



WHITE PAPER

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

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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/CLEPS47150

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/ehf.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.

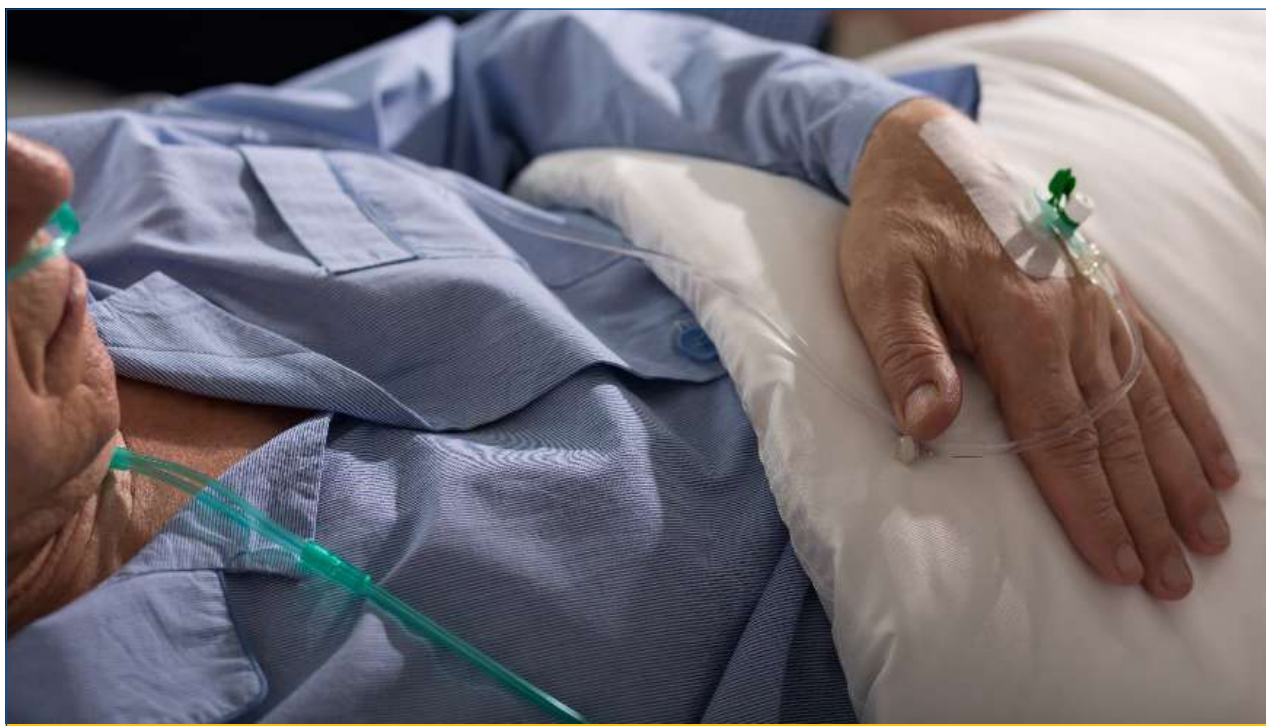
In light of the above, this white paper intends to provide an up-to-date overview of the most recent scientific evidence per comorbidity, to show the relevance and level of the burden of comorbidities on cancer patients and to propose some recommendations for policy makers to implement to help better 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 & Valiyaveetil, 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-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

1 Noble, S.; Pasi, J. Epidemiology and pathophysiology of cancer-associated thrombosis. *Br. J. Cancer* 2010, 102, S2–S9.

2 Khorana AA. Cancer-associated thrombosis: updates and controversies. *Hematology Am Soc Hematol Educ Program*. 2012;2012:626-30

3 Kourlaba G, Relakis J, Mylonas C, Kapaki V, Kontodimas S, Holm MV et al. The humanistic and economic burden of venous thromboembolism in cancer patients: a systematic review. *Blood Coagul Fibrinolysis*. 2015;26(1):13-31.

4 Jha AK, Larizgoitia I, Audera-Lopez C, Prasopa-Plaisier N, Waters H, Bates DW. The global burden of unsafe medical care: analytic modeling of observational studies. *BMJ Qual Saf* 2013; 22:809-15. Retrieved from: <http://qualitysafety.bmj.com/content/22/10/809.full.pdf+html>

5 Heit, JA. Poster 68 presented at: American Society of Hematology, 47th Annual Meeting, Atlanta, GA, December 10-13, 2005.

6 ECPC & LEO Pharma. Cancer- Associated Thrombosis (CAT), A neglected cause of cancer death: actions needed to increase health outcomes and reduce mortality.

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}, ethnicity¹², comorbidities¹³, immobility¹⁴, previous history of VTE¹⁵, cancer type^{17,16}, cancer stage,^{15,17} time after diagnosis,^{18,19} chemotherapy,^{20,21,22,23} hospitalization or surgery²⁴ and the presence of central venous catheters.^{21,25}



7 Levi, M. Cancer-related coagulopathies. *Thromb. Res.* 2014, 133, S70–S75.

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9 Abdol Razak, N. B., Jones, G., Bhandari, M., Berndt, M. C., & Metharom, P. (2018). Cancer-associated thrombosis: an overview of mechanisms, risk factors, and treatment. *Cancers*, 10(10), 380.

10 Vergati, M.; Della-Morte, D.; Ferroni, P.; Cereda, V.; Toso, L.; La Farina, F.; Guadagni, F.; Roselli, M. Increased Risk of Chemotherapy-Associated Venous Thromboembolism in Elderly Patients with Cancer. *Rejuvenation Res.* 2013, 16, 224–231.

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14 Al Diab, A.I. Cancer-related venous thromboembolism: Insight into underestimated risk factors. *Hematol. Oncol. Stem Cell Ther.* 2010, 3, 191–195.

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25 DeLoughery, T.G. Hemostasis and Thrombosis, 3rd ed.; DeLoughery, T.G., Ed.; Springer International Publishing: Cham, Switzerland, 2015.

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/cardiological³⁴ and oncological clinical guidelines^{35,36,37} recommend prophylactic anticoagulant treatment in specific groups of cancer patients.

26 Noble S, Prout H, Nelson A. Patients' experiences of living with cancer associated thrombosis: the PELICAN study. *Patient Prefer Adherence* 2015; 9: 337–345.

27 Mockler A, O'Brien B, Emed J, et al. The experience of patients with cancer who develop venous thromboembolism: an exploratory study. *Oncol Nurs Forum*. 2012; 39(3): E233–E240.

28 Benelhaj, N. B., Hutchinson, A., Maraveyas, A. M., Seymour, J. D., Ilyas, M. W., & Johnson, M. J. (2018). Cancer patients' experiences of living with venous thromboembolism: a systematic review and qualitative thematic synthesis. *Palliative medicine*, 32(5), 1010-1020.

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30 Noble S, Nelson A, Fitzmaurice D, et al. A feasibility study to inform the design of a randomised controlled trial to identify the most clinically effective and cost-effective length of (ALICAT). *Health Technol Assess*. 2015; 19(83): 52–93.

31 Cohoon KP, Leibson CL, Ransom JE, et al (2015) Costs of venous thromboembolism associated with hospitalization for medical illness. *Am J Manag Care* 21(4):e255–e263

32 Cohoon KP, Leibson CL, Ransom JE, et al (2015) Direct medical costs attributable to venous thromboembolism among persons hospitalized for major operation: a population-based longitudinal study. *Surgery* 157:423–431

33 Cohoon, K. P., Ransom, J. E., Leibson, C. L., Ashrani, A. A., Petterson, T. M., Long, K. H., ... & Heit, J. A. (2016). Direct medical costs attributable to cancer-associated venous thromboembolism: a population-based longitudinal study. *The American journal of medicine*, 129(9), 1000-e15.

34 Kahn SR, Lim W, Dunn AS, Cushman M, Dentali F, Akl EA et al. Prevention of VTE in Nonsurgical Patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2, Supplement):e195S–e226S.

35 Gradishar, William J., et al. "NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)." *Journal of the National Comprehensive Cancer Network* 18.4 (2020).

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.

37 Mandala M, Falanga A, Roila F. Management of venous thromboembolism (VTE) in cancer patients: ESMO Clinical Practice Guidelines. *Ann Oncol*. 2011;22 Suppl 6:vi85-92.

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.

40 Streiff MB. Association between cancer types, cancer treatments, and venous thromboembolism in medical oncology patients. *Clin Adv Hematol Oncol.* 2013;11(6):349-57

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. Chemotherapy-induced 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 process⁷.

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.

9 Lancellotti, Patrizio, et al. "Expert consensus for multi-modality imaging evaluation of cardiovascular complications of radiotherapy in adults: a report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography." *European Heart Journal–Cardiovascular Imaging* 14.8 (2013): 721-740.

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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 chemotherapy³⁴, 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.

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- 16 Chun SG, Hu C, Choy H, et al. Impact of intensity-modulated radiation therapy technique for locally advanced non-small-cell lung cancer: a secondary analysis of the NRG Oncology RTOG 0617 randomized clinical trial. *J Clin Oncol Off J Am Soc Clin Oncol*. 2017;35(1):56–62.
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- 19 Cardinale D, Salvatici M, Sandri MT. Role of biomarkers in cardioncology. *Clin Chem Lab Med*. 2011;49:1937–48.
- 20 Christenson ES, James T, Agrawal V, Park BH. Use of biomarkers for the assessment of chemotherapy-induced cardiac toxicity. *Clin Biochem*. 2015;48:223–35.
- 21 Nitiss K, Nitiss J. Twisting and ironing: doxorubicin cardiotoxicity by mitochondrial DNA damage. *Clin Cancer Res*. 2014;20:4737–9.
- 22 Van Dalen EC, Caron HN, Dickinson HO, Kremer LC. Cardioprotective interventions for cancer patients receiving anthracyclines. *Cochrane Database Syst Rev*. 2011;CD003917.
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- 30 Cadeddu C, Piras A, Mantovani G, et al. Protective effects of the angiotensin II receptor blocker telmisartan on epirubicin-induced inflammation, oxidative stress, and early ventricular impairment. *Am Heart J*. 2010;160:4871.e1–7.
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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.

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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 anticancer 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 factors¹⁸.

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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 - 6 Caccialanza R , Cereda E , Pinto C . Awareness and consideration of malnutrition among oncologists: insights from an exploratory survey. *Nutrition* . 2016;32:1028–1032 .
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 - 15 Sharma A , Negi E F , Arora B , et al. A survey of nutritional practices for children with cancer in India. *Indian J Cancer* . 2015;52:191–193.
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 - 17 Caccialanza R , De Lorenzo F , Gianotti L , et al. Nutritional support for cancer patients: still a neglected right? *Support Care Cancer* . 2017;25:3001–3004.
 - 18 Lorenzon L , Brandl A , Guiral DC , et al Nutritional assessment in surgical oncology: An ESSO-EYSAC global survey. *Eur J Surg Oncol*. 2020 Nov;46(11):2074-2082. doi: 10.1016/j.ejso.2020.08.028. Epub 2020 Sep 3. PMID: 32938568.
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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

20 Arrieta O, Michel Ortega RM, Villanueva-Rodriguez G, et al. Association of nutritional status and serum albumin levels with development of toxicity in patients with advanced non-small cell lung cancer treated with paclitaxel-cisplatin chemotherapy: a prospective study. *BMC Cancer* 2010;10:50.

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31 Huang TH, Chi CC, Liu CH, Chang CC, Kuo LM, Hsieh CC. Nutritional status assessed by scored patient-generated subjective global assessment associated with length of hospital stay in adult patients receiving an appendectomy. *Biom J* 2014;37:71–7.

32 Kaibori M, Ishizaki M, Matsui K, et al. Geriatric assessment as a predictor of postoperative complications in elderly patients with hepatocellular carcinoma. *Langenbecks Arch Surg* 2016;401:205–14.

33 Schwegler I, von HA, Gutzwiller JP, Schlumpf R, Muhlebach S, Stanga Z. Nutritional risk is a clinical predictor of postoperative mortality and morbidity in surgery for colorectal cancer. *Br J Surg* 2010;97:92–7.

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36 Hill A, Kiss N, Hodgson B, Crowe TC, Walsh AD. Associations between nutritional status, weight loss, radiotherapy treatment toxicity and treatment outcomes in gastrointestinal cancer patients. *Clin Nutr* 2011;30:92–8.

37 Kufeldt J, Viehig M, Schweikert D, Fritsche A, Bamberg M, Adolph M. Treatment of malnutrition decreases complication rates and shortens the length of hospital stays in a radiation oncology department. *Strahlenther Onkol* 2018;194:1049–59.

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39 Osborne GEC, Appleyard SA, Gilbert DC, et al. Comprehensive geriatric assessment in men aged 70 years or older with localised prostate cancer undergoing radical radiotherapy. *Clin Oncol (R Coll Radiol)* 2017;29:609–16.

40 Wang J, Yu B, Ye Y, et al. Predictive value of nutritional risk screening 2002 and prognostic nutritional index for esophageal cancer patients undergoing definitive radiochemotherapy. *Nutr Cancer* 2018;70:879–85.

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}

41 Calleja FA, Pintor DIM, Vidal CA et al. food intake and nutritional status influence outcomes in hospitalized hematology-oncology patients. *Nutr Hosp* 2015;31: 2598–605.

42 Garth AK, Newsome CM, Simmance N, Crowe TC. Nutritional status, nutrition practices and post-operative complications in patients with gastrointestinal cancer. *J Hum Nutr Diet* 2010;23:393–401.

43 Gioulbasanis I, Baracos VE, Giannousi Z, et al. Baseline nutritional evaluation in metastatic lung cancer patients: mini nutritional assessment versus weight loss history. *Ann Oncol* 2011;22:835–41.

44 GuoW, Ou G, Li X, Huang J, Liu J, Wei H. Screening of the nutritional risk of patients with gastric carcinoma before operation by NRS 2002 and its relationship with postoperative results. *J Gastroenterol Hepatol* 2010;25:800–3.

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48 Mendes J, Alves P, Amaral TF. Comparison of nutritional status assessment parameters in predicting length of hospital stay in cancer patients. *Clin Nutr* 2014;33: 466–70.

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50 van RS, Carli F, Dalton SO, et al. Preoperative modifiable risk factors in colorectal surgery: an observational cohort study identifying the possible value of prehabilitation. *Acta Oncol* 2017;56:329–34.

51 Goineau A, Campion L, D'Aillieres B, et al. Comprehensive geriatric assessment and quality of life after localized prostate cancer radiotherapy in elderly patients. *PLoS One* 2018;13:e0194173.

52 Laky B, Janda M, Kondalsamy-Chennakesavan S, Cleghorn G, Obermair A. Pretreatment malnutrition and quality of life - association with prolonged length of hospital stay among patients with gynecological cancer: a cohort study. *BMC Cancer* 2010;10:232.

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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.^{6,6} 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

1 Brousse N, Meijer JW (2005) Malignant complications of coeliac disease. *Best Pract Res Clin Gastroenterol* 19(3):401–412.

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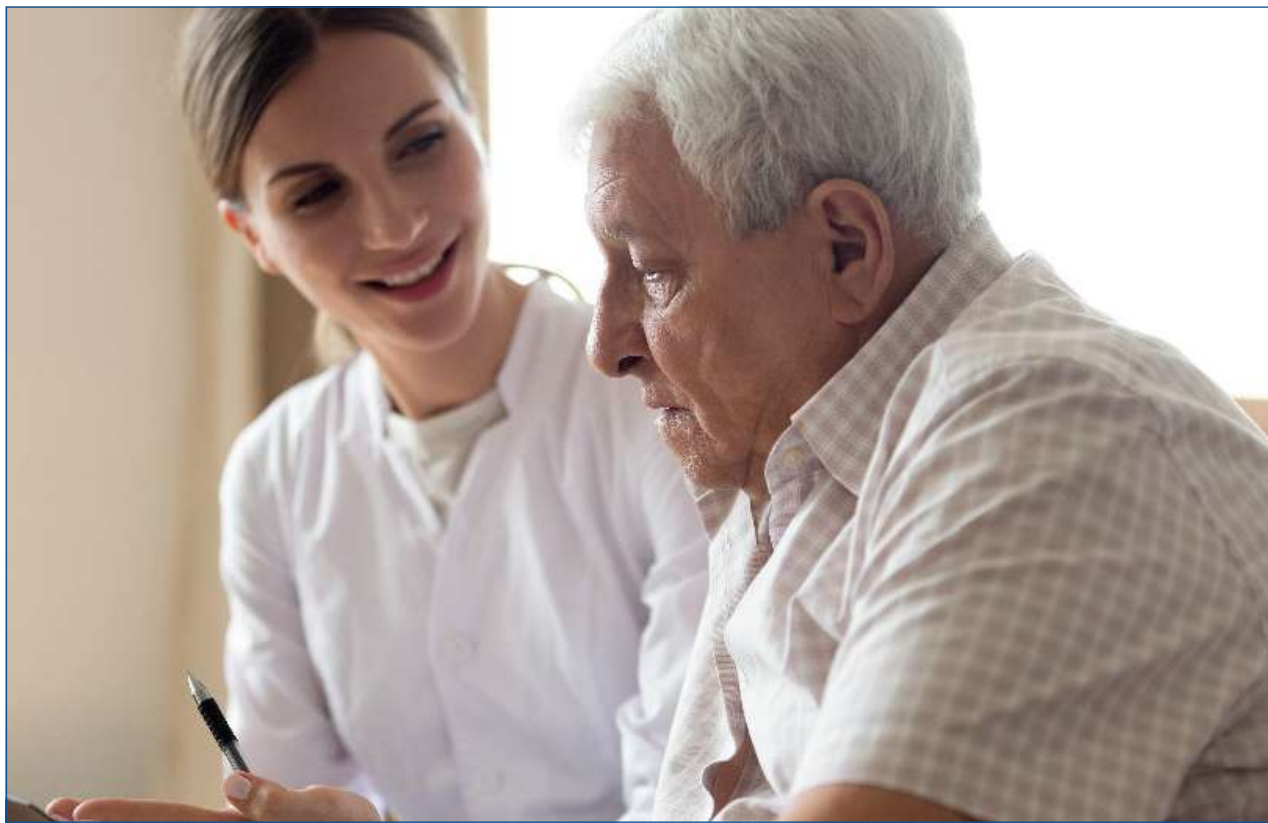
4 Abadie V, Sollid LM, Barreiro LB, Jabri B. Integration of genetic and immunological insights into a model of celiac disease pathogenesis. *Annu Rev Immunol*. 2011;29(1):493-525.

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8 Potter DD, Murray JA, Donohue JH, et al. (2004) The role of defective mismatch repair in small bowel adenocarcinoma in celiac disease. *Cancer Res* 64(19):7073–7077.



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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2 Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *New England Journal of Medicine* 2003; 348(17):1625-1638.

3 Schmitz KH, Neuhauser ML, Agurs-Collins T, et al. Impact of obesity on cancer survivorship and the potential relevance of race and ethnicity. *Journal of the National Cancer Institute* 2013; 105(18):1344-1354.

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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 weight¹⁸. 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 mortality¹⁷, 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

5 Mapp S, Sandhu G, Carrington C, Hennig S. A systematic review of treatment outcomes with weight-based dosing of chemotherapy in obese adult patients with acute leukemia or lymphoma. *Leuk Lymphoma*. 2016;57(4):981–4.

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7 Gallo, Marco, et al. "Expected and paradoxical effects of obesity on cancer treatment response." *Reviews in Endocrine and Metabolic Disorders* (2020): 1-22.

8 Helyer LK, Varnic M, Le LW, Leong W, McCready D. Obesity is a risk factor for developing postoperative lymphedema in breast cancer patients. *Breast J*. 2010;16:48-54.

9 Guo S, Dipietro LA. Factors affecting wound healing. *J Dent Res*. 2010;89:219-229.

10 Lindner U, Lawrentschuk N, Abouassaly R, Fleshner NE, Trachtenberg J. Radical prostatectomy in obese patients: Improved surgical outcomes in recent years. *Int J Urol*. 2010;17:727-732.

11 Ross, K. H., Gogineni, K., Subhedar, P. D., Lin, J. Y., & McCullough, L. E. (2019). Obesity and cancer treatment efficacy: Existing challenges and opportunities. *Cancer*, 125(10), 1588-1592.

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15 Hourdequin KC, Schpero WL, McKenna DR, Piazik BL, Larson RJ. Toxic effect of chemotherapy dosing using actual body weight in obese versus normal-weight patients: a systematic review and meta-analysis. *Ann Oncol*. 2013;24(12):2952–62.

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18 Gross JP, Strauss JB, Lurain J, et al. Impact of obesity on treatment related adverse events, disease recurrence, and survival in women with cervical carcinoma. *J Radiat Oncol*. 2016;5:197-203.

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.

19 De Langhe S, Mulliez T, Veldeman L, et al. Factors modifying the risk for developing acute skin toxicity after whole-breast intensity modulated radiotherapy [serial online]. BMC Cancer. 2014;14:711.

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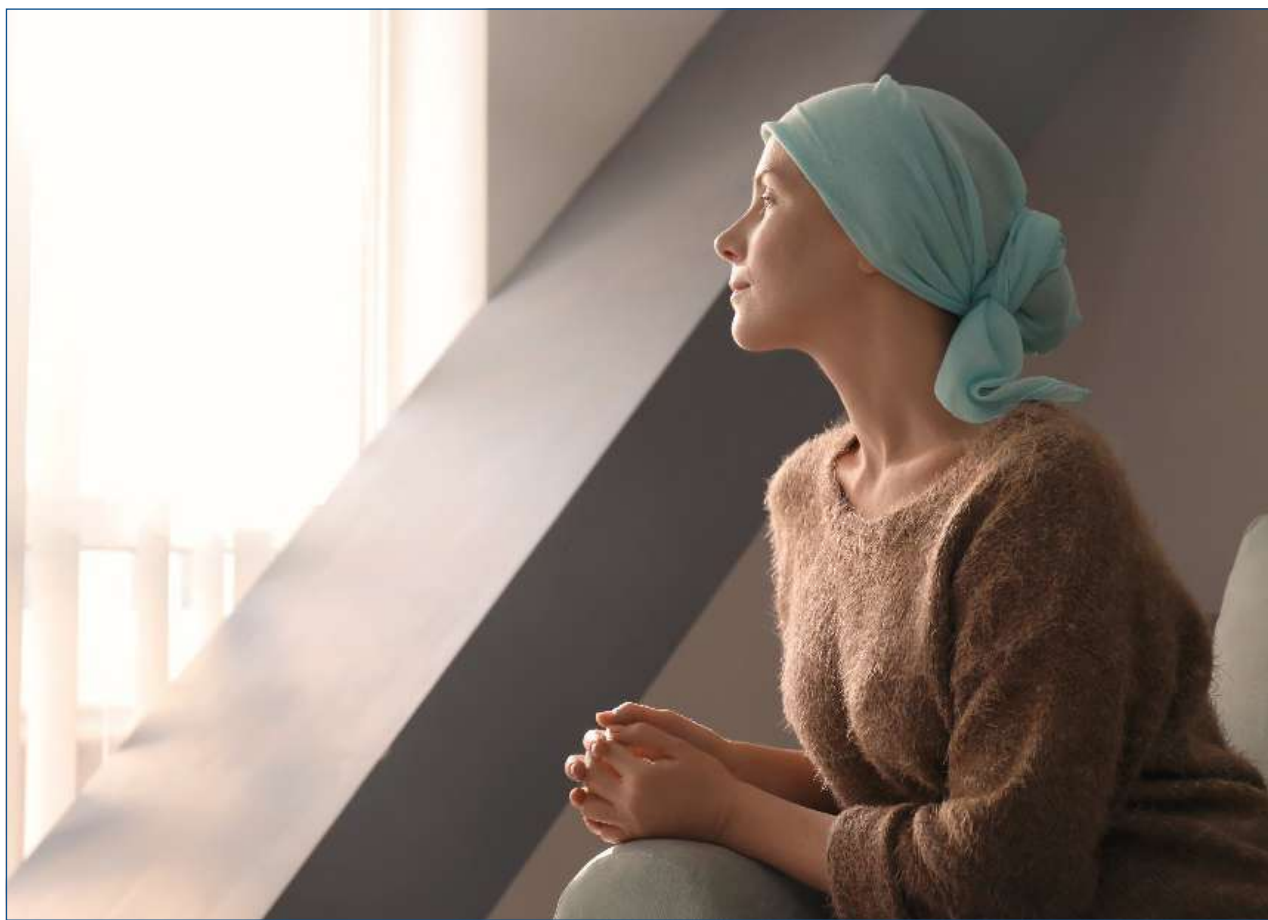
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34 Andrykowski MA, Donovan KA, Laronga C, et al. Prevalence, predictors, and characteristics of off-treatment fatigue in breast cancer survivors. Cancer. 2010;116(24):5740-5748

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36 Gerber LH, Stout N, McGarvey C, et al. Factors predicting clinically significant fatigue in women following treatment for primary breast cancer. Support Care Cancer. 2011;19(10):1581-1591



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 years⁴ (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 depression⁵.

1 US National Cancer Institute. Depression (PDQ®)–Health Professional Version.

2 Cohen, A. (WHO) (2017) Addressing comorbidity between mental disorders and major noncommunicable diseases.

3 Friedland C.J. (2019) Head and Neck Cancer: Identifying Depression as a Comorbidity Among Patients. Clinical Journal of Oncology Nursing

4 Mitchell, A. J., Ferguson, D. W., Gill, J., Paul, J., & Symonds, P. (2013). Depression and anxiety in long-term cancer survivors compared with spouses and healthy controls: A systematic review and meta-analysis. Lancet Oncology, 14(8), 721–732.

5 Yan, R., Xia, J., Yang, R., Lv, B., Wu, P., Chen, W., ... & Yu, J. (2019). Association between anxiety, depression, and comorbid chronic diseases

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-

among cancer survivors. *Psycho-oncology*, 28(6), 1269-1277.

6 Grassi L, Biancosino B, Marmai L, et al.: Psychological factors affecting oncology conditions. *Adv Psychosom Med*. 2007; 28: 57–71.

7 Caruso R, Nanni MG, Riba MB, et al.: The burden of psychosocial morbidity related to cancer: patient and family issues. *Int Rev Psychiatry*. 2017; 29(5): 389–402.

8 Vodermaier A, Linden W, Siu C: Screening for emotional distress in cancer patients: a systematic review of assessment instruments. *J Natl Cancer Inst*. 2009; 101(21): 1464–88.

9 Watts S, Leydon G, Birch B, et al. Depression and anxiety in prostate cancer: a systematic review and meta-analysis of prevalence rates. *BMJ Open*. 2014;4:e003901.

10 Maass, S. W., Roorda, C., Berendsen, A. J., Verhaak, P. F., & de Bock, G. H. (2015). The prevalence of long-term symptoms of depression and anxiety after breast cancer treatment: a systematic review. *Maturitas*, 82(1), 100-108.

11 Lim, C. C., Devi, M. K., & Ang, E. (2011). Anxiety in women with breast cancer undergoing treatment: a systematic review. *International Journal of Evidence-Based Healthcare*, 9(3), 215-235.

12 Kim, J., Cho, J., Lee, S. K., Choi, E. K., Kim, I. R., Lee, J. E., ... & Nam, S. J. (2020). Surgical impact on anxiety of patients with breast cancer: 12-month follow-up prospective longitudinal study. *Annals of Surgical Treatment and Research*, 98(5), 215.

13 Jesse R, Fann JR, Anne M, et al. Major depression after breast cancer: a review of epidemiology and treatment. *Gen Hosp Psychiatry*. 2008;30:112–126.

14 Chida Y, Hamer M, Wardle J, Steptoe A. Do stress-related psychosocial factors contribute to cancer incidence and survival? *Nat Clin Prac Oncol* 2008; 5: 466–475.

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 depression²⁸.

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 stages³⁷ or incurable cancer^{30,31,32,33,34} showed an increased psychological burden. Finally, anxiety and depressive symptoms were positively associated,³⁵

15 Prasad SM, Eggener SE, Lipsitz SR et al. Effect of depression on diagnosis, treatment, and mortality of men with clinically localized prostate cancer. *J Clin Oncol* 2014; 32: 2471–2478.

16 Wikman A, Ljung R, Johar A et al. Psychiatric morbidity and survival after surgery for esophageal cancer: a population-based cohort study. *J Clin Oncol* 2015; 33: 448–454.

17 Lee, S. A., Nam, C. M., Kim, Y. H., Kim, T. H., Jang, S. I., & Park, E. C. (2020). Impact of Onset of Psychiatric Disorders and Psychiatric Treatment on Mortality Among Patients with Cancer. *The Oncologist*, 25(4), e733.

18 Batty GD, Russ TC, Stamatakis E, Kivimaki M. Psychological distress in relation to site specific cancer mortality: pooling of unpublished data from 16 prospective cohort studies. *Br Med J* 2017; 356: j108.

19 Epplein M, Zheng Y, Zheng W et al. Quality of life after breast cancer diagnosis and survival. *J Clin Oncol* 2011; 29: 406–412.

20 Pirl WF, Greer JA, Traeger L et al. Depression and survival in metastatic non-small-cell lung cancer: effects of early palliative care. *J Clin Oncol* 2012; 30: 1310–1315.

21 Zhu, J., Fang, F., Sjölander, A., Fall, K., Adami, H. O., & Valdimarsdóttir, U. (2017). First-onset mental disorders after cancer diagnosis and cancer-specific mortality: a nationwide cohort study. *Annals of Oncology*, 28(8), 1964–1969.

22 Dauchy S, Dolbeault S, Reich M. Depression in cancer patients. *EJC Suppl.* 2013;11(2):205–215.

23 Rodin G. Effective treatment for depression in patients with cancer. *Lancet* 2014;384: 1076–1078.

24 Nightingale CL, Lagorio L, Carnaby G. A prospective pilot study of psychosocial functioning in head and neck cancer patient-caregiver dyads. *J Psychosoc Oncol* 2014;32(05):477–492.

25 Longacre ML, Ridge JA, Burtress BA, Galloway TJ, Fang CY. Psychological functioning of caregivers for head and neck cancer patients. *Oral Oncol* 2012;48(01):18–25.

26 Lee Y, Lin PY, Chien CY, Fang FM. Prevalence and risk factors of depressive disorder in caregivers of patients with head and neck cancer. *Psychooncology* 2015;24(02):155–161.

27 Badr H, Gupta V, Sikora A, Posner M. Psychological distress in patients and caregivers over the course of radiotherapy for head and neck cancer. *Oral Oncol* 2014;50(10):1005–1011.

28 Geng, H. M., Chuang, D. M., Yang, F., Yang, Y., Liu, W. M., Liu, L. H., & Tian, H. M. (2018). Prevalence and determinants of depression in caregivers of cancer patients: A systematic review and meta-analysis. *Medicine*, 97(39).

29 Patterson JM, Rapley T, Carding PN, Wilson JA, McColl E. Head and neck cancer and dysphagia; caring for carers. *Psychooncology* 2013;22(08):1815–1820.

30 Rosenberger C, Höcker A, Cartus M, Schulz-Kindermann F, Härter M, Mehnert A. Outpatient psycho-oncological care for family members and patients: access, psychological distress and supportive care needs. *Psychother Psychosom Med Psychol.* 2012;62:185–94.

31 Fujinami R, Sun V, Zachariah F, Uman G, Grant M, Ferrell B. Family caregivers' distress levels related to quality of life, burden, and preparedness. *Psychooncology.* 2015;24:54–62.

32 Halkett GK, Lobb EA, Shaw T, Sinclair MM, Miller L, Hovey E, Nowak AK. Distress and psychological morbidity do not reduce over time in carers of patients with high-grade glioma. *Support Care Cancer.* 2017;25:887–93.

33 Areia NP, Fonseca G, Major S, Relvas AP. Psychological morbidity in family caregivers of people living with terminal cancer: prevalence and predictors. *Palliat Support Care.* 2018;26:1–8.

34 Oechsle, Karin, et al. "Psychological burden in family caregivers of patients with advanced cancer at initiation of specialist inpatient palliative care." *BMC Palliative Care* 18.1 (2019): 102.

35 Jacobs JM, Shaffer KM, Nipp RD, Fishbein JN, MacDonald J, El-Jawahri A, Pirl WF, Jackson VA, Park ER, Temel JS, Greer JA. Distress is interdependent in patients and caregivers with newly diagnosed incurable cancers. *Ann Behav Med.* 2017;51:519–31.

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}



36 Dionne-Odom JN, Demark-Wahnefried W, Taylor RA, Rocque GB, Azuero A, Acemgil A, Martin MY, Astin M, Ejem D, Kvale E, Heaton K, Pisu M, Partridge EE, Bakitas MA. The self-care practices of family caregivers of persons with poor prognosis cancer: differences by varying levels of caregiver well-being and preparedness. *Support Care Cancer*. 2017;25:2437–44.

37 Hwang IC, Kim YS, Lee YJ, Choi YS, Hwang SW, Kim HM, Koh SJ. Factors associated with caregivers' resilience in a terminal cancer care setting. *Am J Hosp Palliat Care*. 2018;35:677–83.

38 Paek MS, Nightingale CL, Tooze JA, Milliron BJ, Weaver KE, Sterba KR. Contextual and stress process factors associated with head and neck Oechsle et al. *BMC Palliative Care* (2019) 18:102 Page 13 of 14
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 problems⁹ 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

1 Barrow Neurological Institute (2017). Neurologic Complications of Cancer.

2 Giglio, P., & Gilbert, M. R. (2010). Neurologic complications of cancer and its treatment. *Current oncology reports*, 12(1), 50–59. doi: 10.1007/s11912-009-0071-x

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>

5 Wefel J, Vardy J, Ahles T, Schagen SB. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. *Lancet Oncol*. 2011;12:703–708.

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.

7 Denlinger C, Ligibel J, Are M, et al. Survivorship: cognitive function, version 1.2014: clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2014;12:976–986.

8 Moore H. An overview of chemotherapy-related cognitive dysfunction, or “chemobrain.” *Oncology (Williston Park)*. 2014;28:797–804.

9 Jean-Pierre P, Winters P, Ahles T, et al. Prevalence of self-reported memory problems in adult cancer survivors: a national cross-sectional study. *J Oncol Pract*. 2012;8:30–34.

10 Pergolotti, Mackenzi, et al. “Embracing the complexity: Older adults with cancer-related cognitive decline—A Young International Society of Geriatric Oncology position paper.” *Journal of geriatric oncology* 11.2 (2020): 237-243.

11 Bradshaw M, Wefel J. The neuropsychology of oncology. In: Parsons M, Hammeke T (eds). *Clinical Neuropsychology: A pocket handbook for assessment*, Third edition. Washington DC: American Psychological Association;2014:313–337.



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}

12 IJzerman-Korevaar, M., Snijders, T. J., de Graeff, A., Teunissen, S. C., & de Vos, F. Y. (2018). Prevalence of symptoms in glioma patients throughout the disease trajectory: a systematic review. *Journal of neuro-oncology*, 140(3), 485-496.

13 Boone M, Roussel M, Chauffert B, Le Gars D, Godefroy O (2016) Prevalence and profile of cognitive impairment in adult glioma: a sensitivity analysis. *J Neuro-oncol* 129(1):123–130

14 Koekkoek JAF, Kerkhof M, Dirven L, Heimans JJ, Reijneveld JC, Taphoorn MJB (2015) Seizure outcome after radiotherapy and chemotherapy in low-grade glioma patients: a systematic review. *Neuro-oncology* 17(11), pp. 924–934

15 Gehring K, Aaronson N, Taphoorn M, Sitskoorn M. Interventions for cognitive deficits in patients with a brain tumour: an update. *Expert Rev Anticancer Ther*. 2010;10:1779–1795.

16 Aaronson N, Taphoorn M, Heimans J, et al. Compromised health-related quality of life in patients with low-grade glioma. *J Clin Oncol*. 2011;29:4430–4435.

17 Jansen C, Cooper B, Dodd M, Miaskowski C. A prospective longitudinal study of chemotherapy-induced cognitive changes in breast cancer patients. *Support Care Cancer*. 2011;19:1647–1656.

18 Wefel J, Vidrine D, Veramonti T, et al. Cognitive impairment in men with testicular cancer prior to adjuvant therapy. *Cancer*. 2010;117:190–196.

19 Tager F, McKinley P, Schnabel F, et al. The cognitive effects of chemotherapy in post-menopausal breast cancer patients: a controlled longitudinal study. *Breast Cancer Res Treat*. 2010;123:25–34.

20 Taillibert, S., Le Rhun, E., & Chamberlain, M. C. (2016). Chemotherapy-related neurotoxicity. *Current neurology and neuroscience reports*, 16(9), 81.

21 StaffNP, et al. Chemotherapy-induced peripheral neuropathy: a current review. *Ann Neurol*. 2017;81(6):772–81.

22 Grisold, W., Löscher, W., & Grisold, A. (2019). Neurological complications of systemic tumour therapy. *Wiener Medizinische Wochenschrift*, 169(1-2), 33-40.

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 period⁷ 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

23 Ahles T, Saykin A, McDonald B, et al. Longitudinal assessment of cognitive changes associated with adjuvant treatment for breast cancer: impact of age and cognitive reserve. *J Clin Oncol.* 2010;28:4434–4440.

24 Selamat MH, Loh SY, Mackenzie L, Vardy J (2014) Chemobrain experienced by breast cancer survivors: a meta-ethnography study investigating research and care implications. *PLoS One* 9(9):e108002

25 Torrente, N. C., Pastor, J. B. N., & de la Osa Chaparro, N. (2020). Systematic review of cognitive sequelae of non-central nervous system cancer and cancer therapy. *Journal of Cancer Survivorship*, 1-19.

26 Mounier, N. M., Abdel-Maged, A. E. S., Wahdan, S. A., Gad, A. M., & Azab, S. S. (2020). Chemotherapy-induced cognitive impairment (CICI): An overview of etiology and pathogenesis. *Life Sciences*, 118071.

27 Hodgson K, Hutchinson A, Wilson C, Nettelbeck T. A meta-analysis of the effects of chemotherapy on cognition in patients with cancer. *Cancer Treat Rev.* 2013;39:297–304.

28 Lindner O, Phillips B, McCabe M, et al. A meta-analysis of cognitive impairment following adult cancer chemotherapy. *Neuropsychology.* 2014;28:726–740.

29 Jim H, Phillips K, Chait S, et al. Meta-analysis of cognitive functioning in breast cancer survivors previously treated with standard dose chemotherapy. *J Clin Oncol.* 2012;30:3578–3587.

30 Koppelmans V, Breteler M, Boogerd W, et al. Neuropsychological performance in survivors of breast cancer more than 20 years after adjuvant chemotherapy. *J Clin Oncol.* 2012;30:1080–1086.

31 Hardy, S. J., Krull, K. R., Wefel, J. S., & Janelins, M. (2018). Cognitive changes in cancer survivors. *American Society of Clinical Oncology Educational Book*, 38, 795-806.

32 Di Iulio, F., Cravello, L., Shofany, J., Paolucci, S., Caltagirone, C., & Morone, G. (2019). Neuropsychological disorders in non-central nervous system cancer: a review of objective cognitive impairment, depression, and related rehabilitation options. *Neurological Sciences*, 1-16.

33 Soffietti R, Kocher M, 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 expectations⁵³ 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

35 Klaver, K. M., Duijts, S. F., Engelhardt, E. G., Geusgens, C. A., Aarts, M. J., Ponds, R. W., ... & Schagen, S. B. (2020). Cancer-related cognitive problems at work: experiences of survivors and professionals. *Journal of Cancer Survivorship*, 14(2), 168-178.

36 Von Ah D, et al. Cancer, cognitive impairment, and work-related outcomes: an integrative review. *Oncol Nurs Forum*. 2016;43(5): 602–16.

37 Duijts SFA, et al. Cancer-related cognitive impairment and patients' ability to work: a current perspective. *Curr Opin Support PalliatCare*. 2017;11(1):19–23.

38 Cheng ASK, Zeng Y, Liu X, Liu S, Cheng SWC, Kwok CTT, et al. Cognitive challenges while at work and work output in breast cancer survivors employed in a rapidly evolving economy. *J Cancer Surviv*. 2018;12(6):753–61.

39 Dorland HF, et al. Work functioning trajectories in cancer patients: results from the longitudinal Work Life after Cancer (WOLICA) study. *Int J Cancer*. 2017;141(9):1751–62.

40 Kamal, K. M., Covey, J. R., Dashputre, A., Ghosh, S., Shah, S., Bhosle, M., & Zacker, C. (2017). A systematic review of the effect of cancer treatment on work productivity of patients and caregivers. *Journal of managed care & specialty pharmacy*, 23(2), 136-162.

41 Dhillon HM, Tannock IF, Pond GR et al. Perceived cognitive impairment in people with colorectal cancer who do and do not receive chemotherapy. *J Cancer Surviv* 2018; 12(2): 178–185.

42 Vardy JL, Dhillon HM, Pond GR et al. Cognitive function in patients with colorectal cancer who do and do not receive chemotherapy: a prospective, longitudinal, controlled study. *J Clin Oncol* 2015; 33(34):4085–4092.

43 Schilder CM, Seynaeve C, Linn SC et al. Self-reported cognitive functioning in postmenopausal breast cancer patients before and during endocrine treatment: findings from the neuropsychological TEAM sidestudy. *Psychooncology* 2012; 21(5): 479–487.

44 Vardy JL, Stouten-Kemperman MM, Pond G et al. A mechanistic cohort study evaluating cognitive impairment in women treated for breast cancer. *Brain Imaging 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.

46 Berman M, Askren M, Jung M, et al. Pretreatment worry and neurocognitive responses in women with breast cancer. *Health Psychology*. 2014;33:222–231.

47 Gehring, K., Taphoorn, M. J., Sitskoorn, M. M., & Aaronson, N. K. (2015). Predictors of subjective versus objective cognitive functioning in patients with stable grades II and III glioma. *Neuro-Oncology Practice*, 2(1), 20–31.

48 McDowell, L. J., Ringash, J., Xu, W., Chan, B., Lu, L., Waldron, J., Bernstein, L. J. (2019). A cross sectional study in cognitive and neuro-behavioural impairment in long-term nasopharyngeal cancer survivors treated with intensity-modulated radiotherapy. *Radiotherapy and Oncology*, 131, 179–185.

49 Pranckeviciene, A., Deltuva, V. P., Tamasauskas, A., & Bunevicius, A. (2017). Association between psychological distress, subjective cognitive complaints and objective neuropsychological functioning in brain tumour patients. *Clinical Neurology and Neurosurgery*, 163, 18–23.

50 Hermelink K, Kuchenhoff H, Untch M, et al. Two different sides of 'chemobrain': determinants and nondeterminants of self-perceived cognitive dysfunction in a prospective, randomized, multicenter study. *Psycho-Oncology*. 2010;19:1321–1328.

51 Koppelmans V, Breteler M, Boogerd W, et al. Neuropsychological performance in survivors of breast cancer more than 20 years after adjuvant chemotherapy. *J Clin Oncol*. 2012;30:1080–1086.

52 Krolak D, Collins B, Weiss L, et al. Cognitive function and its relationship 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.

54 Linsler, S., Keller, C., Urbschat, S., Ketter, R., & Oertel, J. (2016). Prognosis of meningiomas in the early 1970s and today. *Clinical Neurology and Neurosurgery*, 149, 98–103.



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

1 Kosek, E., Cohen, M., Baron, R., Gebhart, G. F., Mico, J.-A., Rice, A. S.C., Rief, W., Sluka, A. K. (2016). Do we need a third mechanistic descriptor for chronic pain states? *Pain*, 157(7), 1382–1386.

2 Greco MT, Roberto A, Corli O, Deandrea S, Bandieri E, Cavuto S, Apolone G. Quality of cancer pain management: an update of a systematic review of undertreatment of patients with cancer. *J Clin Oncol*. 2014;32(36):4149–54.

3 Te Boveldt ND, Vernooij-Dassen MJ, Jansen A, Vissers KC, Engels Y. Pain is not systematically registered in Dutch medical oncology outpatients. *Pain Practice* 2015; 15(4):364–370.

4 Gagnon B, Scott S, Nadeau L, Lawlor PG. Patterns of community-based opioid prescriptions in people dying of cancer. *J Pain Symptom Manage* 2015; 49(1): 36–44.

5 Ziegler L, Mulvey M, Blenkinsopp A, Petty D, Bennett MI. Opioid prescribing for patients with cancer in the last year of life: a longitudinal population cohort study. *Pain* 2016; 157(11):2445–51.

6 Bennett MI, Eisenberg E, Ahmedzai SH, Bhaskar A, O'Brien T, Mercadante S, Škvarč NK, Vissers K, Wirz S, Wells C, Morlion B. Standards for the management of cancer-related pain across Europe. A position paper from the EFIC Task Force on Cancer Pain. *European Journal of Pain* 2019; 23:660–668.

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 stages⁹.

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 pain¹⁵. Very intense and severe pain may also lead to an unwillingness to take medications and a desire to end life earlier²²

7 Lu Q, Krull KR, Leisenring W, Owen JE, Kawashima T, Tsao JCI, et al. Pain in long-term adult survivors of childhood cancers and their siblings: a report from the Childhood Cancer Survivor Study. *Pain* 2011;152(11):2616–24.

8 Zucca AC, Boyes AW, Linden W, Girgis A. All's well that ends well? Quality of life and physical symptom clusters in long-term cancer survivors across cancer types. *J Pain Symptom Manage* 2012;43(4):720–31.

9 Van Den Beuken-Van, M. H., Hochstenbach, L. M., Joosten, E. A., Tjan-Heijnen, V. C., & Janssen, D. J. (2016). Update on prevalence of pain in patients with cancer: systematic review and meta-analysis. *Journal of pain and symptom management*, 51(6), 1070-1090.

10 Mayer DK, Travers D, Wyss A, Leak A, Waller A. Why do patients with cancer visit emergency departments? Results of a 2008 population study in North Carolina. *J Clin Oncol* 2011; 29(19):2683–8.

11 Gallaway, M. S., Townsend, J. S., Shelby, D., & Puckett, M. C. (2020). Peer Reviewed: Pain Among Cancer Survivors. *Preventing Chronic Disease*, 17.

12 Forsythe LP, Alfano CM, George SM, McTiernan A, Baumgartner KB, Bernstein L, et al. Pain in long-term breast cancer survivors: the role of body mass index, physical activity, and sedentary behaviour. *Breast Cancer Res Treat* 2013;137(2):617–30.

13 Potter J, Higginson IJ. Pain experienced by lung cancer patients: a review of prevalence, causes and pathophysiology. *Lung Cancer* 2004;43(3):247–57.

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.

15 Kim YS, Do H, Lee JW, et al. Patient reporting pain intensity immediately after surgery can be associated with underlying depression in women with breast cancer. *Psychooncology*. 2016;25(3):308–315.

16 Owayolu N, Owayolu Ö, Serçe S, Tuna D, Pirbudak Çöçelli L, Sevinç A. Pain and quality of life in Turkish cancer patients. *Nurs Health Sci*. 2013;15(4):437–443.

17 He QH, Liu QL, Li Z, Li KZ, Xie YG. Impact of epidural analgesia on quality of life and pain in advanced cancer patients. *Pain Manag Nurs*. 2015;16(3):307–313.

18 Oliveira KG, von Zeidler SV, Podestá JR, et al. Influence of pain severity on the quality of life in patients with head and neck cancer before antineoplastic therapy. *BMC Cancer*. 2014;14(1):39.

19 Alkan A, Guc ZG, Senler FC, et al. Breast cancer survivors suffer from persistent postmastectomy pain syndrome and posttraumatic stress disorder (ORTHUS study): a study of the palliative care working committee of the Turkish Oncology Group (TOG). *Support Care Cancer*. 2016;24(9):3747–3755.

20 Ahmed A, Bhatnagar S, Rana SP, Ahmad SM, Joshi S, Mishra S. Prevalence of phantom breast pain and sensation among postmastectomy patients suffering from breast cancer: a prospective study. *Pain Pract*. 2014;14(2):E17–E28.

21 Rau KM, Chen JS, Wu HB, et al. The impact of pain control on physical and psychiatric functions of cancer patients: a nation-wide survey in Taiwan. *Jpn J Clin Oncol*. 2015;45(11):1042–1049.

22 O'Mahony S, Goulet J, Kornblith A, et al. Desire for hastened death, cancer pain and depression: report of a longitudinal observational study. *J Pain Symptom Manage*. 2005;29(5):446–457.

Moreover, approximately 41.5% of cancer patients report chronic pain²³ 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

23 Kurita GP, Sjögren P. Pain management in cancer survivorship. *Acta Oncol* 2015;54:629-34.

24 Pidgeon T, Johnson CE, Currow D, Yates P, Banfield M, Lester L, et al. A survey of patients' experience of pain and other symptoms while receiving care from palliative care services. *BMJ Support Palliat Care* 2016;6:315-22.

25 Green CR, Hart-Johnson T, Loeffler DR. Cancer-related chronic pain: examining quality of life in diverse cancer survivors. *Cancer* 2011;117(9):1994-2003.

26 Pachman DR, Barton DL, Swetz KM, Loprinzi CL. Troublesome symptoms in cancer survivors: fatigue, insomnia, neuropathy, and pain. *J Clin Oncol* 2012;30(30):3687-96.

27 Portenoy R, Koh M (2010) Cancer pain syndromes. In: Bruera E, Portenoy RK (eds) *Cancer pain. Assessment and management*, vol 4. Cambridge University Press, Cambridge, pp 53-88

28 Higginson IJ, Murtagh FEM (2010) Cancer pain epidemiology. In: Bruera E, Portenoy RK (eds) *Cancer pain. Assessment and management*, vol 3. Cambridge University Press, Cambridge, pp 37-52

29 Chang KL, Fillingim R, Hurley RW, Schmidt S. Chronic pain management: nonpharmacological therapies for chronic pain. *FP Essent* 2015;432:21-6.

30 Søgaard M, Thomsen RW, Bossen KS, et al. The impact of comorbidity on cancer survival: a review. *Clin Epidemiol* 2013;5(Suppl 1):3-29.

31 Paice JA, Portenoy R, Lacchetti C, Campbell T, Cheville A, Citron M, et al. Management of chronic pain in survivors of adult cancers: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* 2016;34(27):3325-45.

32 National Cancer Institute. Cancer Pain (PDQ®)-Health Professional Version. 2019; <https://www.cancer.gov/aboutcancer/treatment/side-effects/pain/pain-hp-pdq>.



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 treatments², increased mortality³, 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-Stone KM, 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 be 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.

7 Rocque GB, Williams GR. Bridging the data-free zone: decision making for older adults with cancer. *J Clin Oncol*. 2019. Jco1902588.

8 Tack L, et al. Underrepresentation of vulnerable older patients with cancer in phase II and III oncology registration trials: a case-control study. *J Geriatr Oncol*. 2019.

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 prefrailty²⁶.

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.

12 Sun Myint, A.; Smith, F.M.; Gollins, S.; Wong, H.; Rao, C.; Whitmarsh, K.; Sripadam, R.; Rooney, P.; Hertsman, M.; Pritchard, D.M. Dose escalation using contact X-ray brachytherapy after external beam radiotherapy as nonsurgical treatment option for rectal cancer: Outcomes from a single center experience. *Int. J. Radiat. Oncol. Biol. Phys.* 2018, 100, 565–573.

13 Bonet, M.; Bonfil, T.; Nunez, M.; De Vergones, L.; Mur, E.; Gallardo, E.; Fernandez-Morales, L.; Aguilar, A.; Prats, J.; Arenas, M. Curative radiation therapy for very elderly bladder cancer patients with localized disease. *Clin. Trans. Oncol.* 2018, 20, 899–905.

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15 Gan, W.; Liu, X.-L.; Yu, T.; Zou, Y.-G.; Li, T.-T.; Wang, S.; Deng, J.; Wang, L.-L.; Cai, J.-P. Urinary 8-oxo-7,8-dihydroguanosine as a potential biomarker for ageing. *Front. Ageing Neurosci.* 2018, 10, 34.

16 Chen, J.; Chen, J.; Wu, X.; Shi, T.; Kang, M. Efficacy of targeted agents in the treatment of elderly patients with advanced non-small lung cancer: A systematic review and meta-analysis. *Oncotargets Ther.* 2016, 9, 4797–4803.

17 Daste, A.; Dombildes, C.; Gross-goupil, M.; Chakiba, C.; Quivy, A.; Cochin, V.; de Mones, E.; Larmonier, N.; Soubeyran, P.; Ravaud, A. Immune checkpoint inhibitors and elderly people: A review. *Eur. J. Cancer* 2017, 82, 155–166.

18 Hurria A., Levit LA, Dale W., et al. Improving the evidence base for treating older adults with cancer: American Society of Clinical Oncology Statement. *J Clin Oncol* 2015;33:3826–3833.26195697

19 Wildiers H., Mauer M., Pallis A., et al. End points and trial design in geriatric oncology research: A joint European Organisation for Research and Treatment of Cancer–Alliance for Clinical Trials in Oncology–International Society of Geriatric Oncology position article. *J Clin Oncol* 2013;31:3711–3718.24019549

20 Turner JP, Jansen KM, Shakib S et al. Polypharmacy cut-points in older people with cancer: How many medications are too many? *Support Care Cancer* 2016;24:1831–1840.

21 Williams GR, Deal AM, Nyrop KA et al. Geriatric assessment as an aide to understanding falls in older adults with cancer. *Support Care Cancer* 2015;23:2273–2280.

22 Vande Walle N, Kenis C, Heeren P et al. Fall predictors in older cancer patients: A multicenter prospective study. *BMC Geriatr* 2014;14:135.

23 van Abbema D, van Vuuren A, van den Bergmolen F et al. Functional status decline in older patients with breast and colorectal cancer after cancer treatment: A prospective cohort study. *J Geriatr Oncol* 2017;8:176–184.

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 depression³¹ 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-Poitine 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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48 Loeb S, Carter HB, Berndt SI, Ricker W, Schaeffer EM. Complications after prostate biopsy: data from SEER-Medicare. *The Journal of urology*. 2011; 186(5):1830-1834.

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 men⁵⁵ 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 risk⁵⁸ 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

51 Carlsson S, Estimating the harms and benefits of prostate cancer screening as used in common practice versus recommended good practice: A microsimulation screening analysis, *Cancer*, Volume 122 - Issue 21 p. 3386- 3393

52 Schoots I, Osses DF, Drost FJ, et al. Reduction of MRI-targeted biopsies in men with low-risk prostate cancer on active surveillance by stratifying to PIRADS and PSA-density, with different thresholds for significant disease. *Trans Androl Urol*. 2018;7:132-44.

53 Schoots I, Padhani A. Personalizing prostate cancer diagnosis with multivariate risk prediction tools: how should prostate MRI be incorporated? *World Journal of Urology*. 2020;38:531-45.

54 USPSTF. Prostate Cancer Screening Recommendations. 2017. <https://screeningforprostatecancer.org/>

55 Gandaglia et al Structured Population-based Prostatespecific Antigen Screening for Prostate Cancer: The European Association of Urology Position in 2019 found at [https://www.europeanurology.com/article/S0302-2838\(19\)30347-1/pdf](https://www.europeanurology.com/article/S0302-2838(19)30347-1/pdf)

56 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/>

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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.

59 Garg V, Gu NY, Borrego ME, et al. A literature review of costeffectiveness analyses of prostate-specific antigen test in prostate cancer screening. *Expert Rev Pharmacoecon Outcomes Res* 2013;13(3):327–42.

60 Schonberg MA, Li VW, Eliassen AH, et al. Accounting for individualized competing mortality risks in estimating postmenopausal breast cancer risk. *Breast Cancer Res Treat*. Dec. 2016; 160(3):547–562.

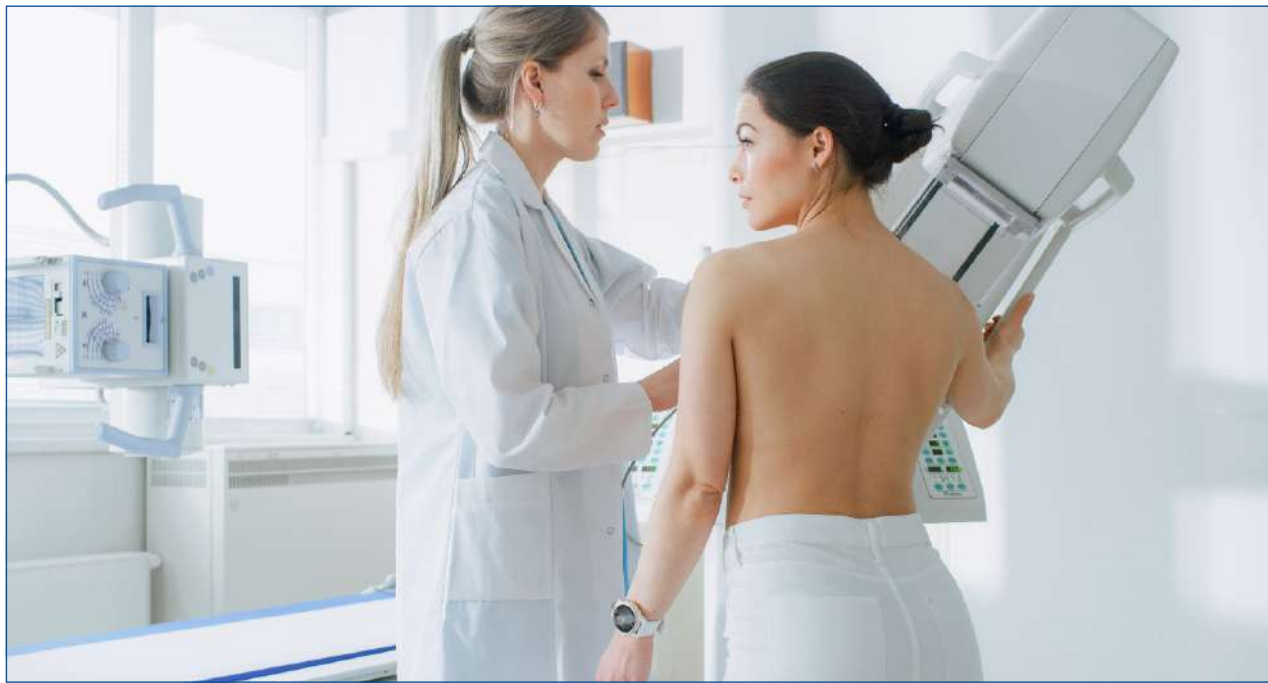
61 Siu AL. Screening for breast cancer: US Preventive Services Task Force recommendation statement. *Annals of internal medicine*. 2016; 164(4):279–296. [

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.

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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.⁶³ 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.

67 Ayer T, Alagoz O, Stout N (2012) A POMDP Approach to Personalize Mammography Screening Decisions. *Operations Research* 60: 1019-1034.

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69 Trentham-Dietz A, Kerlikowske K, Stout NK, et al; Breast Cancer Surveillance Consortium and the Cancer Intervention and Surveillance Modeling Network. Tailoring breast cancer screening intervals by breast density and risk for women aged 50 years or older: collaborative modeling of screening outcomes. *Ann Intern Med.* 2016;165(10):700-712.

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.

71 Gray E, Donten A, Karssemeijer N, et al. Evaluation of a stratified national breast screening program in the United Kingdom: an early model-based cost-effectiveness analysis. *Value Health.* 2017;20(8):1100-1109.

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

1 Knoll LJ, Hogan DA, Leong JM, Heitman J, Condit RC (2018) Pearls collections: What we can learn about infectious disease and cancer. *PLoS Pathog*, **14**(3), pp. 1-7.

2 Moore PS, Chang Y. (2010). Why do viruses cause cancer? Highlights of the first century of human tumour virology. *Nat Rev Cancer*, **10**(12), pp. 878-89.

3 Metzger MJ, Goff SP (2016). A sixth modality of infectious disease: contagious cancer from devils to clams and beyond. *PLoS Pathog*, **12**(10), pp. 1-7.

4 Knoll LJ, Hogan DA, Leong JM, Heitman J, Condit RC (2018) Pearls collections: What we can learn about infectious disease and cancer. *PLoS Pathog*, **14**(3), pp. 2.

5 Pappas, G. (2009). Infectious causes of cancer: an evolving educational saga, *Clinical Microbiology and Infection*, **15** (11), p. 961.

6 Nagai, H. & Young Hak, K. (2017). Cancer prevention from the perspective of global cancer burden patterns, *Journal of Thoracic Disease*, **9**(3), pp. 448-451.

7 De Martel C, Georges D, Bray F, Ferlay J, Clifford GM (2020). Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. *The Lancet: Global Health*, **8**(2), pp. 189.

8 Masrou-Roudsari, Ebrahimpour, S. (2017). Causal role of infectious agents in cancer: An overview. *Caspian J Intern Med*, **8**(3), pp. 153-158.

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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11 Asrani SK, et al. J Hepatol 2019;70:151–171

12 Sanduzzi-Zamparelli M, et al. Dig Liver Dis 2020;52:1041–1046

13 Wilson GC, et al. Ann Surg Oncol 2019;26:576–582

14 Maucourt-Boulch D, de Martel C, Franceschi S, Plummer M (2018). Fraction and incidence of liver cancer attributable to hepatitis B and C viruses worldwide. *Int J Cancer*, **142**(12): 2471–7.

15 Wild, C. P. (WHO) (2020). World Cancer Report. Cancer Research for Cancer Prevention, p. 61.

16 Xia J, Jiang S-C, Peng H-J, et al. (2015). Association between liver fluke infection and hepatobiliary pathological changes: a systematic review and meta-analysis. *PLoS One*, **10**(7), pp. 2–9.

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19 International Agency for Research on Cancer (WHO) (2020). Liver Cancer Fact Sheet. Accessed from <https://gco.iarc.fr/today/data/factsheets/cancers/11-Liver-fact-sheet.pdf>

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-](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.

22 European Cancer Organisation. (2020) It Can Be Done – Beating Inequalities in Cancer Care. Action Report. Accessed from <https://www.europeanecancer.org/resources/164:beating-inequalities-in-cancer-care.html>

23 Romano, L., Paladini, S., Van Damme, P., et al. (2011). The worldwide impact of vaccination on the control and protection of viral hepatitis B. *Digestive and Liver Disease*, **43**(1), pp. 2–7.

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.

25 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), pp. 563-582.

26 Guyton, K. Z. & Kensler, T. (2002). Prevention of liver cancer, *Current Oncology Reports*, 4, pp. 464-470.

27 Wei, M. T., Henry, L., Nguyen M. H. (2019). *Nonliver Comorbidities in Patients with Chronic Hepatitis B*. *Clinical Liver Disease* 14(3), pp. 126-130.

28 Masrour-Roudsari, Ebrahimpour, S. (2017). Causal role of infectious agents in cancer: An overview. *Caspian J Intern Med*, 8(3), p. 157.

29 Behnoosh, M., Millman, A. J., Beauchesne Nielsen, D. B. et al. (2018). Promising practices for the prevention of liver cancer: a review of the literature and cancer plan activities in the National Comprehensive Cancer Control Program. *Cancer Causes Control*, 29(12), pp. 1265-1275.

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

¹ Nick Sheron, Alcohol and liver disease in Europe – Simple measures have the potential to prevent tens of thousands of premature deaths, *Journal of Hepatology* 2016 vol. 64 | 957–967

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 smoking² 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

1 American Cancer Society 2012. Cancer facts & figures 2012. 2012. <http://www.cancer.org/acs/groups/content/@epidemiologysurveillance/documents/document/acspc-031941.pdf> .

2 Institute for Health Metrics and Evaluation. Global burden of disease 2015. 2015 <http://vizhub.healthdata.org/gbd-compare/>

3 Reitsma MB, Fullman N, Ng M, et al. Smoking prevalence and attributable disease burden in 195 countries and territories, 1990-2015: a systematic analysis from the global burden of disease study 2015. *Lancet* 2017;389:1885–906

4 O’Keeffe, Linda M., et al. “Smoking as a risk factor for lung cancer in women and men: a systematic review and meta-analysis.” *BMJ open* 8.10 (2018): e021611.

5 Alyahya, Mohammad S., Nihaya A. Al-Sheyab, and Batool Amro. “Parental Smoking Behavior and Childhood Cancer: A Case-control Study.” *American Journal of Health Behavior* 44.5 (2020): 572-590.

6 American Cancer Society: <https://www.cancer.org/cancer/cervical-cancer/causes-risks-prevention/risk-factors.html>

7 McGee, Emma E., et al. “Smoking, alcohol, and biliary tract cancer risk: a pooling project of 26 prospective studies.” *JNCI: Journal of the*

- **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
- **Esophageal 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 worldwide¹⁶ 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

National Cancer Institute 111.12 (2019): 1263-1278.

8 Capitanio, Umberto, et al. "Epidemiology of renal cell carcinoma." *European urology* 75.1 (2019): 74-84.

9 Cheng, Jiemin, et al. "Meta-analysis of prospective cohort studies of cigarette smoking and the incidence of colon and rectal cancers." *European Journal of Cancer Prevention* 24.1 (2015): 6-15.

10 Jain S, Dhir S. Pathology of esophageal cancer and Barrett's esophagus. *Ann Cardiothorac Surg.* 2017;6(2):99-109. doi:10.21037/acs.2017.03.06.

11 Okamura A, Watanabe M. [Perioperative Management Team in Esophageal Cancer Surgery]. *Kyobu Geka.* 2017;70(8):712-715.

12 Song, Ashley, et al. "Incident testicular cancer in relation to using marijuana and smoking tobacco: A systematic review and meta-analysis of epidemiologic studies." *Urologic Oncology: Seminars and Original Investigations.* Elsevier, 2020.

13 <https://www.mayoclinic.org/diseases-conditions/bladder-cancer/symptoms-causes/syc-20356104>

14 Iodice S, Gandini S, Maisonneuve P, et al: Tobacco and the risk of pancreatic cancer: A review and meta-analysis *Langenbecks Arch Surg* 393:535-545, 2008

15 Qin, Ling, et al. "Relationship between cigarette smoking and risk of chronic myeloid leukaemia: a meta-analysis of epidemiological studies." *Hematology* 22.4 (2017): 193-200.

16 Wyss, Annah, et al. "Cigarette, cigar, and pipe smoking and the risk of head and neck cancers: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium." *American journal of epidemiology* 178.5 (2013): 679-690.

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19 NCI. Smoking cessation and continued risk in cancer patients (PDQ®). 2012. <http://www.cancer.gov/cancertopics/pdq/supportivecare/smokingcessation/HealthProfessional/page3>

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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 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

With the support of unrestricted grants from:



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Sanofi



Ipsen – Innovation for patient care



AbbVie



Bristol-Myers Squibb

