html (accessed April 25, 2021).

126 Schuurman MS, Hollestein LM, Bastiaannet E, et al. Melanoma in older patients: declining gap in survival between younger and older patients with melanoma. *Acta Oncol* 2020; **59:** 4–12.

127 Weiss SA, Han J, Darvishian F, et al. Impact of aging on host immune response and survival in melanoma: an analysis of 3 patient cohorts. *J Transl Med* 2016; **14:** 299.

128 Ciocan D, Barbe C, Aubin F, et al. Distinctive features of melanoma and its management in elderly patients: a population-based study in France. *JAMA Dermatol* 2013; **149:** 1150–57.

129 Macdonald JB, Dueck AC, Gray RJ, et al. Malignant melanoma in the elderly: different regional disease and poorer prognosis. *J Cancer* 2011; **2:** 538–43.

130 Shen S, Wolfe R, McLean CA, Haskett M, Kelly JW. Characteristics and associations of high-mitotic-rate melanoma. *JAMA Dermatol* 2014; **150:** 1048–55.

131 Cavanaugh-Hussey MW, Mu EW, Kang S, Balch CM, Wang T. Older age is associated with a higher incidence of melanoma death but a lower incidence of sentinel lymph node metastasis in the SEER Databases (2003-2011). *Ann Surg Oncol* 2015; **22:** 2120–26.

132 Bauer J, Büttner P, Murali R, et al. *BRAF* mutations in cutaneous melanoma are independently associated with age, anatomic site of the primary tumor, and the degree of solar elastosis at the primary tumor site. *Pigment Cell Melanoma Res* 2011; **24:** 345–51.

133 Menzies AM, Visintin L, Chatfield MD, et al. *BRAF* mutation by age-decade and body mass index in metastatic melanoma. *J Clin Oncol* 2011; **29:** 8507.

134 Devitt B, Liu W, Salemi R, et al. Clinical outcome and pathological features associated with *NRAS* mutation in cutaneous melanoma. *Pigment Cell Melanoma Res* 2011; **24:** 666–72.

135 Thomas NE, Busam KJ, From L, et al. Tumor-infiltrating lymphocyte grade in primary melanomas is independently associated with melanoma-specific survival in the population-based genes, environment and melanoma study. *J Clin Oncol* 2013; **31:** 4252–59.

136 Heppt MV, Siepmann T, Engel J, et al. Prognostic significance of *BRAF* and *NRAS* mutations in melanoma: a German study from routine care. *BMC Cancer* 2017; **17:** 536.

137 Geller AC, Elwood M, Swetter SM, et al. Factors related to the presentation of thin and thick nodular melanoma from a population-based cancer registry in Queensland Australia. *Cancer* 2009; **115:** 1318–27.

138 Kalkhoran S, Milne O, Zalaudek I, et al. Historical, clinical, and dermoscopic characteristics of thin nodular melanoma. *Arch Dermatol* 2010; **146:** 311–18.

139 Kvaskoff M, Pandeya N, Green AC, et al. Solar elastosis and cutaneous melanoma: a site-specific analysis. *Int J Cancer* 2015; **136:** 2900–11.

140 Thomas NE, Kricker A, From L, et al. Associations of cumulative sun exposure and phenotypic characteristics with histologic solar elastosis. *Cancer Epidemiol Biomarkers Prev* 2010; **19:** 2932–41.

141 Huismans AM, Haydu LE, Shannon KF, et al. Primary melanoma location on the scalp is an important risk factor for brain metastasis: a study of 1,687 patients with cutaneous head and neck melanomas. *Ann Surg Oncol* 2014; **21:** 3985–91.

142 Gardner LJ, Ward M, Andtbacka RHI, et al. Risk factors for development of melanoma brain metastasis and disease progression: a single-center retrospective analysis. *Melanoma Res* 2017; **27:** 477–84.

143 Ozao-Choy J, Nelson DW, Hiles J, et al. The prognostic importance of scalp location in primary head and neck melanoma. *J Surg Oncol* 2017; **116:** 337–43.

144 Xie C, Pan Y, McLean C, Mar V, Wolfe R, Kelly J. Impact of scalp location on survival in head and neck melanoma: a retrospective cohort study. *J Am Acad Dermatol* 2017; **76:** 494–98.

145 Shaikh WR, Xiong M, Weinstock MA. The contribution of nodular subtype to melanoma mortality in the United States, 1978 to 2007. *Arch Dermatol* 2012; **148:** 30–36.

146 Akbani R, Akdemir KC, Aksoy BA, et al. Genomic classification of cutaneous melanoma. *Cell* 2015; **161:** 1681–96.

147 Ekedahl H, Cirenajwis H, Harbst K, et al. The clinical significance of *BRAF* and *NRAS* mutations in a clinic-based metastatic melanoma cohort. *Br J Dermatol* 2013; **169:** 1049–55.

148 Long GV, Menzies AM, Nagrial AM, et al. Prognostic and clinicopathologic associations of oncogenic BRAF in metastatic melanoma. *J Clin Oncol* 2011; **29:** 1239–46.

149 Thomas NE, Edmiston SN, Alexander A, et al. Association between *NRAS* and *BRAF* mutational status and melanoma-specific survival among patients with higher-risk primary melanoma. *JAMA Oncol* 2015; **1:** 359.

150 Dummer R, Schadendorf D, Ascierto PA, et al. Binimetinib versus dacarbazine in patients with advanced *NRAS*-mutant melanoma (NEMO): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2017; **18:** 435–45.

151 Johnson DB, Lovly CM, Flavin M, et al. Impact of *NRAS* mutations for patients with advanced melanoma treated with immune therapies. *Cancer Immunol Res* 2015; **3:** 288–95.

152 Taylor RC, Patel A, Panageas KS, Busam KJ, Brady MS. Tumor-infiltrating lymphocytes predict sentinel lymph node positivity in patients with cutaneous melanoma. *J Clin Oncol* 2007; **25:** 869–75.

153 Clemente CG, Mihm MC Jr, Bufalino R, Zurrida S, Collini P, Cascinelli N. Prognostic value of tumor infiltrating lymphocytes in the vertical growth phase of primary cutaneous melanoma. *Cancer* 1996; **77:** 1303–10.

154 Krynitz B, Rozell BL, Lyth J, Smedby KE, Lindelöf B. Cutaneous malignant melanoma in the Swedish organ transplantation cohort: a study of clinicopathological characteristics and mortality. *J Am Acad Dermatol* 2015; **73:** 106–13.

155 Siegel RL, Miller KD, Goding Sauer A, et al. Colorectal cancer statistics, 2020. *CA Cancer J Clin* 2020; **70:** 145–64.

156 Ferlay J, Parkin DM, Steliarova-Foucher E. Estimates of cancer incidence and mortality in Europe in 2008. *Eur J Cancer* 2010; **46:** 765–81.

157 Sante Publique France. Projection de l'incidence et de la mortalité par cancer en France métropolitaine en 2017. Jan 1, 2017. https://www.santepubliquefrance.fr/docs/projection-de-l-incidence-et-de-la-mortalite-par-cancer-en-france-metropolitaine-en-2017 (accessed April 30, 2021).

158 NCIN. Cancer information tools. 2021. http://www.ncin.org.uk/cancer_information_tools/ukcis (accessed April 21, 2021).

159 Yang L, Xiong Z, He W, et al. Proximal shift of colorectal cancer with increasing age in different ethnicities. *Cancer Manag Res* 2018; **10:** 2663–73.

160 Kotake K, Asano M, Ozawa H, Kobayashi H, Sugihara K. Tumour characteristics, treatment patterns and survival of patients aged 80 years or older with colorectal cancer. *Colorectal Dis* 2015; **17:** 205–15.

161 Patel SS, Nelson R, Sanchez J, et al. Elderly patients with colon cancer have unique tumor characteristics and poor survival. *Cancer* 2013; **119:** 739–47.

162 Derwinger K, Kodeda K, Gerjy R. Age aspects of demography, pathology and survival assessment in colorectal cancer. *Anticancer Res* 2010; **30:** 5227–31.

163 Wu X, Lin H, Li S. Prognoses of different pathological subtypes of colorectal cancer at different stages: a population-based retrospective cohort study. *BMC Gastroenterol* 2019; **19:** 164.

164 Vedeld HM, Merok M, Jeanmougin M, et al. CpG island methylator phenotype identifies high risk patients among microsatellite stable *BRAF* mutated colorectal cancers. *Int J Cancer* 2017; **141:** 967–76.

165 Barault L, Charon-Barra C, Jooste V, et al. Hypermethylator phenotype in sporadic colon cancer: study on a population-based series of 582 cases. *Cancer Res* 2008; **68:** 8541–46.

166 Jia M, Jansen L, Walter V, et al. No association of CpG island methylator phenotype and colorectal cancer survival: population-based study. *Br J Cancer* 2016; **115:** 1359–66.

167 Bläker H, Alwers E, Arnold A, et al. The association between mutations in *BRAF* and colorectal cancer-specific survival depends on microsatellite status and tumor stage. *Clin Gastroenterol Hepatol* 2019; **17:** 455–462.e6.

168 Aasebø KØ, Dragomir A, Sundström M, et al. Consequences of a high incidence of microsatellite instability and *BRAF*-mutated tumors: a population-based cohort of metastatic colorectal cancer patients. *Cancer Med* 2019; **8:** 3623–35.

169 Aparicio T, Schischmanoff O, Poupardin C, et al. High prevalence of deficient mismatch repair phenotype and the V600E *BRAF* mutation in elderly patients with colorectal cancer. *J Geriatr Oncol* 2014; **5:** 384–88.

170 Sorbye H, Dragomir A, Sundström M, et al. High *BRAF* mutation frequency and marked survival differences in subgroups according to *KRAS/BRAF* mutation status and tumor tissue availability in a prospective population-based metastatic colorectal cancer cohort. *PLoS One* 2015; **10:** e0131046.

171 Phipps AI, Buchanan DD, Makar KW, et al. *BRAF* mutation status and survival after colorectal cancer diagnosis according to patient and tumor characteristics. *Cancer Epidemiol Biomarkers Prev* 2012; **21:** 1792–98.

172 Dai D, Wang Y, Zhu L, Jin H, Wang X. Prognostic value of *KRAS* mutation status in colorectal cancer patients: a population-based competing risk analysis. *PeerJ* 2020; **8:** e9149.

173 Fariña-Sarasqueta A, van Lijnschoten G, Moerland E, et al. The *BRAF* V600E mutation is an independent prognostic factor for survival in stage II and stage III colon cancer patients. *Ann Oncol* 2010; **21:** 2396–402.

174 Berg M, Danielsen SA, Ahlquist T, et al. DNA sequence profiles of the colorectal cancer critical gene set *KRAS-BRAF-PIK3CA-PTEN-TP53* related to age at disease onset. *PLoS One* 2010; **5:** e13978.

175 Carini F, Mazzola M, Rappa F, et al. Colorectal carcinogenesis: role of oxidative stress and antioxidants. *Anticancer Res* 2017; **37:** 4759–66.

176 Vogelstein B, Kinzler KW. The multistep nature of cancer. *Trends Genet* 1993; **9:** 138–41.

177 Markowitz SD, Bertagnolli MM. Molecular origins of cancer: molecular basis of colorectal cancer. *N Engl J Med* 2009; **361:** 2449–60.

178 Nagtegaal ID, Odze RD, Klimstra D, et al. The 2019 WHO classification of tumours of the digestive system. *Histopathology* 2020; **76:** 182–88.

179 De Palma FDE, D'Argenio V, Pol J, Kroemer G, Maiuri MC, Salvatore F. The molecular hallmarks of the serrated pathway in colorectal cancer. *Cancers (Basel)* 2019; **11:** E1017.

180 Li P, Xiao ZT, Braciak TA, Ou QJ, Chen G, Oduncu FS. Impact of age and mismatch repair status on survival in colorectal cancer. *Cancer Med* 2017; **6:** 975–81.

181 Dejea CM, Wick EC, Hechenbleikner EM, et al. Microbiota organization is a distinct feature of proximal colorectal cancers. *Proc Natl Acad Sci USA* 2014; **111:** 18321–26.

182 Arnold D, Lueza B, Douillard JY, et al. Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. *Ann Oncol* 2017; **28:** 1713–29.

183 Issa JP. CpG island methylator phenotype in cancer. *Nat Rev Cancer* 2004; **4:** 988–93.

184 Jass JR. Serrated adenoma of the colorectum and the DNA-methylator phenotype. *Nat Clin Pract Oncol* 2005; **2:** 398–405.

185 Pritchard CC, Grady WM. Colorectal cancer molecular biology moves into clinical practice. *Gut* 2011; **60:** 116–29.

186 Bylsma LC, Gillezeau C, Garawin TA, et al. Prevalence of *RAS* and *BRAF* mutations in metastatic colorectal cancer patients by tumor sidedness: a systematic review and meta-analysis. *Cancer Med* 2020; **9:** 1044–57.

187 Sanz-Garcia E, Argiles G, Elez E, Tabernero J. *BRAF* mutant colorectal cancer: prognosis, treatment, and new perspectives. *Ann Oncol* 2017; **28:** 2648–57.

188 Kopetz S, Grothey A, Yaeger R, et al. Encorafenib, binimetinib, and cetuximab in *BRAF* V600E-mutated colorectal cancer. *N Engl J Med* 2019; **381:** 1632–43.

189 Serebriiskii IG, Connelly C, Frampton G, et al. Comprehensive characterization of *RAS* mutations in colon and rectal cancers in old and young patients. *Nat Commun* 2019; **10:** 3722.

190 Juo YY, Johnston FM, Zhang DY, et al. Prognostic value of CpG island methylator phenotype among colorectal cancer patients: a systematic review and meta-analysis. *Ann Oncol* 2014; **25:** 2314–27.

191 Molina-Cerrillo J, San Román M, Pozas J, et al. *BRAF* mutated colorectal cancer: new treatment approaches. *Cancers (Basel)* 2020; **12:** E1571.

192 Aparicio T, Schischmanoff O, Poupardin C, et al. Deficient mismatch repair phenotype is a prognostic factor for colorectal cancer in elderly patients. *Dig Liver Dis* 2013; **45:** 245–50.

193 Mlecnik B, Bifulco C, Bindea G, et al. Multicenter international society for immunotherapy of cancer study of the consensus immunoscore for the prediction of survival and response to chemotherapy in stage III colon cancer. *J Clin Oncol* 2020; **38:** 3638–51.

194 Pagès F, Mlecnik B, Marliot F, et al. International validation of the consensus immunoscore for the classification of colon cancer: a prognostic and accuracy study. *Lancet* 2018; **391:** 2128–39.

195 Malka D, Lièvre A, André T, Taïeb J, Ducreux M, Bibeau F. Immune scores in colorectal cancer: where are we? *Eur J Cancer* 2020; **140:** 105–18.

196 Chatsirisupachai K, Lesluyes T, Paraoan L, Van Loo P, de Magalhães JP. An integrative analysis of the age-associated multi-omic landscape across cancers. *Nat Commun* 2021; **12:** 2345.