WHITE PAPER

The impact of cancer-related comorbidities on patient treatment, treatment efficacy, survivorship, and quality of life

Contents

The burden of cancer-related complications and comorbidities

Cancer-related complications and comorbidities add a highly significant burden on patients across Europe – and are in many cases fatal.[1, 2,3] Research shows that most cancer patients, even up to almost 90% depending on the cancer type and age, report at least one comorbid condition.[4, 5,6] In addition, cancer patients report more comorbid medical conditions than patients without a history of cancer.[7] Patients with comorbidities may be more affected by the toxicity of cancer treatment, which can have a detrimental impact on their chances of survival following cancer treatment. The relationship also works in the other direction, as both cancer and its treatment can affect comorbidity outcomes. For example, cancer therapies can increase the risk of cardiovascular, metabolic, musculoskeletal, neuro(-psycho)logical and other conditions and can worsen pre-existing comorbidities while some treatments, like, i.e., anticoagulation, entail peculiar management difficulties if to be administered in cancer patients.[8]

1 Søgaard, M., Thomsen, R. W., Bossen, K. S., Sørensen, H. T., & Nørgaard, M. (2013). The impact of comorbidity on cancer survival: a review. ***Clinical epidemiology, 5*** (Suppl. 1), 3–29. doi:10.2147/CLEP.S47150

2 Zamorano J.L. et al (2016). 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). ***European Journal of Heart Failure.*** 19: 9-42. doi: 10.1002/ejhf.654

3 Armenian SH et al. J Clin Oncol 34:1122-1130. © 2016: Overall survival in survivors who develop CVD is poor, emphasizing the need for targeted prevention strategies for individuals at highest risk of developing CVD.

4 Koroukian SM, Murray P, Madigan E. (2006) Comorbidity, disability, and geriatric syndromes in elderly cancer patients receiving home health care. ***J Clin Oncol***.24(15):2304-10. doi: 10.1200/JCO.2005.03.1567

5 Lee L., Cheung W.Y, Atkinson E., & Krzyzanowska M.K. (2011). Impact of Comorbidity on Chemotherapy Use and Outcomes in Solid Tumours: A Systematic Review. ***Journal of Clinical Oncology.*** 29:1, 106-117. doi: 10.1200/JCO.2010.31.3049

6 Sarfati, Diana, Bogda Koczwara, and Christopher Jackson. "The impact of comorbidity on cancer and its treatment." CA: a cancer journal for clinicians 66.4 (2016): 337-350.

7 Bellizzi K.M. and Rowland J.H. (2007). The Role of Comorbidity, Symptoms and Age in the Health of Older Survivors Following Treatment for Cancer. ***Future Medicine.*** Ageing and Health 3(5):625–635. doi: 10.2217/1745509X.3.5.625

8 Sarfati D., Koczwara B. & Jackson C. (2016). The Impact of Comorbidity on Cancer and Its Treatments. ***A Cancer Journal for Clinicians***. 2016; 66:337-350. doi: 10.3322/caac.21342

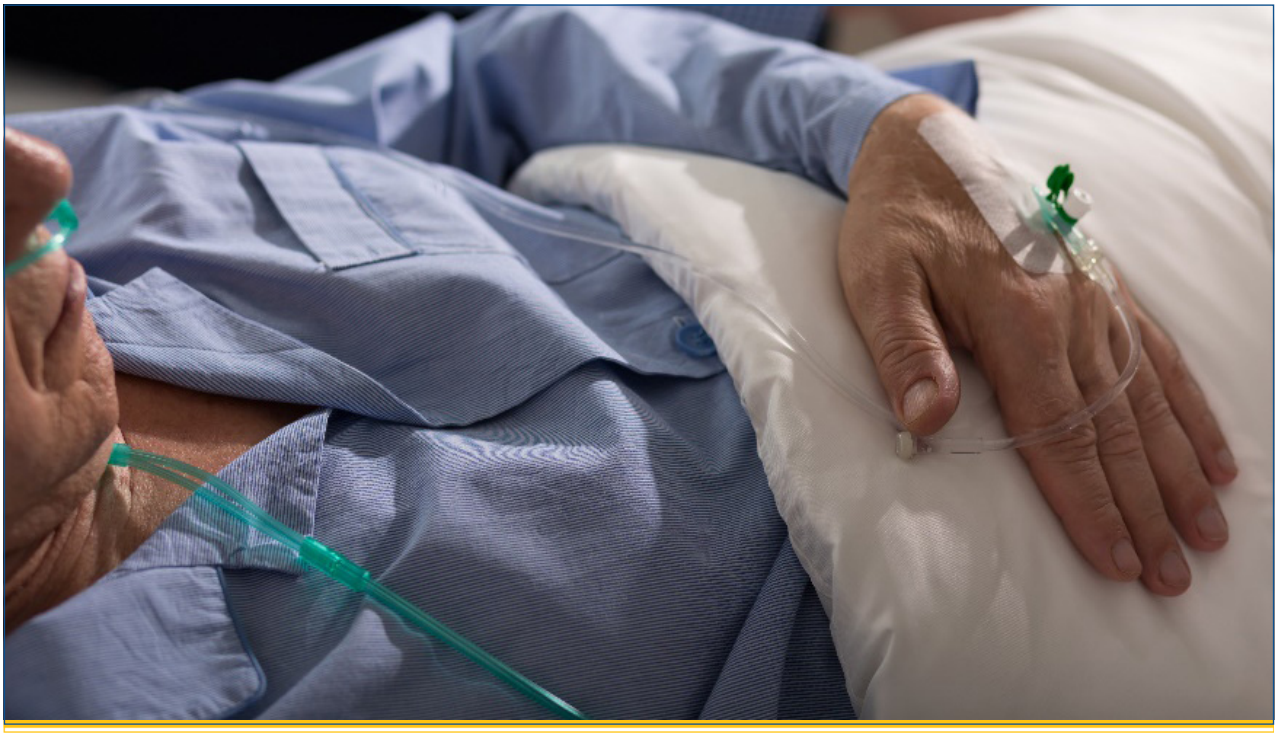
There is a need to alleviate the burden of cancer-related comorbidities and complications through better risk assessment and treatment, based on a conventional detection approach, which can reduce suffering and the number of premature deaths from complications and comorbidities. Patients with comorbidities are less likely to receive anti-cancer treatment with curative intent.[9,10] while they have a lower life expectancy and experience an inferior quality of life.[11] Furthermore, comorbidities are negatively associated with multiple indicators of quality of life, including nutritional status, physical functioning, general health, and pain.[12]

All the above highlight the paramount significance of comorbidities and their impact on cancer treatment, treatment efficacy, survivorship, and quality of life. It is time to increase the attention given to cancer patients' long-term well-being and quality of life, addressing the often-debilitating comorbidities and complications of cancer, both in terms of the disease itself and its treatments. An increasing population of survivors with needs for long-term follow-up care and management of complications and comorbid conditions will place a substantial burden on health systems, as well as on informal carers who provide essential support to them.

In light of the above, this white paper intends to provide an up-to-date overview of the most recent scientific evidence per comorbidity, to show the relevance and level of the burden of comorbidities on cancer patients and to propose some recommendations for policy makers to implement to help better manage cancer-related comorbidities. Indeed, the white paper comes at a crucial time for the EU, as the implementation phase of the Europe's Beating Cancer Plan will set the priorities of the European Union for the next years.

9 Sarfati D., Koczwara B. & Jackson C. (2016). The Impact of Comorbidity on Cancer and Its Treatments. ***A Cancer Journal for Clinicians***. 2016; 66:337-350. doi: 10.3322/caac.21342
10 Joseph M. Unger et al. Association of Patient Comorbid Conditions With Cancer Clinical Trial Participation JAMA Oncol. 2019 Mar; 5(3): 326–333. doi: 10.1001/jamaoncol.2018.5953 PMID: 30629092
11 Piccirillo JF, Feinstein AR. Clinical symptoms and comorbidity: significance for the prognostic classification of cancer. Cancer. 1996;77(5):834–842. doi: 10.1002/(SICI)1097-0142(19960301)77:5<834::AID-CNCR5>3.0.CO;2-E.
12 Malik, Monica & Vaghmare, Rama & Joseph, Deepa & Fayaz Ahmed, Syed & Jonnadula, Jyothi & Valiyaveettil, Deepthi (2016). Impact of Comorbidities on Quality of Life in Breast Cancer Patients. ***Indian Journal of Cardiovascular Disease in Women WINCARS***. doi: 10.1055/s-0038-1656491.

Cancer and associated thrombosis (CAT)/ venous thromboembolism (VTE)



Cancer-associated thrombosis (CAT) is one of the leading causes of death in cancer patients.[1,2] Thrombosis in cancer patients carries a high risk of recurrence, bleeding and mortality as compared with non-cancer patients. Given the numerous ways in which tumours, chemotherapy, and pre-existing patient risk factors can increase blood clotting, cancer patients are estimated to have a 2- to 20-fold higher risk of developing venous thromboembolism (VTE) when compared to non-cancer patients.[3] Up to 60% of VTE cases occur during or after hospitalisation, making it a leading preventable cause of hospital death.[4] Among survivors of VTE, a significant burden of chronic morbidity (including painful post-thrombotic syndrome) has been reported and is associated with a significant impact on the quality of life. The devastation that it can cause to survivors should not be understated, particularly among those that have already been given a life-altering cancer diagnosis. Therefore, there is a need to invest in CAT information, as well as recovery and support programs for patients.[5] The specific profiles of cancer patients, co-morbidities, the use of anti-cancer treatment, and the cancer progression itself represent a major therapeutic anticoagulant challenge while CAT remains the number one cause of death during chemotherapy and the second-leading cause of all cancer deaths (after disease progression).[6]

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The potential impact of CAT/VTE in cancer management

There are several thrombotic manifestations that can occur in cancer patients, such as arterial thrombosis (e.g. stroke) or venous thromboembolism (e.g. pulmonary embolism and deep vein thrombosis -DVT), and disseminated intravascular coagulation (a severe complication of abnormal clotting activation in cancer often characterised by both thrombosis and bleeding).[7,8] Several factors can increase cancer patients' risk of developing thrombosis,[9] related to both individual patient characteristics and cancer-related factors including age[10,11], ethnicity[12], comorbidities[13], immobility[14], previous history of VTE[15], cancer type[17,16], cancer stage,[15,17] time after diagnosis,[18,19] chemotherapy,[20,21,22,23] hospitalization or surgery[24] and the presence of central venous catheters.[21,25]

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8 Eichinger, S. Cancer associated thrombosis: Risk factors and outcomes. Thromb. Res. 2016, 140, S12–S17.
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The potential impact of VTE/CAT on cancer patients' quality of life and treatment costs

VTE is a life-changing diagnosis for cancer patients. Apart from the fact that it interferes with the cancer treatment and outcomes course, it is also both physically and emotionally stressful, negatively impacting patients' treatment experience and quality of life.[26]

The diagnosis of CAT can negatively impact cancer patients' treatment, leading to delays in cancer treatment and further afflicting their health.[38,27,28] A CAT diagnosis can be distressing, especially in those without prior knowledge of the symptoms, and significantly impact their lives as it is perceived as life threatening.[38,39,29,30] In addition, patients with pulmonary embolisms may have difficulty breathing, preventing them from completing even small tasks at home while symptoms of CAT may prevent them from resuming their normal life and daily activities without aid or die suddenly or in short time.[42,43]

Finally, treatment of VTE not only affects cancer patients' quality of life but also adds an extra financial burden to the healthcare system, mostly due to hospitalisation.[1,31,32,33]

The effectiveness and safety of thromboprophylaxis in cancer patients

CAT has devastating implications for affected individuals. However, CAT may be preventable in many patients if resources are put in place to ensure that high-risk patient subgroups are identified and treated appropriately with preventative measures. Moreover, adequate education around thrombosis risk may ensure that patients who develop thrombosis and their caregivers are equipped with the knowledge to realise the importance of seeking emergency medical attention. This can be lifesaving.

Both vascular/cardiological[34] and oncological clinical guidelines[35,36,37] recommend prophylactic anticoagulant treatment in specific groups of cancer patients.

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36 Key, Nigel S., et al. "Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO clinical practice guideline update." Journal of Clinical Oncology 38.5 (2020): 496-520.
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Thromboprophylaxis is recommended for most hospitalized patients with cancer, as well as outpatients with cancer who have other VTE risk factors.[50,51,52]

It is therefore vital that hospitalised cancer patients should be risk –assessed and considered for thromboprophylaxis.[38,39] As up to 78% of cancer patients who experience thrombosis do so as outpatients,[40] European guidelines should also recommend the routine and widespread use of thromboprophylaxis in this care setting.[1] It is also important that patients get greater education and awareness about the signs and risks of VTE (and ideally their treatment options).

38 Guijarro R, de Miguel-Diez J, Jimenez D, Trujillo-Santos J, Otero R, Barba R et al. Pulmonary embolism, acute coronary syndrome and ischemic stroke in the Spanish National Discharge Database. Eur J Intern Med. 2016;28:65-9.
39 Lyman GH, Eckert L, Wang Y, Wang H, Cohen A. Venous thromboembolism risk in patients with cancer receiving chemotherapy: a real-world analysis. Oncologist. 2013;18(12):1321-9.
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Cancer and cardiovascular complications

Most risk factors for cancer and cardiovascular diseases are the same. Due to ageing, a large part of the population has coexisting cancer and cardiovascular diseases. Active cancer strongly complicates the management of many cardiovascular diseases and leads to heavy ethic decisions (e.g., high invasive and costly therapy in cancer patients with uncertain prognosis). Many cancer treatments may lead to a cardiovascular complication (i.e., heart failure, coronary artery diseases, arrhythmias, stroke, etc.), which may occur acutely during treatment administration or also after many years requiring a tight long-term follow-up. Cardio-oncology is a relatively new subspecialty facing prevention, identification, and management of these toxic effects.

Cardioprotective Strategies on the prevention, early identification, and management of cancer treatment toxic effects

Nowadays, cardiotoxicity produced by cancer therapies is still a major limitation that can significantly affect the clinical benefits and cancer patients' survival and quality of life.[1,2,3] The increased burden of cancer treatment-related cardiotoxicity is also rising due to the increasing number of cancer survivors, the frequent use of anthracyclines, new antitumour agents with potential cardiotoxic effects, and treatments combinations[2,4,5]

1 DeSantis C, Lin C, Mariotto A, et al. Cancer treatment and survivorship statistics, 2014. CA Cancer J Clin. 2014;64:252–71.
2 Truong J, Yan AT, Cramarossa G, Chan KKW. Chemotherapyinduced cardiotoxicity: detection, prevention and management. Can J Cardiol. 2014;30:869–78.
3 Sturgeon, Kathleen M., et al. "A population-based study of cardiovascular disease mortality risk in US cancer patients." European heart journal 40.48 (2019): 3889-3897.
4 Lenihan D, Cardinale D. Late cardiac effects of cancer treatment. J Clin Oncol. 2012;30:3657–64
5 Zamorano, José Luis, et al. "The cancer patient and cardiology." European journal of heart failure (2020).

Some of the most important cancer treatment-related abnormalities include left ventricular dysfunction (LVD), acute coronary syndromes, hypertension, arrhythmias, and thromboembolic events.[2] LVD is the most common and feared one as it has an impact on cancer patients' cardiac outcomes but also limits the therapeutic options in case oncologic therapy for cancer relapse or persistence is necessary[2,6]

The best practice against cancer treatment cardiotoxicity is prevention. A multidisciplinary team of dedicated professionals should provide specialised cardiovascular evaluation and care at all stages of the cancer process[7].

Prior to cancer therapy, factors that play an important role are: the identification of potential cancer risk factors, the treatment-related cardiovascular complications**,** the optimisation of cardiovascular health to ensure safe cancer surgery and allow optimal local and systemic anti-cancer therapy, and the interdisciplinary discussion to ensure most efficacious cancer treatment without substantial cardiovascular harm, when the optimisation of cardiovascular health cannot be achieved.

During cancer treatment: early identification of cardiovascular complications**,** appropriate treatment of cardiovascular complications and interdisciplinary discussion about making clinical decisions in cancer patients experiencing cardiovascular side effects.

After cancer treatment: optimisation of preventive strategies and screening for late-onset complications re-assessment of risk for cardiovascular complications in patients in need of treatment for secondary cancers.[8,9,10]

Cardiotoxicity prevention should be the first step of cancer treatment by evaluating the cardiovascular profile of each cancer patient individually and selecting the best approach in terms of drugs and administration process.[4] However, pre-existing cardiovascular risk factors may increase the risk of cardiotoxicity.[2,11] Managing these factors by reducing the blood pressure, cholesterol, blood glucose, and smoking cessation are suggested actions to reduce the potential risk for cardiotoxicity during cancer treatment.[12,13]

6 Cardinale, D., Biasillo, G., & Cipolla, C. M. (2016). Curing cancer, saving the heart: a challenge that cardioncology should not miss. Current cardiology reports, 18(6), 51.
7 Lancellotti, Patrizio, et al. "Cardio-oncology services: rationale, organisation, and implementation: a report from the ESC Cardio-Oncology council." European heart journal 40.22 (2019): 1756-1763.
8 Zamorano, Jose Luis, et al. "2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC)." European heart journal 37.36 (2016): 2768-2801.
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13 Armstrong GT, Oeffinger KC, Chen Y, et al. Modifiable risk factors and major cardiac events among adult survivors of childhood cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2013;31(29):3673–80.

Therefore, the prevention of cardiotoxicity occurring from cancer treatment is an important issue for both cardiologists and oncologists. Close collaboration in these two areas and further research led to the development of novel medical protocols on cardio-oncology by investigating innovative strategies such as, recent innovations with regards to radiation therapy for cancer patients that have reduced the radiation doses to non-target structures,[14,15,16,17] serum biomarkers which are a valuable tool for the baseline risk assessment and diagnosis of cardiovascular disease in cancer patients under cardiotoxic cancer treatments,[18,19,20] adding cardioprotectants[13,21,22,23] such as dexrazoxane[24,25] or cardiovascular agents[26,27,28,29,30,31,32,33] to chemotherapy, myocardial deformation parameters and strain rate imaging in detecting early subclinical changes in cardiac function during and after chemotherapy[34], collecting evidence-based indications, and developing interdisciplinary expertise that we guarantee correct clinical administration, and provide the best therapeutic opportunities for cancer patients is of paramount significance.

Finally, the clinical problem "competing risks" between treatments for different diseases such as cancer and the co-existence of comorbidities is a reality often faced in onco-cardiology. This problem raises ethical questions that future research should stress.

14 Lai J, Hu S, Luo Y, et al. Meta-analysis of deep inspiration breath hold (DIBH) versus free breathing (FB) in postoperative radiotherapy for left-side breast cancer. Breast Cancer. 2020;27(2):299–307.
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18 Pudil, Radek, et al. "Role of serum biomarkers in cancer patients receiving cardiotoxic cancer therapies: a position statement from the Cardio-Oncology Study Group of the Heart Failure Association and the Cardio-Oncology Council of the European Society of Cardiology." European Journal of Heart Failure 22.11 (2020): 1966-1983.
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23 FDA statement on Dexrazoxane. www.fda.gov/Drugs/DrugSafety/ucm263729.htm.
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28 Seicean S, Seicean A, Alan N, Plana JC, Budd GT, Marwick TH. Cardioprotective effect of β-adrenoceptor blockade in patients with breast cancer undergoing chemotherapy: follow-up study of heart failure. Circ Heart Fail. 2013;6:420–6.
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31 Akpek M, Ozdogru I, Sahin O, et al. Protective effects of spironolactone against anthracycline-induced cardiomyopathy. Eur J Heart Fail. 2015;17:81–9.
32 Henninger C, Huelsenbeck S,Wenzel P, et al. Chronic heart damage following doxorubicin treatment is alleviated by lovastatin. Pharmacol Res. 2015;91:47–56
33 Seicean S, Seicean A, Plana JC, Budd GT, Marwick TH. Effect of statin therapy on the risk for incident heart failure in patients with breast cancer receiving anthracycline chemotherapy: an observational clinical cohort study. J Am Coll Cardiol. 2012;60:2384–90.
34

The combination of cancer and comorbidities also influence the nutrition status. Comorbidities can change the priority and influence individual recommendations. For this reason it is important that individualised nutritional care is included as a standard part of care, particularly for patients with comorbidities.

Many patients may present with weight changes (loss or gain), whilst focusing on a BMI to assess for, and highlight those at risk misses the majority of patients at risk of malnutrition or poor diet quality.[1] It is estimated that the deaths of 10-20% of patients with cancer can be attributed to malnutrition rather than to the malignancy itself.[2] Thus, nutrition is an important aspect of multimodal cancer care. There is consensus on a framework for the definition and classification of cancer cachexia and assessment should include: anorexia or reduced food intake, catabolic drive, muscle mass and strength, functional and psychosocial impairment.[2] Yet, recent studies in European hospitals found that only 30%-60% of patients with cancer who were at risk of malnutrition received nutritional support (i.e., oral nutritional supplements, enteral and/or parenteral nutrition)[3].

1 Sarfati D., Koczwara B. & Jackson C. (2016). The Impact of Comorbidity on Cancer and Its Treatments. A Cancer Journal for Clinicians. 2016; 66:337-350. doi: 10.3322/caac.21342
2 Fearon, Kenneth, et al. "Definition and classification of cancer cachexia: an international consensus." The lancet oncology 12.5 (2011): 489-495.
3 Arends J, Baracos V, Bertz, H, et al. ESPEN expert group recommendations for action against cancer related malnutrition. Clinical Nutrition 2017; 36:1187-1196

Availability of nutritional support

There are several international guidelines and recommendations which include evidence-based practices in order to translate current evidence and expert opinion into recommendations for the identification, prevention, and treatment of reversible elements of malnutrition in adult cancer patients.[4,5] However, evidence from the existing literature[6,7,8,9,10,11,12,13,14,15] shows that oncologists and patients are often unaware of cancer-related malnutrition and its impact on oncologic and antic-cancer treatment outcomes and survival. Furthermore, little research exist providing nutrition recommendation for cancer and comorbidities. This important issue varies, resulting in the fact that many patients who are in need of adequate and timely nutritional support do not receive it.[16,17] The need for undernutrition screening is also an issue in oncology. The use of screening tools is largely neglected; nutritional status is often assessed by the surgeons, and nutrition is not consistently modified according to risk factors[18].

An important issue to address is the fact that nutritional support and care standards (including access to screening for malnutrition and access to specialist oncology dietitians) vary considerably between countries and within the regions of the same country in many cases.[19] During the past years, some countries such as Scotland and the Netherlands have established mandatory screening for malnutrition in cancer patients.[3]

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Nutrition and course of treatment, disease progression and recovery

Scientific data support the association between nutritional status and chemotherapy-related toxicity[20,21] and chemotherapy completion[22,23,24,25,26,27] while more post-operative complications (particularly wound infections), were recorded in patients with increased risk of malnourishment.[28,29,30,31,32,33,34]

With regards to the association between nutritional status and course of treatment of radiotherapy, the results are inconsistent.[35,36,37,38,39,40] Irrespective of treatment path, healthcare costs and resources utilisation such as hospital admissions, length of stay, readmission

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rate) is higher in patients with a risk of malnutrition/malnourishment.[41,42,43,44,45,46,47,48,49,50] Finally, the risk of malnutrition is associated with poorer QoL of cancer patients.[51,52] This is also an important issue among older cancer patients associated with increased geriatric assessment, reduced QoL, and increased health care utilization.[53]

Overall, malnutrition is associated with an increase in treatment-related toxicity, reduced response to cancer treatment, impaired quality of life and a worse overall prognosis.[54,55]

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Cancer and coeliac disease

Lymphomas, mostly T-cell type, and other malignant tumours, particularly carcinoma of the small bowel, less frequently of stomach and oesophagus, are associated with coeliac disease (CeD).[1] If diagnosed only in adults or with a substantial delay, the risk for complications increases. Depending on the diagnostic latency or non-adherence to the therapy, some of these long-term consequences are only partially reversible. If untreated, patients still may develop long-term health consequences later in life. If symptoms and signs of CeD do not resolve or re-occur on a gluten-free diet, patients may suffer from a severe but rare complication called refractory celiac disease (RCD).[2]

In the past, untreated CeD was associated with higher rates of malignancies than the general population (oropharyngeal and oesophageal cancer, lymphoma, and small bowel carcinoma).[3] However, this risk is now downgraded.[4] Unlike the general population, small bowel adenocarcinoma as a complication of CeD is more likely to be developed in the jejunum than in the duodenum.[66] In addition, strict adherence has been correlated with histological remission, while patients on a gluten-free diet for more than five years have the same overall risk of malignancy as the general population.[5,6,]

As for the treatment options, this includes surgical resection and adjuvant chemotherapy for positive lymph nodes, while for metastatic disease, chemotherapy is the most recommended option. The prognosis of 5-year survival for small bowel adenocarcinoma ranges between 39% and 46%.[7] However, survival in CeD-associated small bowel adenocarcinoma is significantly better than that in stage-matched patients without CeD.[8]

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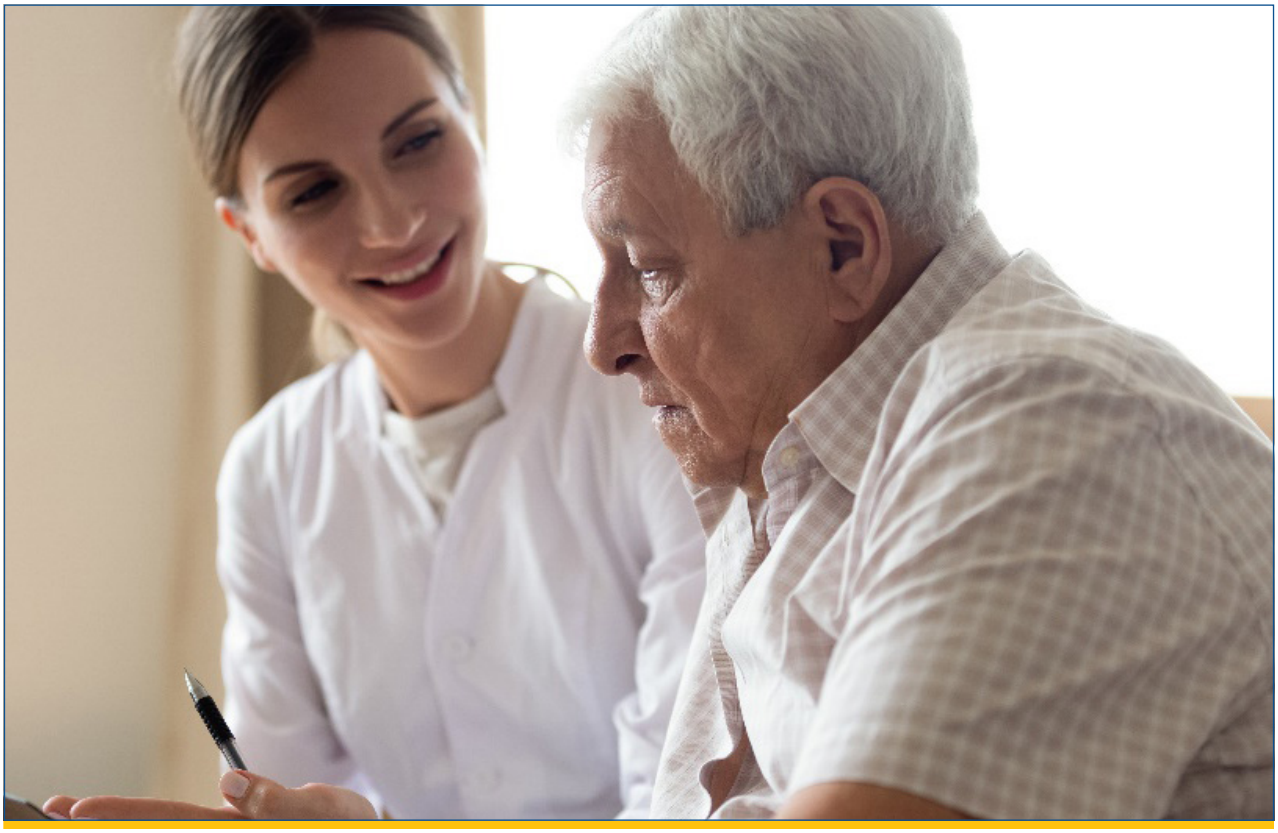

There is consistent evidence that people living with obesity have an increased risk of developing several types of cancer.[1] It does not only have to do with more fat mass that causes comorbidities or complications but the lack of muscle mass while being overweight, i.e., sarcopenic obesity. This can have a significant impact on patients', cancer progression, quality of life, survivorship and the likelihood of recurrence.[2, 3] This is particularly important in Europe, as the percentage of new cancer cases attributable to overweight and obesity is higher in the region than the global average.[4]

The impact of obesity in cancer progression, treatment efficacy and recurrence

The association of cancer and obesity may be a multifactorial issue due to the fact that with obesity people tend to undergo less frequent screening, delaying the diagnosis and eventually being diagnosed at a more advanced stage of the disease. In addition, increased BMI is associated with higher levels of mortality from cardiovascular disease and cancer-associated thrombotic microangiopathy, while several diagnostic tests, such as endoscopies,

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mammography, and magnetic resonance imaging, may be more difficult to perform on people of a higher weight/with obesity.[5]

Recent literature supports that treating cancer with surgery, surgical recovery and outcomes are more challenging and can worsen the condition of cancer patients with obesity.[5] Treatment of cancer may also be a more challenging situation as there is a higher anaesthetic risk during surgery, intraoperative bleeding and post-operative complications.[6,7,8,9,10] It is important to highlight the role of obesity in surgical outcomes for cancer patients even if it is minor complications, as this affects the course of treatment and their quality of life and in addition increases the cost of their therapy and delays in the receipt of adjuvant therapy, such as chemotherapy and radiation.[11]

As chemotherapy involves systemic treatment with cytotoxic drugs, most of the doses and drug combinations provided are calculated based on their body surface area (BSA)[12,13], although a large number of cancer patients of a higher weight/with obesity receive limited dosages as oncologists often worry about the treatment toxicity if patients receive a dose based on their actual body weigh[18]. Adding to that, many cancer patients with obesity are likely to suffer from several comorbidities such as vascular disease or diabetes, increasing like this the peripheral neuropathy.[14] Reducing the chemotherapy dose provided is associated with disease reduced efficacy of the treatment[18,15], recurrence and mortality[17], potentially contributing to reduced survival among patients with obesity.[16]

Results from studies on cancer patients with obesity and radiotherapy indicated a link between obesity and inferior outcomes in prostate cancer,[17] increased treatment-related toxicities on obese patients with cervical cancer,[18] while for breast cancer patients, large breast size and high BMI was associated with increased risk of acute late dermatitis after

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whole-breast radiation therapy.[19,20] Finally, there was a 21-25% increase in recurrence or biochemical failure in prostate cancer patients with increased BMI.[21] These results are indicative of the need for appropriate research into treatments of cancer for those of a higher weight as the current situation for these patients may be causing harm.

The goal for the weight of cancer patients after treatment is very important as both pre-diagnostic and post-diagnostic obesity are associated with higher cancer-specific (breast) and overall mortality after adjusting for multiple confounders, including tumour stage.[22,23,24,25]

The impact of obesity in cancer patients QoL

Cancer patients after treatment often are experiencing reduced quality of life, including functional impairment, psychosocial distress, limitations in social functioning, and emotional problems.[26] Moreover, obesity is associated with lower physical and functional well-being and poorer quality of life for endometrial,[27] breast,[28] prostate,[29] and colorectal cancer survivors,[30] while studies with heterogeneous samples of cancer survivors from several cancer types confirmed the impact of obesity on the patients quality of life.[31] It is finally associated with higher prevalence and severity of site-specific symptoms, such as incontinence, in prostate cancer survivors.[35,36,37,32] Cancer-related fatigue (CRF) is very common among cancer survivors,[33] while obesity is positively associated with CRF,[34,35,36] and the severity of CRF is also associated with higher BMI.[34] Appropriate support, treatment and reserach needed agnin this population.

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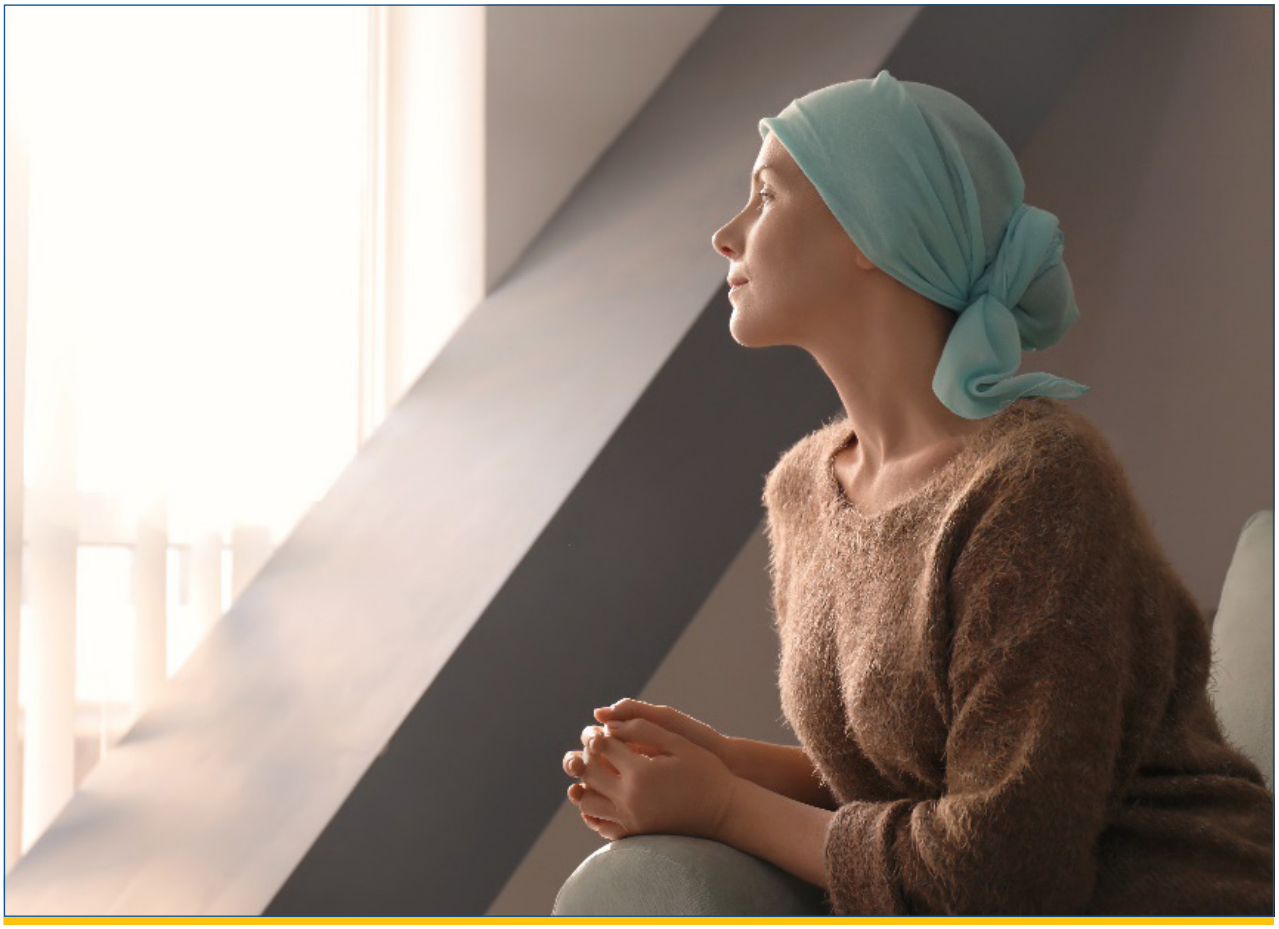
Cancer and mental health



Depression is a comorbid disabling syndrome that affects approximately 15% to 25% of cancer patients.[1] Only 20% of people with cancer who also have anxiety and/or depression are recognised as having a mental health disorder and receive appropriate treatment.[2] Besides, some cancer patients (particularly those with head and neck cancers, which have the highest incidence of suicide in all oncology populations) are at high risk for developing depressive symptoms and a major depressive disorder as comorbidities.[3]

Elevated levels of anxiety are a common condition for cancer patients, with 10.3% of those receiving treatment for cancer meeting clinical criteria for an anxiety disorder.[4] Prevalence of anxiety is even higher for patients who have been living with cancer for >2 years[4] (17.9%).

Evidence also supports that anxiety and depression are more prevalent among cancer patients with comorbidities, while the presence of comorbidities was negatively associated with cancer occurring anxiety and depression[5].

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Cancer treatment and patients' mental health

Cancer diagnosis and treatment does not have an impact only on patients' body but also their psychological health. Cancer, depending on whether it affects a visible part of the body (i.e., breast cancer, head and neck cancers) or not (i.e., leukaemia, lung cancer, etc.), has evident repercussions for the patients' body image. The type of therapy (i.e., surgery, chemotherapy, radiotherapy, etc.) also have an impact on a patient's psychological functioning due to physical changes such as amputations, hair loss, etc., or the concurrent symptoms such as fatigue, pain, nausea, etc[6].

In addition, the daily life experience of cancer patients is also affected by other factors which are important in their everyday life, such as performance status and functional activity, problems in carrying on daily activities, poor concentration, memory impairment, or altered sexuality,[7] loss of certainty, the fact that they need to depend on others, reduction of self-esteem, the change of perspective about the future, problem on returning to work, and the threat of possible death and may be evident in different phases from cancer diagnosis to survivorship or palliative care and the course of cancer of the end of life. [6,7]The prevalence of major depression is higher in patients with lung cancer, gynaecological cancer, breast cancer, colorectal cancer, and genitourinary cancer.[8] Depression and anxiety levels also vary according to the treatment stage. [9,10,11,12,13]

The impact of mental health on cancer patients' treatment and disease progression

Despite the heterogeneity within the available studies, the evidence for the role of mental disorders in tumour progression and cancer-related mortality has been rapidly accumulating.[14] The presence of mental disorders is associated with a higher rate of all-

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cause[15,16,17] or cancer-specific[18,19,20,21] mortality which appears to be stronger in the case of early-stage cancers.[30] In addition, anxiety, and depression might result in decreased adherence to treatment, poorer cancer survival, increased suicide risk, and additional health expenditures.[22] Finally, cancer patients with psychiatric distress must be treated immediately, as delayed diagnosis and treatment may affect their overall health.[23]

Cancer treatment and caregivers' mental health

The impact of providing informal care in cancer patients is well documented.[24] Between 4 and 38% of cancer patients' caregivers suffer from psychiatric disorders[25,26] and they often reported neglected health and more anxiety and fear of cancer recurrence than the patients themselves.[27] Factors such as patient's condition, caregiving burden, duration of caregiving, spouse caregiver, caregiver being unemployed, a caregiver with chronic disease, caregiver's sleep quality, caregiver's avoidance, financial problems, and female sex were positively associated with depression[28].

In addition, there is a strong relationship between the patients' and caregivers' distress and QoL, depicting how important care is for caregivers .[29] Caregivers of cancer patients with more advanced tumour stages[37] or incurable cancer[30,31,32,33,34] showed an increased psychological burden. Finally, anxiety and depressive symptoms were positively associated,[35]

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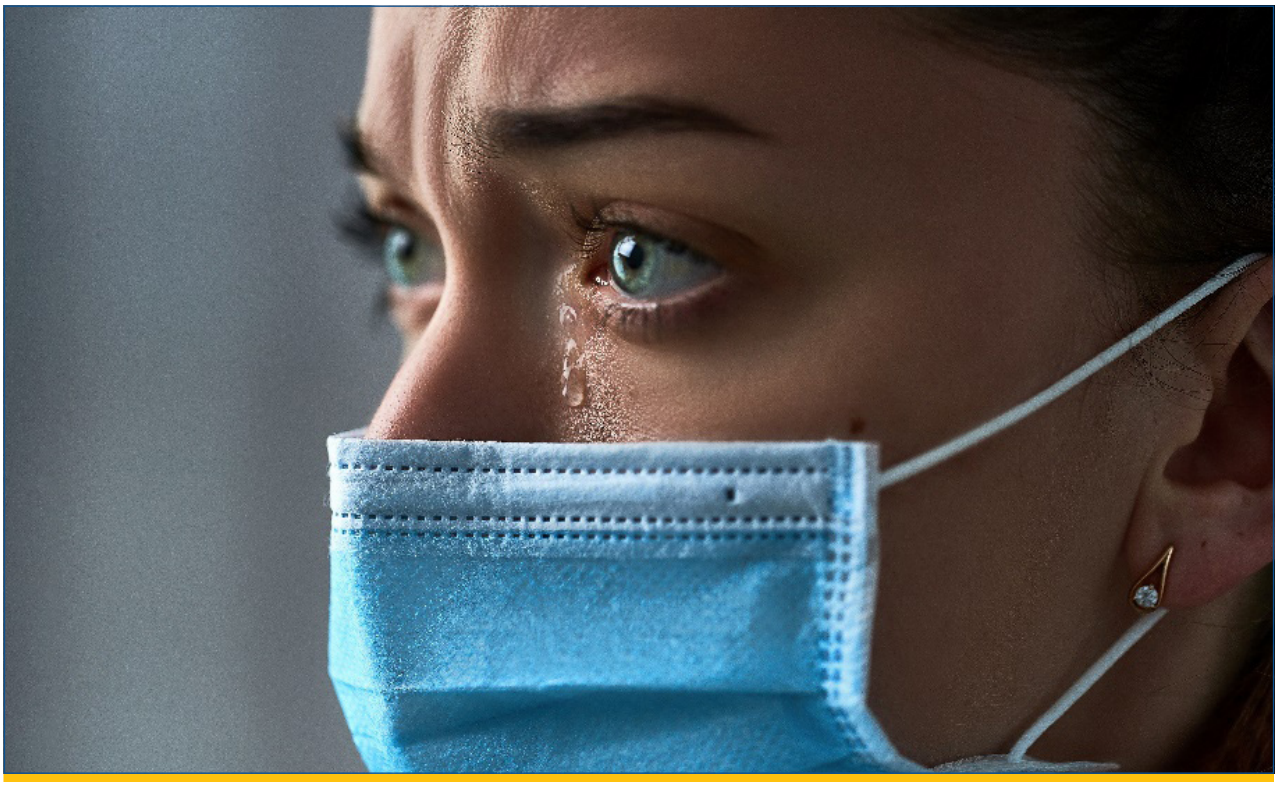
while caregivers perceived hope, burden, resilience, coping strategies, self-care practices, night-time sleep, physical activity, and pre-loss grief were also associated with depressive symptoms.[46,48,51,36,37,38]



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cancer caregivers' physical and psychological well-being. Eur J Cancer Care. 2018;27:e12833

Cancer and neuro(-psycho)logical complications

Cancer and its treatment can affect the nervous system and may result in significant neurologic morbidity and mortality. These effects may be direct or indirect, as in paraneoplastic neurological syndromes. Around 15-20% of cancer patients have neurological complications during their illness.[1] Treatments of cancer, including neurosurgery, cranial radiotherapy (both in case of CNS cancer), and chemotherapy, can each damage the nervous system;[2] of which chemotherapy-induced peripheral neuropathy (CIPN) is a common dose-limiting side effect experienced by patients receiving treatment for cancer.[3] Complications are associated with age; the impact will depend on several issues such as tolerance of treatment, development of persisting or late toxicity, and the influence of other concomitant diseases.[4] With improved cancer treatments and longer survival, the late effects of CIPN continue to affect cancer survivors.

Neurological or cognitive complications during and after cancer treatment. The impact on survivorship and quality of life

Cognitive impairment in cancer patients is frequently observed both during the treatment stage and remission.[5,6,7,8] Literature reveals that a history of cancer is associated with a 40% increased likelihood of self-reported memory problems[9] while 30% of cancer patients exhibit cognitive impairment before the treatment, 75% develop measurable cognitive impairment during the treatment, and 35% will continue to deal with cognitive difficulties for short or longer periods after the treatment.[6] Cancer-related cognitive decline may have significant consequences, especially for older adults, functional and physical abilities, level of independence, ability to make decisions, treatment adherence, overall quality of life, and ultimately survival.[10]

Cancer itself could lead to cognitive changes and impairment. In cancer patients with brain tumours specifically, the location and state of the lesion can eventually influence the presence, intensity, and pattern of resulting cognitive impairments.[11] Different papers

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3 Nathan P. Staff, MD, PhD, Anna Grisold, MD, Wolfgang Grisold, MD, and Anthony J. Windebank, MD (2017). Chemotherapy-Induced Peripheral Neuropathy: A Current Review
4 Grisold W., Grisold A. Loscher W.N. (2016) Neuromuscular complications in cancer. doi: https://doi.org/10.1016/j.jns.2016.06.002
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6 Janelsins M, Kesler S, Ahles T, Morrow G. Prevalence, mechanisms, and management of cancer-related cognitive impairment. Int Rev Psychiatry. 2014;26:102–113.
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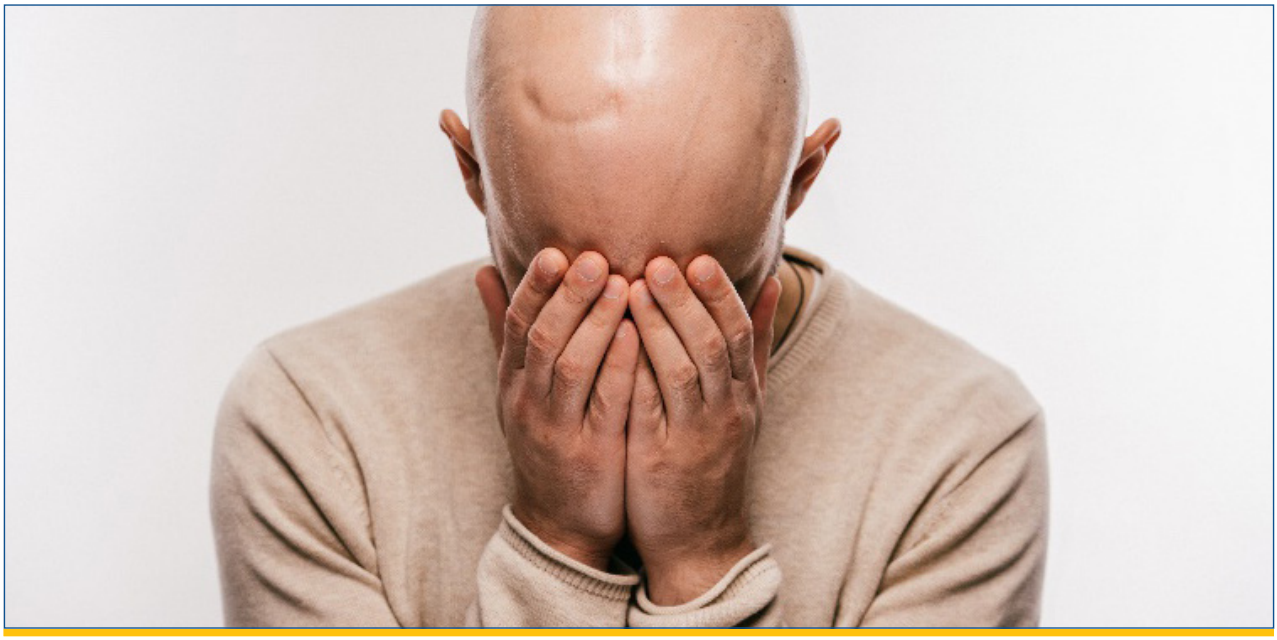

have reviewed the symptoms in glioma patients describing as the most important ones being cognitive deficits, seizures, depression, drowsiness, dysphagia, headache, confusion, aphasia, motor deficits, fatigue, and dyspnoea.[12,13,14]

Cancer patients with brain tumours can develop cognitive impairments related to their attention, memory, and executive function.[15,16] However, cancer-related cognitive impairment (CRCI) also have been documented in patients with non-central nervous system (non-CNS) cancer before the treatment, including verbal memory, language, visual-spatial skills, executive function, and psychomotor function.[17,18,19]

Chemotherapy-induced neurotoxicity is most well-described for peripheral neuropathy (CIPN) and myopathy. CIPN is the most commonly manifested as a dose-dependent length-dependent sensory axonopathy. In severe cases of CIPN, alterations of treatment such as the reduction of the chemotherapy dose, administration delays, or discontinuation of treatment may occur.[20.21,22]

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In addition, the impact of chemotherapy on the central nervous system increasingly receives attention, with the occurrence of CRCI in approximately 13-70% of cancer patients.[5,8,23,24,25,26] The developed impairment due to treatment may be short term or persist for a longer period[7] for cancer patients under treatment or remission. They may experience problems in memory, attention, executive function, processing speed, visual and verbal memory, and language.[16,27,28,29,30,31]

A recent review also found that chemotherapy, either alone or in combination with hormonal therapy, can have an impact on the cognition of patients from several cancer types.[32]

Patients who are under radiation treatment to the brain have been reported to experience fatigue and headaches, as well as cognitive impairment, with the strongest effects in the case of whole-brain radiotherapy (WBRT). [33]

It was also reported that CNS cancer patients receiving radiotherapy are at risk of developing subacute toxicity shortly after the therapy, which has been associated with impairment in multiple cognitive domains, such as processing information, attention, verbal memory, executive functioning, and fine motor dexterity.[10] More specifically, increased exposure of radiation to the bilateral hippocampi has been associated with severe, irreversible long-term memory loss, which can occur after months or even years from the treatment.[11]

All the above mentioned impairments on cognition negatively impact cancer patients' daily functioning, quality of life and capacity to work.[34] Several studies have also highlighted the fact that cancer treatment can pose a significant burden on patients' productivity and ability

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33 Soffietti R, KocherM, Abacioglu UM, et al. A European Organisation for Research and Treatment of Cancer phase III trial of adjuvant whole-brain radiotherapy versus observation in patients with one to three brain metastases from solid tumours after surgical resection or radiosurgery: quality-of-life results. *J Clin Oncol*. 2013;31:65–72.

34 Pendergrass, J. C., Targum, S. D., & Harrison, J. E. (2018). Cognitive impairment associated with cancer: A brief review. Innovations in clinical neuroscience.

to work because of the adverse effects that can lead to either cognitive impairments[35,36,37,38,39] or difficulty in lifting heavy loads and keeping pace with others at work.[40]

In addition, several comorbidities can impact the cognitive function of patients with cancer and those in remission. Depression, anxiety and fatigue[41,42,43,44,45] can each adversely affect cognitive functioning, whereas pre-treatment worry was found to be associated with cognitive impairment and alterations in brain function.[46,47,48,49] Other studies have found a relationship between reported mood symptoms[15,50,51,52] and treatment expectations[53] of cognitive impairment in patients with cancer resulting in poorer quality of life.

As cancer patients now live longer and, in many cases, with cognitive problems due to treatments, prevention and management of these problems are important.[54]

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44 Vardy JL, Stouten-Kemperman MM, Pond G et al. A mechanistic cohort study evaluating cognitive impairment in women treated for breast cancer. Brain Imageing Behav 2019; 13(1): 15–26.
45 Li J, Yu L, Long Z et al. Perceived cognitive impairment in Chinese patients with breast cancer and its relationship with post-traumatic stress disorder symptoms and fatigue. Psychooncology 2015; 24(6): 676–682.
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52 Krolak D, Collins B, Weiss L, et al. Cognitive function and its relationoship to other psychosocial factors in lymphoma survivors. Support Care Cancer. 2017;25:905–913.
53 Schagen S, Das E, Vermeulen I. Information about chemotherapy-associated cognitive problems contributes to cognitive problems in cancer patients. Psychooncology. 2012;21:1132–1135.
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Cancer and pain

Pain is the most common symptom of cancer at diagnosis and rises in prevalence throughout and beyond cancer treatment. Persistent cancer pain can, in some individuals, lead to the development of widespread chronic pain.[1] Improved early cancer diagnosis and enhanced treatments will continue to enable many patients to live with cancer as a chronic disease. In patients who survive cancer or in those who live with advanced progressive disease, pain is a very common symptom and affects up to 40% of cancer survivors and at least 66% of patients with advanced progressive disease. Between 33% and 40% of cancer survivors suffer from chronic pain, and studies have shown that at least one-third of patients are often undertreated due to inadequate attention to pain during regular oncological treatment and unfair or delayed access to opioids.[2,3,4,5] Some of these patients will continue to experience pain that negatively affects their quality of life, and some patients may continue to use high doses of opioids, previously required for adequate pain control, which is no longer needed while causing severe side effects.[6]

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Pain and impact on survivor's quality of life

Pain during cancer treatment is associated with the stage of the disease and the location of the cancer.[7,8] Results have showed that depending on the stage of the disease, pain prevalence rates were 39.3% after curative treatment, 55.0% during anti-cancer treatment, 66.4% in advanced, metastatic, or terminal disease, and 50.7% in all cancer stages[9].

Increased pain is also associated with specific cancer types[10,11] such as lung cancer, breast cancer, leukemia/lymphoma, and colorectal cancer. Breast cancer patients' level of pain may increase depending on the size of the tumour, the location, lymphedema, and potential spread to the nervous system, which can cause lingering neuropathic pain.[12] Increased pain for lung cancer patients is a possibility regardless of the cancer stage (early or advanced), often attributed to neurologic damage from cancer treatment or metastasis to other organs.[13]

Pain, as it is experienced from cancer patients and especially untreated or inadequately treated pain, can severely impact their physical and psychological health[14,15] , functional status, and QoL[15,16] of cancer patients. In addition, experienced pain has a negative impact on patients' daily activity, mobility, functioning, sleep quality, entertainment, social interaction, and professional life. [15,17,17,18] The level of the pain experience and the duration affects cancer patients QoL, [16,19,20,21] while poor QoL exacerbates the severity of the pain[15]. Very intense and severe pain may also lead to an unwillingness to take medications and a desire to end life earlier[22]

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14 Deng D, Fu L, Zhao YX, et al. The relationship between cancer pain and quality of life in patients newly admitted to Wuhan Hospice Center of China. Am J Hosp Palliat Care. 2012;29(1):53–59.
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Moreover, approximately 41.5% of cancer patients report chronic pain[23] and they suffer from psychological symptoms such as depression,[24 25,26] psychological distress and anxiety.[27,28] They also report lack of sleep, fatigue,[29] while cancer patients with comorbidities may have significantly greater physical functional pain and associated limitations and may be less likely to improve with standard pain management therapies.[30]

Sufficient assessment of pain, including its impact on function and quality of life, is a very important aspect for cancer patients, while long-term assessment can possibly identify new or previously unrecognised painful consequences of treatment.[31] Finally, the management of pain can effectively be accomplished by regular screening, which will contribute to recognizing pain in an early stage, the proper characterization of the pain, the determination of optimal pharmacologic or nonpharmacologic treatment options, patients education on coping skills and patient follow-up to titrate and adjust pain treatment if necessary.[32]

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Cancer and ageing

Cancer is increasingly prevalent with increasing age, suggesting the necessity to better understand the biology of ageing and its impact on cancer. This would enable a more comprehensive and cancer-specific assessment and management of older cancer patients.[1] Although there is not a unified approach for ageing, the broader one refers to ageing as the "*all time-associated events that occur during the post maturation period in the life span of an organism. For humans, ageing is defined as a universal biological process that manifests itself as a decline in functional capacity and an increased risk of morbidity and mortality over time*".

All the above highlight the fact that chronological age alone adds little information on frailty, which is characterised by decreased physiologic reserve and increased vulnerability to stressors leading to severe adverse health outcomes in older adults, including post-operative complications on anticancer treatments[2], increased mortality[3], and crucial impact on survivorship.[4]

Treatment-related decisions on older cancer patients are frequently a challenge that can be influenced by many factors, such as the type of cancer, the clinical setting, and patients'

1 Zhang, X., Meng, X., Chen, Y., Leng, S. X., & Zhang, H. (2017). The biology of ageing and cancer: frailty, inflammation, and immunity. The Cancer Journal, 23(4), 201-205.
2 Courtney-Brooks M, Tellawi AR, Scalici J, et al. Frailty: an outcome predictor for elderly gynecologic oncology patients. Gynecol Oncol. 2012; 126:20–24.
3 Aaldriks AA, van der Geest LG, Giltay EJ, et al. Frailty and malnutrition predictive of mortality risk in older patients with advanced colorectal cancer receiving chemotherapy. J Geriatr Oncol. 2013;4:218–226.
4 Bennett JA,Winters-StoneKM,Dobek J, et al. Frailty in older breast cancer survivors: age, prevalence, and associated factors. Oncol Nurs Forum.2013;40:E126–E134.

fitness and comorbidities. In the context of more limited survival benefits in older individuals receiving standard anticancer therapeutic approaches, treatment decisions should also take into consideration potential effects on QoL throughout the entire disease trajectory. In older patients with cancer, it is key to consider not only tumour characteristics but also pursuing geriatric assessments able to systematically investigate factors crucial to their wellbeing, such as comorbidities, polypharmacy, functional status, mobility, nutritional status, mental health, cognitive status, social support and QoL.[5]

Access to innovative cancer treatments by older cancer patients with comorbidities

Treating cancer in older patients at risk of complications remains challenging, mostly due to the lack of resources and workforce training in the management of the complex needs of this specific population. Also, although the majority of cancer incidence and mortality occurs in patients ≥ 65 years old, this age group is still underrepresented in randomised clinical trials (RCTs) that constitute the evidence base informing standard anticancer treatment decisions.[6,7,8] This leads to a remaining discrepancy between those fitting the criteria to be selected for a study and the real-world patients who may have a higher risk of complications based on geriatric assessments and ultimately are considered for the treatments investigated in clinical trials. Factors such as alterations in pharmacokinetics and pharmacodynamics of systemic agents due to ageing, comorbidities, and polypharmacy are significant for the course of treatment and need to be taken into consideration in the management of older patients with cancer.[9,10]

Once new drugs, treatment options or indications are approved and due to this gap of evidence, oncologists are often asked to extrapolate evidence supporting specific treatment approaches that has been generated in younger, healthier patients, who may have fewer comorbidities, higher medication tolerances, and lower risks of adverse drug effects. This practically means that in most cases, the recommended drug dosages are different for older cancer patients, and some of them may are at increased risk of treatment-related complications.[5]

In addition, despite the presence of comorbidities and frailty in older cancer patients, which often excludes them from specific therapeutic options such as surgery, older

5 Scotté, Florian, et al. "Addressing the quality of life needs of older patients with cancer: a SIOG consensus paper and practical guide." Annals of Oncology 29.8 (2018): 1718-1726.
6 Abbasi J. Older patients (still) left out of cancer clinical trials. JAMA. 2019.
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9 Loh KP, et al.What every oncologist should know about geriatric assessment for older patients with cancer: Young International Society of Geriatric Oncology position paper. J Oncol Pract. 2018;14(2):85–94.
10 Mohile SG, et al. Practical assessment and management of vulnerabilities in older patients receiving chemotherapy: ASCO guideline for geriatric oncology. J Clin Oncol. 2018;36(22):2326–47

cancer patients tolerated radiotherapy[11,12] and chemotherapy[13,14] very well. Urinary 8-oxo-7, 8-dihydroguanosine (8-oxoGsn) is a promising way to assess older cancer patients' functional status and determine whether systemic therapy can be integrated with radiotherapy for patients with locally advanced or systemic disease.[15] Moreover, targeted therapy or immunotherapy might provide a safe and effective treatment because of its favourable therapeutic ratio.[16,17]

Several organisations, such as the American Society of Clinical Oncology (ASCO)[18], the International Society of Geriatric Oncology (SIOG, https://siog.org/), the Cancer and Aging Research Group (CARG, https://www.mycarg.org/) and the European Organisation for Research and Treatment of Cancer (EORTC)[19], advocate for the improvement of the evidence base for the management of cancer in older patients with the increase of their recruitment in RCTs and the improvement of trial designs to make them more meaningful for this specific population of individuals.

Polypharmacy as a factor that negatively affects the course of treatment and therapy for older cancer patients

Recent research in cancer patients revealed that polypharmacy is associated with post-operative complications, chemotherapy-related toxicities, and several physical and functional consequences. Polypharmacy also correlates with several physical and functional complications, such as falls, [20,21,22] impairments in the activity of daily living or instrumental activity of daily living,[23,24,25] frailty, and prefrailty[26].

11 Nguyen, N.P.; et al. Is surgery indicated for elderly patients with early stage non-small cell lung cancer, in the era of stereotactic body radiotherapy. Medicine 2016, 95, e5212.
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24 Prithviraj GK, Koroukian S, Margevicius S et al Patient Characteristics associated with polypharmacy and inappropriate prescribing of medication among older adults with cancer. J Geriatr Oncol 2012;3:228–237.
25 Pamoukdjian F, Aparicio T, Zelek L et al. Impaired mobility, depressed mood, cognitive impairment and polypharmacy are independently associated with disability in older cancer outpatients: The prospective Physical Frailty in Elderly Cancer patients (PF-EC) cohort study. J Geriatr Oncol 2017;8:190–195.
26 Turner JP, Shakib S, Singhal N et al. Prevalence and factors associated with polypharmacy in older people with cancer. Support Care

Finally, the association of polypharmacy with medication adherence,[27,28,29] receiving nonoperative radiotherapy despite being a candidate for surgery,[30] clinical depression[31] use of complementary and alternative medications and caregivers' increased burden is well known.[32,33]

Cost-effectiveness of cancer early detection for certain cancer types in the older age group

Colorectal cancer early detection

Comorbidities may impact both the development of colorectal cancer and screening and treatment options for older patients. In the context of an increased burden of health conditions, the benefit of screening is reduced. Evidence has shown that older and more ill patients are those who are mostly in danger to die from colorectal cancer. However, adverse outcomes associated with screening are often more frequent compared with the benefits in this group of patients.[34] In addition, patients with more comorbidities have lower survival rates after diagnosis of colorectal cancer,[35] poorer survival after chemotherapy,[36] and prolonged hospitalisations.[37] Factors such as health, life expectancy, functional status and age should be taken into account when considering colorectal cancer screening. [38,39]

Results from studies examining the cost-effectiveness of colorectal cancer screening to older patients support that there are a number of factors associated with cost-effectiveness of screening in the older age group: these include less intensive screening history, higher background risk for colorectal cancer, and fewer comorbidities. On the contrary, the current

Cancer 2014;22:1727–1734.

27 Ting YT, Yin TX, Si P et al. Drug-related problems in elderly patients with cancer receiving outpatient chemotherapy. J Geriatr Oncol 2015; 6:280–287.

28 Jun D, Lee W, Xing S, Calip G. Polypharmacy and adherence to adjuvant endocrine therapy for breast cancer. J Am Pharm Assoc 2016;56 (3):e13.

29 Kuo SZ, Haftek M, Lai JC. Factors associated with medication non-adherence in patients with end-stage liver disease. Dig Dis Sci 2017;62: 543–549.

30 Parks RM, Hall L, Tang SW et al. The potential value of comprehensive geriatric assessment in evaluating older women with primary operable breast cancer undergoing surgery or nonoperative treatment—A pilot study. J Geriatr Oncol 2015;6:46–51.

31 Canoui-Poitrine F, Reinald N, Laurent M et al. Geriatric assessment findings independently associated with clinical depression in 1092 older patients with cancer: The ELCAPA Cohort Study. Psychooncology 2016;25:104–111.

32 Nightingale G, Hajjar E, Guo K et al. A pharmacist- led medication assessment used to determine a more precise estimation of the prevalence of complementary and alternative medication (CAM) use among ambulatory senior adults with cancer. J Geriatr Oncol 2015;6:411–417.

33 Rajasekaran T, Tan T, Ong WS et al. Comprehensive Geriatric Assessment (CGA) based risk factors for increased caregiver burden among elderly Asian patients with cancer. J Geriatr Oncol 2016;7: 211–218.

34 Warren JL, Klabunde CN, Mariotto AB, et al. Adverse events after outpatient colonoscopy in the Medicare population. Ann Intern Med 2009;150:849-857.

35 van de Poll-Franse LV, Haak HR, Coebergh JW, Janssen-Heijnen ML, Lemmens VE. Disease-specific mortality among stage I-III colorectal cancer patients with diabetes: a large population-based analysis. Diabetologia 2012;55:2163-2172

36 Stavrou EP, Lu CY, Buckley N, Pearson S. The role of comorbidities on the uptake of systemic treatment and 3-year survival in older cancer patients. Ann Oncol 2012;23:2422-2428

37 Sarfati D, Tan L, Blakely T, Pearce N. Comorbidity among patients with colon cancer in New Zealand. N Z Med J 2011;124:76-88.

38 Lewis CL, Esserman D, DeLeon C, Pignone MP, Pathman DE, Golin C. Physician decision making for colorectal cancer screening in the elderly. J Gen Intern Med 2013;28:1202-1207.

39 Mittal S, Lin YL, Tan A, Kuo YF, El-Serag HB, Goodwin JS. Limited life expectancy among a subgroup of medicare beneficiaries receiving screening colonoscopies. Clin Gastroenterol Hepatol 2014;12:443-450.e1.

approach to colorectal cancer screening in older patients based primarily on age is inefficient and not cost-effective.[40,41]

Prostate cancer early detection

Prostate cancer has more frequently poorer prognostic features in the older age group.[42] Risk stratified early detection using Prostate-Specific Antigen (PSA) testing in well-informed men is the recommended screening approach in Europe.[43]

The benefits from PSA early detection involve a significant decrease in prostate cancer-specific mortality in men with minimal or no comorbidities.[44,45,46,47] Early detected prostate cancer can be cured without unbearable side effects. Another benefit of early detection includes reassurance due to negative screening. In general, the benefits of screening decrease with increasing age and comorbidities.

Although PSA early detection reduces the risk of mortality, the risks associated with overdiagnosis and overtreatment are frequently the main drivers for recommendations against PSA screening. False positives may increase the psychological distress and unneeded prostate biopsies, while prostate biopsies can cause several short-term risks, such as anxiety, moderate to severe pain, moderate to severe haematuria, infections, and hospitalisations.[48,49,50]

Many of the side effects of screening may be reduced due to new insights and techniques; transperineal biopsies reduce infections, risk calculators and MRI reduce unnecessary biopsies and diagnosis of indolent disease/cancer, active surveillance reduces overtreatment

40 van Hees, F., Habbema, J. D. F., Meester, R. G., Lansdorp-Vogelaar, I., van Ballegooijen, M., & Zauber, A. G. (2014). Should colorectal cancer screening be considered in elderly persons without previous screening? A cost-effectiveness analysis. Annals of internal medicine, 160(11), 750-759.

41 Van Hees, F., Saini, S. D., Lansdorp-Vogelaar, I., Vijan, S., Meester, R. G., de Koning, H. J., ... & van Ballegooijen, M. (2015). Personalizing colonoscopy screening for elderly individuals based on screening history, cancer risk, and comorbidity status could increase cost effectiveness. Gastroenterology, 149(6), 1425-1437.

42 Bechis SK, Carroll PR, Cooperberg MR. Impact of Age at Diagnosis on Prostate Cancer Treatment and Survival. Journal of Clinical Oncology. 2011; 29(2):235–241.

43 Mottet N., Cornford P., van den Bergh R.C.N., Briers E., De Santis M., Fanti S., Gillessen S., Grummet J., Henry A.M., Lam T.B., Mason M.D., van den Kwast T.H., van den Poel H.G., Rouvière O., Schoots I.G., Tilki D., Wiegel T.; members of the EAU–EANM-ESTRO-ESUR-SIOG Prostate Cancer Guidelines Panel. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer. Edn. presented at the EAU Annual Congress Amsterdam 2020. ISBN: 978-94-9267107-3. Publisher: EAU Guidelines Office. Place published: Arnhem, The Netherlands. https://uroweb.org/guideline/ prostate-cancer/ Carter HB. Carter HB. American Urological Association (AUA) guideline on prostate cancer detection: process and rationale. BJU international. 2013; 112(5):543–547.

44 Crawford ED, Grubb R III, Black A, et al. Comorbidity and mortality results from a randomized prostate cancer screening trial. Journal of Clinical Oncology. 2010; 29(4):355–361.

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49 Loeb S, Vellekoop A, Ahmed HU, et al. Systematic review of complications of prostate biopsy. European urology. 2013; 64(6):876–892.

50 Rosario DJ, Lane JA, Metcalfe C, et al. Short term outcomes of prostate biopsy in men tested for cancer by prostate specific antigen: prospective evaluation within ProtecT study. Bmj. 2012; 344:d7894.

of insignificant cancers, and new techniques of surgery and radiation reduce side effects of radical therapy.[51,52,53]

USPSTF guidelines highlight the importance of informed decision making prior to screening for men 55–69 years old and for those >70 years old not be screened.[54] EAU guidelines recommend PSA based risk-adapted early diagnosis in well-informed men[55] and a life expectancy of 10-15 years before starting screening.[56] A data on the cost-effectiveness of prostate cancer screening found that it can be cost-effective when it is limited to two or three screens between ages 55-59 years. While for the age 63 years and above is less cost-effective due to overdiagnosis.[57] Others found that screening can be cost-effective when it is limited to men with high risk [58] while screening is less cost-effective in the older age group.[59]

Breast cancer early detection

Parameters such as age, hormone replacement therapy use, family history of breast cancer, history of a benign breast biopsy, age at menopause, age at first birth/parity, obesity, alcohol, and cigarette use are among the most important risk factors for breast cancer in women.[60] Biennial mammograms are recommended for women 55–74 years at average risk.[61] However, there is significant variation in the different European countries, with some countries still lacking breast cancer screening programs.

While mammography screening is estimated to reduce breast cancer mortality by 19% among women 40–69 years,[62] it is not certain whether mammography screening reduces breast cancer mortality for women older than 70.[63] The American Cancer Society (ACS) recommends continuing mammography screening if women are in good health and their life expectancy is >10 years.[64]

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58 Shteynshlyuger A, Andriole GL. Cost-effectiveness of prostate specific antigen screening in the United States: extrapolating from the European study of screening for prostate cancer. *J Urol* 2011;185(3):828–32.

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62 Pace LE, Keating NL. A systematic assessment of benefits and risks to guide breast cancer screening decisions. JAMA. Apr 2; 2014 311(13):1327–1335.

63 Nystrom L, Andersson I, Bjurstam N, Frisell J, Nordenskjold B, Rutqvist LE. Long-term effects of mammography screening: updated overview of the Swedish randomised trials. Lancet. Mar 16; 2002 359(9310):909–919.

64 Oeffinger KC, Fontham ET, Etzioni R, et al. Breast cancer screening for women at average risk: 2015 guideline update from the American Cancer Society. Jama. 2015; 314(15):1599–1614.

However, there are also potential harms of mammography screening, such as anxiety associated with false-positive tests, false reassurance from an erroneously negative test, overdiagnosis, and complications from work-up and/or treatment of cancer.[83] In addition, overdiagnosis is particularly worrying as it increases with age.[65] Ideally, older women would consider their risk of breast cancer, life expectancy, and their preferences when deciding whether or not to do it.

Cost-effectiveness of screening mammography was found to be associated with age, breast density, family history, and history of breast biopsy, while mammography every two years is found to be cost-effective for women 40-49 years of age with relatively high breast density or additional risk factors for breast cancer. For the age group of 50-79 years, mammography was found to be effective every three to four years with low breast density and no other risk factors.[66] Breast cancer screening is less beneficial for women over 74 years old, whereas it provides significant benefits for higher-risk women in the age group 40–49.[67] Finally, several studies evaluated the cost-effectiveness of tailoring the screening interval by breast cancer risk and mammographic density.[68,69,70,71] However, due to uncertainties in detection rates, sensitivity, and mortality due to lack of data, these results are only indicative of a benefit in the context of risk-tailored approaches allowing to reduce harms and costs of screening.[92]

65 Schonberg MA, Marcantonio ER, Li D, Silliman RA, Ngo L, McCarthy EP. Breast cancer among the oldest old: tumour characteristics, treatment choices, and survival. J Clin Oncol. Apr 20; 2010 28(12):2038–2045.
66 Schousboe JT, Kerlikowske K, Loh A, Cummings SR (2011) Personalizing mammography by breast density and other risk factors for breast cancer: analysis of health benefits and cost-effectiveness. Ann Intern Med 155: 10–20.
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70 Schousboe JT, Kerlikowske K, Loh A, Cummings SR. Personalizing mammography by breast density and other risk factors for breast cancer: analysis of health benefits and cost-effectiveness. Ann Intern Med. 2011;155(1):10-20.
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Cancer and infectious diseases

The association between infections and cancer is well established. Infectious agents are major contributors to cancer incidence worldwide and are estimated to be responsible for up to 25 -50% of all cancer cases in the world.[1] Around 10% to 15% of these cases are linked with viruses,[2] such as hepatitis B and C, and the rest to other infectious agents, comprising bacteria, fungi, parasites, prions and infectious tumor cells.[3]

The relationship between viral agents and cancer in humans has been subject to scientific scrutiny. Studies on the processes whereby viruses can cause cancer are often classified as 'direct' and 'indirect'. In the former, a particular form of viral genes – known as oncogenes – directly leads to the development of cancer. In the latter, cancer is the result of a chronic inflammation caused by a viral infection.[4] These studies have helped refine the understanding of these particular forms of cancer with important implications.

Unlike other forms of cancer, carcinomas caused by viral infections are largely preventable through vaccination or treatments against the chronic infection which precedes and creates the conditions for cancer.[5] This offers a great window of opportunity to reduce the burden of the disease, as viral infections are among which are the most important preventable risk factors for cancer mortality in the world.[6] However, cancer prevention is often seen in the context of non-communicable diseases – especially with the focus on lifestyle factors such as alcohol consumption or smoking.[7]

According to the International Agency for Research on Cancer (IARC), the most common viral agents associated with cancer are hepatitis B (HBV) and C viruses (HCV), Epstein-Barr virus (EBV), human papillomavirus (HPV) and human immunodeficiency virus type 1 (HIV-1).[8]

Preventing Liver Cancer by tackling hepatitis

Liver cancer is a global health burden with an estimated 905 677 new cases in 2021, the sixth most common cancer and the third leading cause of cancer death.[9] Hepatocellular

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9 International Agency for Research on Cancer. Liver. Available at: https://gco.iarc.fr/today/data/factsheets/cancers/11-Liver-fact-sheet.pdf. Accessed January 2021

carcinoma (HCC) is the most common liver malignancy accounting for ~90% of all liver cancers. This type of cancer affects hepatocytes, the most abundant cells in the liver.[10] Intrahepatic cholangiocarcinoma is the second type of liver cancer (10–15% of cases) affecting cholangiocytes which refer to the cells that line the small bile ducts within the liver.[11] Hemangioendothelioma and hepatic angiosarcoma are less common and affect the cells lining blood vessels within the liver.[12,13] Finally, hepatoblastoma is a rare liver cancer that affects young children before they turn 5 years old. Causes of liver cancer vary depending on the geographical location, with viral hepatitis being the major cause around the world.[10]

Chronic infections with hepatitis B and C viruses have been established as definite causes of hepatocellular carcinoma in humans.[14] All together, HBV and HCV are responsible for up to 76% of liver cancer cases worldwide,[15] followed by alcohol consumption, cigarette smoking, diabetes, overweight and aflatoxin B1.[16] Whereas there are significant data gaps on the number of people living with chronic hepatitis,[17] scholars estimate that around 9 to 10 million people are affected with chronic hepatitis in the European Union and a vast majority are unaware of their condition.[18] Without receiving treatment, every year up to 90,000 of them develop liver cancer,[19] which has the lowest survival rate among all cancers monitored by the European Commission,[20] making it the deadliest preventable cancer in the EU.

Previous modelling has suggested that cancer prevention efforts targeting viral hepatitis could reduce liver cancer incidence by 70% and liver-related death by 65%,[21] especially among high-risk groups who are associated with higher viral infections' incidence rates.[22] Whereas primary prevention of hepatitis through vaccination programs targeting newborns has proven effective,[23] such efforts will be insufficient to significantly reduce the cancer burden in the short to medium term. This is because such prevention measures do not exploit opportunities in preventing cancer in at-risk adult populations among whom hepatitis

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20 Joint Research Centre (European Commission). European Cancer Information System – ECIS. Estimates of cancer incidence and mortality in 2020, for all cancer sites. Accessed from https://ecis.jrc.ec.europa.eu/explorer.php?$0-0$1-AE27$2-All$4-1,2$3-All$6-0,85$5-2008,2008$7-7,8$CEstByCancer$X0_8-3$CEstRelativeCanc$X1_8-3$X1_9-AE27$CEstBySexByCancer$X2_8-3$X2_-1-
21 European Union HCV Collaborators. (2017). Hepatitis C virus prevalence and level of intervention required to achieve WHO targets for elimination in the European Union by 2030: a modelling study. ***Lancet Gastroenterol Hepatol, 2***(5), pp. 325-336.
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B immunization should be improved. It is widely recognized that the diagnosis, screening and linkage to care of hepatitis B and C should be expanded as well.[24]

Expanding diagnoses among the elderly and high-risk adult populations would facilitate their access to hepatitis treatments,[25] which have generally been proven successful in preventing chronic liver disease – the main risk factor liver cancer,[26] and other hepatitis-associated cancers, such as kidney, colorectal, pancreatic, gallbladder and biliary duct and ovarian cancer.[27] Other measures to prevent liver cancer by tackling hepatitis include raising awareness about safe sex and injection practices,[28] as well as by raising awareness among the population on hepatitis' transmission risks and the need to be tested after being exposed to reduce the likelihood of developing liver cancer in the future.[29]

24 Lonfei, L., Yan, L., Liu, Y., Qu, C., Ni, J., Li, H. (2020). The burden and trends of primary liver cancer caused by specific etiologies from 1990 to 2017 at the global, regional, national, age, and sex level results from the global burden of disease study 2017. ***Liver Cancer Society***, 9***(5)***, p. 580; Epstein, R. L., Sabharwal, V., Wachman, E., et al. (2018). Perinatal Transmission of Hepatitis C Virus: Defining the Cascade of Care. The Journal of Pediatrics, ***203***, pp. 34-40; Waheed, Y., Siddiq, M., Jamil, Z. et al. (2018) Hepatitis elimination by 2030: Progress and challenges. ***World Journal of Gastroenterology***, ***24***(44), p. 4960.

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Cancer and alcohol consumption

The cancer risk associated with alcohol is poorly understood by the public. The harms that result from chronic daily drinking are: the spectrum of alcohol dependency, hypertension, cancer of the gastrointestinal tract, breast, pancreas and liver, preventable nutritional dementia of Wernicke/Korsakoff Syndrome, and teratogenicity to the foetus. All these harms are dose related at an individual level, and alcohol related harm is also dose related at a population level.[1] We estimate the increase in absolute risk of cancer secondary to moderate levels of alcohol and compare these to the risk associated with low levels of smoking, creating a 'cigarette-equivalent of harm.

One bottle of wine per week is associated with an increased absolute lifetime cancer risk for non-smokers of 1.0% (men) and 1.4% (women). Among 1,000 individuals drinking at this level, we estimate an additional ten cancers for men, 14 for women. The overall cancer risk for one bottle of wine per week equals that of five (men) or ten cigarettes per week (women). Gender differences result from moderate levels of drinking leading to 0.8% absolute risk of breast cancer in female non-smokers Conclusions: One bottle of wine per week leads to an increased absolute lifetime risk of alcohol-related cancers in women, driven by breast cancer, equivalent to the overall cancer risk associated with ten cigarettes per week. These findings can help communicate that moderate levels of drinking are an important public health risk for women. The risks for men, equivalent to five cigarettes per week, are also of note.[2]

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2 Hydes, T.J., Burton, R., Inskip, H. et al. A comparison of gender-linked population cancer risks between alcohol and tobacco: how many cigarettes are there in a bottle of wine?. BMC Public Health 19, 316 (2019). https://doi.org/10.1186/s12889-019-6576-9

Cancer and tobacco use

Tobacco use has a substantial impact on cancer as it accounts for at least 30% of all cancer deaths and 80% of lung cancer deaths.[1] In addition, lung cancer is the leading cause of cancer death worldwide with 1.7million global deaths attributed to cigarette smoking[2] in both men and women.[3]

However, data may underestimate the true risks of lung cancer among women, as the smoking epidemic has not yet reached full maturity in women.[4]

However, smoking heightens the risk of more than 10 types of cancers:

- **Childhood Cancer:** Evidence suggest that exposure to smoking by family members during pregnancy or exposure to waterpipe and cigarette smoking during their neonatal period is a risk factor for developing cancer.[5]
- **Cervical cancer:** Women who smoke are about twice as likely as non-smokers to get cervical cancer while smoking also makes the immune system less effective in fighting HPV infections.[6]
- **Gallbladder & Bile Duct Cancer:** Smoking appears to increase the risk of developing all biliary tract cancers except gallbladder cancer.[7]

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- **Kidney Cancer**: Cigarette smoking is a well-established risk factor for renal cell carcinoma (RCC).[8]
- **Colon Cancer**: Smokers had a significantly higher risk for colon cancer.[9]
- **Esophagial cancer**: Smoking is an important risk factor for the development of Esophageal cancer and especially squamous cell carcinoma.[10,11]
- **Testicular cancer**: Testicular cancer is strongly associated with tobacco smoking.[12]
- **Bladder cancer**: Smoking cigarettes, cigars or pipes may increase the risk of bladder cancer by causing harmful chemicals to accumulate in the urine.[13]
- **Pancreatic cancer**: Cigarette smoking is a consistent risk factor for pancreatic cancer, which may contribute to development of approximately 20% of pancreatic cancer cases.[14]
- **Acute myeloid leukaemia**: Scientific research has confirmed cigarette smoking to be associated with increased risk of developing myeloid leukaemia in adults.[15]
- **Head and neck cancer**: Head and neck cancers include cancers of the oral cavity, pharynx, and larynx and are among the most common cancers worldwide[16] while the association between cigarette smoking and the incidence and mortality of head and neck cancers is well established.[17]
- Breast Cancer: smoking is associated with breast cancer and that there is a consistent causality between second-hand smoke exposure and premenopausal breast cancer.[18]

In fact, tobacco use not only increases the risk of developing various cancers, but also worsens cancer outcomes.[19] Lower survival rates among patients who smoked or continue to smoke after diagnosis are also documented only among patients with cancers strongly linked to smoking (lung, esophageal, or head and neck), but also in patients with breast, prostate, and other cancers. Current or past smokers with cancer also have decreased therapeutic responses, increased cancer recurrences, and increased cancer treatment complications, including problems with wound healing, infections, cardiovascular complications, and the development of a secondary malignancy. [20]

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Recommendations

Cancer is set to become a top health priority for the next five years in the EU and will play a central role in the policy agenda through the EU Beating Cancer Plan. It is crucial that, with this renewed focus on cancer, we take a comprehensive and integrated care approach to ensure better health outcomes and quality of life for all European patients, independent of age, gender, and state of treatment.

With this work, we call on EU policymakers to prioritise cancer-related complications and comorbidities by:

1. Making cancer-related complications and comorbidities a central part of all policy discussions about cancer care.
2. Including cancer-related complications and comorbidities as an important pillar of the Europe's Beating Cancer Plan implementation which will focus on:
    1) Multidisciplinary team working and by taking action to improve HCP training and integrated care by applying already-known methods of addressing cancer-related complications and comorbidities through **an inter-specialty cancer training programme on the management of Cancer-related Complications and Comorbidities.**
    2) A new **Knowledge Centre on Cancer** which we expect to put a special attention in research of cancer-related complications and comorbidities during the cancer treatment and survivorship.

3) Including cancer related complications and comorbidities to the '**Better Life for Cancer Patients Initiative**' and to the '**Cancer Survivor Smart-Card'**
4) The creation of a **new European Reference Networks addressing cancer complications and co-morbidities** will be an important step to benefit from cross-border cooperation and EU expertise.
5) Improving **health literacy on cancer risks and determinants** by achieving a tobacco-free Europe, reducing harmful alcohol consumption, improving health promotion through access to healthy diets and physical activity, addressing obesity, reducing environmental pollution and exposure to hazardous substances and radiation and preventing cancers caused by infections but also look throughout the cancer care journey.
6) **Medicines reconciliation**, which has been recognised as a major intervention tackling the burden of medication discrepancies, correcting medication errors and subsequent patient harm at hospital admission and discharge. It allows also identify drug interactions including self-medication with Complementary and Alternative Medicine (CAM). This is particularly acute among cancer patients with comorbidities and complications.

3. Leveraging existing EU funding programs for research on cancer to include cancer-related complications and comorbidities.
4. Proactively coordinating prevention and early detection strategies and establishing fluid communication channels with policymakers, healthcare professionals across several related scientific disciplines, patients and informal carers.
5. Participating in multi-stakeholder dialogue to agree on concrete next steps to address cancer-related complications and comorbidities.
6. Providing policy solutions able to ensure timely access to innovative therapies for all patients as they may have a better impact on health-related outcomes and quality of life.

Eurocarers

European Association for the Study of Obesity (EASO)

European Association of Urology (EAU)

European Brain Council (EBC)

European Cancer Patient Coalition (ECPC) - (Chair)

European Cancer Organisation

European Federation of Neurological Associations (EFNA)

European Federation of Nurses Associations (EFN)

European Geriatric Medicine Society (EuGMS)

European Pain Federation (EFIC)

European Society of Cardiology (ESC)

European Specialist Nurses Organisation (ESNO)

European Thrombosis and Haemostasis Alliance (ETHA)

International Society of Geriatric Oncology (SIOG)

International Society on Thrombosis and Hemostasis (ISTH)

KU Leuven – Leuven Cancer Institute (LKI)

The European Federation of the Associations of Dietitians (EFAD)

The European Nutrition for Health Alliance (ENHA)

The European Society for Clinical Nutrition and Metabolism

The European Society of Surgical Oncology (ESSO)

Obesity Policy Engagement Network (OPEN-EU)

Thrombosis Ireland

Thrombosis UK

International Psycho-Oncology Society

Associations collaborating on hepatitis to immunize and eliminate viruses in Europe

European Association for the Study of the Liver

European Hematology Association

European Society of Oncology Pharmacy

European Network for Smoking and Tobacco Prevention

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