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Adding life to years: heart health and cancer

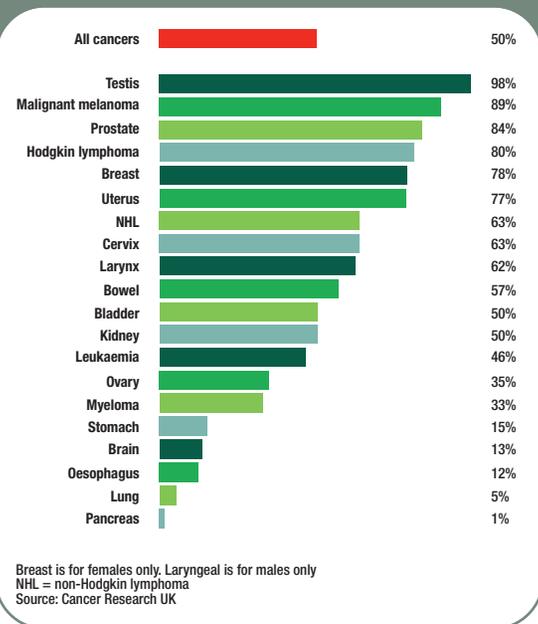
Today over half of patients can expect to survive for at least 10 years after a diagnosis of cancer,¹ but a longer lifespan does not necessarily mean a return to health. Commonly used anticancer therapies are associated with an increased risk of cardiovascular disease that means that today's cancer survivors may be more likely to die of heart disease than a recurrence of their malignancy. Primary healthcare professionals can help to improve cardiovascular outcomes for cancer survivors through effective communication with secondary care colleagues, risk assessment and monitoring, use of evidence-based therapies, and advice to patients about a healthy lifestyle.

Cancer survival has increased substantially in England and Wales over the last 40 years, so that 12 of the most common cancers now have a 10-year survival of $\geq 50\%$ and four types—testicular cancer, malignant melanoma, prostate cancer and Hodgkin lymphoma—have 10-year survival $> 80\%$ (Figure 1).¹ Unfortunately, after surviving their initial cancer, many of this growing population of patients are at high risk of premature disease or death, because they received one or more of the commonly used cancer therapies that are associated with an increased risk of cardiovascular disease (CVD). These risks are of particular concern in older cancer survivors who may have cardiovascular co-morbidities, and in adults who have survived cancer and its treatment during their childhood and who may present with cardiovascular symptoms at a relatively young age.

Heart disease following radiotherapy, chemotherapy and hormone therapy may be the result of direct cardiovascular damage caused by the treatment itself, or may be due to the development of treatment-related cardiovascular risk factors.² Several mechanisms impair endothelial function, accelerate atherosclerosis and increase the risk of thromboembolism (Figure 2). Patients receiving anti-hormonal therapy—for example, for breast cancer or prostate cancer—are at high risk of CVD because these treatments lead to early menopause in women and lower levels of testosterone in men, which in turn promote the development of visceral fat or central adiposity. Visceral fat is an active endocrine organ that synthesises and secretes a range of hormones, adipokines and cytokines that result in the proinflammatory, procoagulant and insulin-resistant state known as the metabolic syndrome with its associated cardiovascular risk.^{3,4}

Table 1 lists the cardiovascular side-effects of some commonly used systemic cancer therapies. The anthracyclines are well-established chemotherapy agents that

Figure 1: Age-standardised 10-year net survival for selected cancers (adults, England and Wales 2010–2011)



are mainly used to treat leukaemia, lymphoma, and cancers of the breast, uterus, lung and ovary. Their cardiotoxic effects are dose-dependent and irreversible and may be undetected for years because they are often subclinical.⁵ Trastuzumab (Herceptin) is a monoclonal antibody that selectively targets the HER2/neu receptor. It improves overall survival in both early and metastatic HER2-positive breast cancer, but it is associated with the risk of reduced left-ventricular ejection fraction and heart failure. These cardiotoxicities are not dose-dependent, and are reversible if detected early.^{6,7}

Radiotherapy to the chest, which is commonly used to treat lymphomas and breast cancer, may have both short-

POINTS FOR THE CLINIC

- Assess cardiovascular risk factors in each patient before, during and after their anticancer treatment
- Include an assessment of cardiovascular risk factors and symptom history in the annual primary care cancer review
- Optimally manage cardiovascular risk factors and co-morbidities: *eg* blood pressure, lipids, diabetes, chronic kidney disease
- Advise patients on the benefits of a healthy lifestyle
- Advise patients to seek help if they experience cardiovascular symptoms

Figure 2: Major mechanisms causing cardiotoxicity of anticancer treatments (and cardioprotective agents)

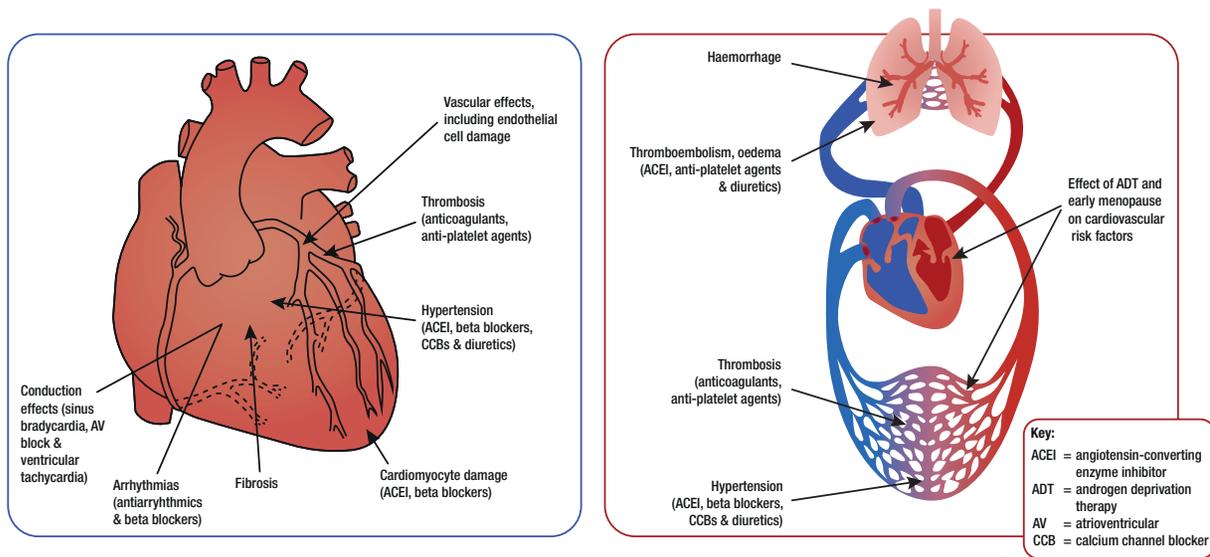


Table 1: Cardiovascular side-effects of systemic anticancer therapies

Cancer therapy	Effect	Long-term effect?	Mechanism
Anthracyclines: <i>eg</i> doxorubicin (Caelyx), epirubicin	Cardiotoxicity type 1 (irreversible)	Yes	Loss of myocardium
Cyclophosphamide	Cardiotoxicity type 1 (irreversible)	Rare	Myocarditis
Cisplatin	Cardiotoxicity type 1 (irreversible)	Rare	Unknown
	Thromboembolism	Rare	Endothelial damage
Anti-HER2 therapies: <i>eg</i> trastuzumab (Herceptin)	Cardiac dysfunction	Unlikely, except when combined with anthracyclines	Mitochondrial dysfunction
Pyrimidine analogues: <i>eg</i> 5-fluorouracil or 5-FU, capecitabine (Xeloda), tegafur	Myocardial ischaemia	Rare	Coronary vasospasm
Anti-VEGF therapies: <i>eg</i> bevacizumab (Avastin)	Myocardial ischaemia	Rare	Arterial thrombosis
	Thromboembolism	Rare	Endothelial damage
	Arterial hypertension	Unknown	Multiple mechanisms
Arsenic trioxide (Trisenox)	Myocardial ischaemia	No	HERG K+ blockage
Selected TKIs: <i>eg</i> lapatinib (Tyverb), pazopanib (Votrient), sorafenib (Nexavar), sunitinib (Sutent)	Myocardial ischaemia	No	HERG K+ blockage
	Pulmonary hypertension	Unknown	Unknown
	Peripheral arterial occlusive disease	Unknown	Unknown
	Pleural effusion	Unknown	Unknown

HER-2 = human epidermal growth factor receptor 2; HERG = human ether-a-go-go-related gene; TKI = tyrosine kinase inhibitor; VEGF = vascular endothelial growth factor

and long-term cardiotoxic effects (Table 2), especially if it is administered with simultaneous chemotherapy. Since tissue damage is related to the dose of radiation, the risk to the heart is lower with modern conformal radiotherapy using cardiac shielding, breath-hold techniques and planning computed tomography (CT) scans. However, some patients may present with cardiac symptoms years after receiving less targeted forms of radiotherapy. Women with left-sided breast cancer may be at particular risk, especially as the possibility of heart disease may be under-estimated by health professionals and by women themselves.

Research presented at EuroEcho-Imaging 2015, the annual meeting of the European Association of Cardiovascular Imaging, has raised the possibility that cancer itself may damage heart muscle irrespective of exposure to cancer drug therapies. According to researchers from the UK's first dedicated cardio-oncology clinic, 43 treated and 36 untreated cancer patients had similar measurements of myocardial strain indicating impaired heart function, compared to 20 healthy age-matched controls. This raises the possibility that the tumour itself may produce inflammatory markers that lead to a subclinical reduction in myocardial function. Since all the cancer patients had

Table 2: Cardiotoxic effects of radiotherapy⁵

Structure/function affected	Long-term effects?	Comments
Small and large vessels, including the coronary arteries	Months to decades	Early changes can be difficult to detect
Valves	Years	Surgical interventions carry increased risk
Pericardium	Weeks to decades	Can recur multiple times following treatment. May progress to constrictive pericarditis

preserved ejection fraction, this study indicates the need to implement closer cardiovascular monitoring of patients with cancer than is currently conducted.⁸

THE ROLE OF PRIMARY CARE

As commissioning becomes more complex within the NHS, there is a real risk that patients may not receive the monitoring and interventions needed to reduce their risk of CVD. Currently, follow-up care after treatment for cancer largely focuses on monitoring for recurrence, and is provided by oncology teams in secondary care. This model is no longer feasible given the increasing numbers of long-term cancer survivors and the pressures on the NHS. Increasingly a 'risk-stratified' approach is being adopted, in which patients at lowest risk of cancer recurrence continue to have regular scans/tests but fewer formal follow-up appointments. As a result, there is potential for late consequences of treatment to be overlooked. Since most cancer survivors are likely to be registered with their local general practice, primary care is potentially well placed to deliver a 'whole person' approach to their care. But a recent survey suggests that GPs are aware that they need information and support to enable them to undertake this role.

Of 500 English GPs surveyed, 77% agreed that primary and secondary care should work together to manage cardiovascular health before and after treatment for cancer. However, only 21% often considered a history of cancer treatment when assessing cardiovascular health, 40% knew about the effects of radiotherapy, 53% knew about effects of hormone therapy and 50% knew about effects of chemotherapy on heart health. The GPs were very interested in learning more about how primary care could improve cardiovascular outcomes in people living with and beyond cancer, with 86% wanting to receive further education on the effects of cancer treatment on cardiovascular health.⁹

Macmillan Cancer Support has published practical recommendations (in the form of a 'Quick Guide' and a 'Tips' sheet) to help GPs, practice nurses and other primary care health professionals to manage the cardiovascular health of cancer survivors. This advice was formulated by a multidisciplinary group of GPs, nurses, cardiologists and oncologists, and outlines the factors to consider and manage in order to maintain patients' heart health before, during and after treatment for cancer. (The Quick Guide includes a helpful table summarising these recommendations.) A complementary self-help guide is also available to help people with cancer keep their hearts healthy during their treatment and in the years ahead (see More information).

ROLE OF ECHOCARDIOGRAPHY

Echocardiography is a key investigation when assessing heart health in people with cancer because it can be used for baseline assessment of cardiac function, surveillance during cancer treatment and to diagnose previously unrecognised problems such as valve damage following radiotherapy. Serial echocardiography is particularly helpful in monitoring changes in left-ventricular function and longitudinal strain to detect early cardiac damage in patients treated with anthracyclines and trastuzumab. Ideally, these patients should have a baseline echocardiogram, followed by further imaging no later than six months after the end of their treatment. Subsequently, five-yearly echocardiograms should be sufficient if the six-monthly result is normal and the patient is asymptomatic.

In areas where access to echocardiography is limited, the alternative is ECG combined with cardiac biomarker testing with B-type natriuretic peptide (BNP) and troponin. Testing for levels of myeloperoxidase (MPO) is not as yet widely available, but as a marker of inflammation it is likely to be another useful biomarker of cardiovascular risk. I would suggest that echocardiography is not indicated if cardiac biomarkers are normal and the patient is asymptomatic, but patients must be advised to get in touch with the practice as soon as they start to experience symptoms such as fatigue or shortness of breath.

INDIVIDUALISING RISK MANAGEMENT

When managing cardiovascular risk in people treated for cancer, one of the challenges is the absence of accepted definitions of cardiotoxicity and cardiac dysfunction in these patients, and the difficulty in differentiating between irreversible type 1 cardiac damage and type 2 damage, which is reversible if it is detected early enough. There are also no reliable 10- to 20-year data or surrogate markers to predict long-term cardiovascular prognosis in cancer survivors. As a result, it is impossible to identify accurately the patients at high cardiovascular risk, especially given the recent introduction of novel, more targeted therapies that may be less (or more) cardiotoxic than established treatments. Individualised risk assessment is therefore essential, and this depends on effective communication between primary and secondary care about each patient's baseline cardiovascular health and the potential cardiotoxicity of their anticancer therapies.

The range of cancer therapies and complexities in case mix mean that there is insufficient evidence to recommend a one-size-fits-all surveillance and monitoring regimen. However, after a patient has been treated for cancer, assessment of cardiovascular risk factors and symptom history is advisable as part of the annual primary care cancer review. This applies especially to patients treated with hormone therapies, anthracyclines and radiotherapy to the chest, and those with a history of cardiovascular disease, diabetes, the metabolic syndrome or chronic kidney disease (CKD).

Ten-year risk assessment based on Framingham tables may be misleading in cancer patients, and lifetime risk assessment with QRISK or the JBS-3 risk calculator is recommended especially as these online tools can show the patient how healthy lifestyle choices can reduce their cardiovascular risk. This highlights the importance of advising cancer survivors on the benefits of a healthy lifestyle to reduce not only their cardiovascular risk, but also the risks associated with their cancer (Table 3). There is evidence that a healthy diet and physical exercise lower the risk of cancer recurrence by 50%, as well as reducing the severity of any recurrence.^{10,11}

Table 3: Healthy heart advice to patients before, during and after treatment for cancer

- Eat a heart-healthy, Mediterranean-style diet (*ie* a diet rich in fruit and vegetables, oily fish, wholegrain cereal, low-fat dairy foods and monounsaturated fats such as olive oil)
- Maintain a healthy weight
- Keep physically active
- Stop smoking
- Avoid drinking too much alcohol and binge drinking. Aim to have at least two alcohol-free days a week, and do not regularly drink more than 3–4 units/day for men or more than 2–3 units/day for women
- Take action to reduce your stress and anxiety
- Get in touch with your GP if you have symptoms, such as chest discomfort and tightness, shortness of breath, rapid or irregular heartbeat, fatigue, swelling of the feet and ankles
- For more information and sources of support for patients, read *Heart health and cancer treatment* from Macmillan and the British Heart Foundation

Patients should receive optimal treatment to address their cardiovascular risk factors and co-morbidities such as diabetes or CKD. Therapies include angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) to lower blood pressure and reduce the risk of cardiac damage, anti-platelet agents and anticoagulants to address the risks of thromboembolism and acute coronary events, and statins to control lipid levels. Recommendations on when to refer patients to secondary care cardiology services are shown in Table 4.

CONCLUSIONS

GPs, practice nurses and other primary healthcare professionals should be aware of the long-term health needs of patients who have received treatment for cancer. To ensure long-term surveillance and reduction in cardiovascular risk, there must be clear communication between primary and secondary care, and education of patients to enable them to take ownership of their heart health and live well during and after their cancer treatment.

References

1. Quaresma M, Coleman MP, Rachet B. 40-year trends in an index of survival for all cancers combined and survival adjusted for age and sex for each cancer in England and Wales, 1971–2011: a population-based study. *Lancet* 2015;**385**:1206–18. doi:

Table 4: Criteria for referral of cancer patients to secondary care cardiology services

- Patients with abnormal cardiac function or cardiovascular symptoms detected during surveillance
- Any new cardiac abnormality in symptomatic patients with established cardiovascular disease
- Women who were treated with cardiotoxic chemotherapy or radiotherapy involving the heart and are pregnant or planning to become pregnant
- Patients who were treated with cardiotoxic chemotherapy or radiotherapy involving the heart and who wish to compete at a high level of exercise

- 10.1016/S0140-6736(14)61396-9.
2. Albini A, Pennesi G, Donatelli F, *et al*. Cardiotoxicity of anticancer drugs: the need for cardio-oncology and cardio-oncological prevention. *J Natl Cancer Inst* 2010;**102**:14–25. doi: 10.1093/jnci/djp440.
3. Coelho M, Oliveira T, Fernandes R. Biochemistry of adipose tissue: an endocrine organ. *Arch Med Sci* 2013;**9**:191–200. doi: 10.5114/aoms.2013.33181.
4. Isomaa B, Almgren P, Tuomi T, *et al*. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 2001;**24**:283–9. doi: 10.2337/diacare.24.4.683.
5. Ewer MS, Ewer SM. Cardiotoxicity of anticancer treatments. *Nat Rev Cardiol* 2015;**12**:620. doi: 10.1038/nrcardio.2015.133.
6. Balduzzi S, Mantarro S, Guarneri V, *et al*. Trastuzumab-containing regimens for metastatic breast cancer. *Cochrane Database Syst Rev* 2014;**6**:CD006242. doi:10.1002/14651858.CD006242.pub2.
7. Moja L, Tagliabue L, Balduzzi S, *et al*. Trastuzumab containing regimens for early breast cancer. *Cochrane Database Syst Rev* 2012;**4**:CD006243. doi:10.1002/14651858.CD006243.pub2.
8. Venneri L, Calicchio F, Manivarmane R, *et al*. Subclinical myocardial dysfunction in cancer patients: is there a direct effect of tumour growth? *Eur Heart J Cardiovasc Imaging Abstracts Supplement* 2015;**16**(Supplement 2):ii127.
9. Walter FM, Usher-Smith JA, Yadlapalli S, Watson E. Caring for people living with, and beyond, cancer: an online survey of GPs in England. *Br J Gen Pract* 2015;**65**:e761–8. doi: 10.3399/bjgp15X687409.
10. Meyerhardt JA, Giovannucci EL, Holmes MD, *et al*. Physical activity and survival after colorectal cancer diagnosis. *J Clin Oncol* 2006;**24**:3527–34. doi: 10.1200/JCO.2006.06.0855
11. Meyerhardt JA, Heseltine D, Niedzwiecki D, *et al*. Impact of physical activity on cancer recurrence and survival in patients with stage III colon cancer: findings from CALGB 89803. *J Clin Oncol* 2006;**24**:3535–41. doi: 10.1200/JCO.2006.06.0863

more information

- Macmillan guides for professionals and patients
 - Managing heart health during and after cancer treatment: a guide for primary care health professionals: http://www.macmillan.org.uk/Documents/AboutUs/Health_professionals/Consequencesoftreatment/Hearthealthguide.pdf
 - Heart health tips for primary care professionals: http://www.macmillan.org.uk/Documents/AboutUs/Health_professionals/Consequencesoftreatment/Healthhealthtips.pdf
 - Heart health and cancer treatment (for patients): <http://be.macmillan.org.uk/be/p-22060-heart-health-and-cancer-treatment.aspx>
- Royal College of General Practitioners. Consequences of cancer toolkit (resources and information for primary care): <http://www.rcgp.org.uk/coc>
- JBS-3 risk calculator: http://www.jbs3risk.com/pages/risk_calculator.htm
- QRISK lifetime cardiovascular risk calculator: <http://www.qrisk.org/lifetime/index.php>