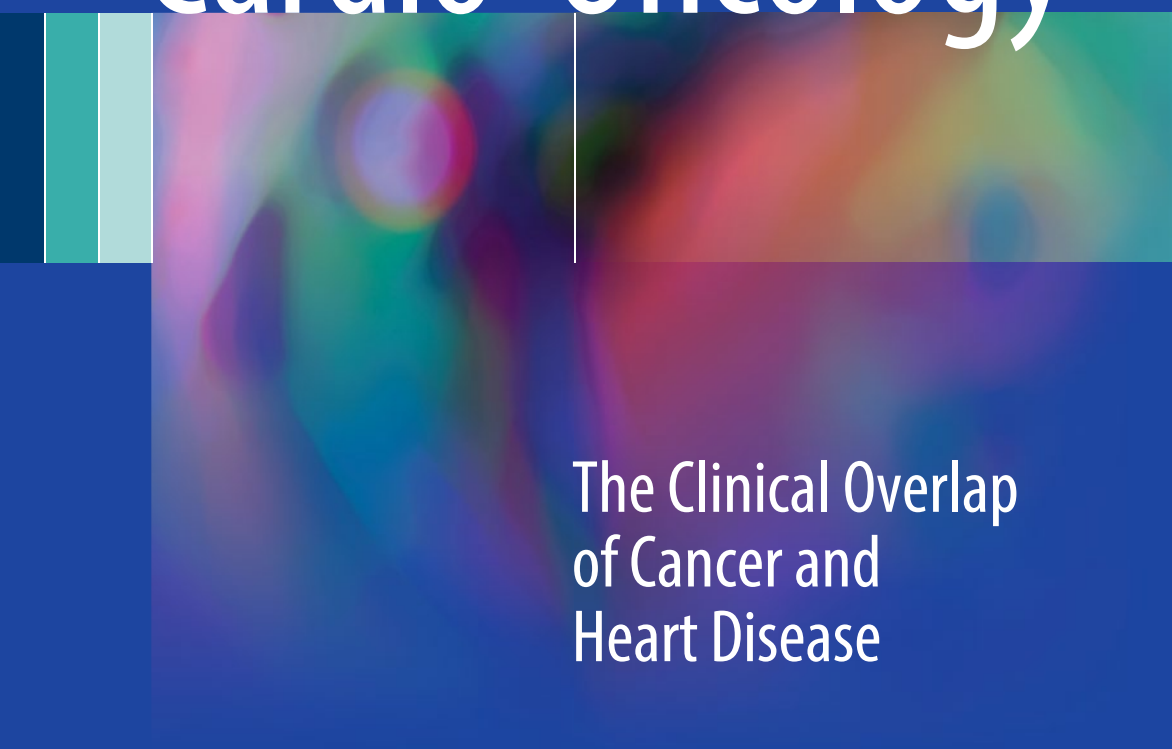
Gretchen G. Kimmick · Daniel J. Lenihan
Douglas B. Sawyer · Erica L. Mayer
Dawn L. Hershman *Editors*

Cardio-Oncology



The Clinical Overlap of Cancer and Heart Disease

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For the inspiration and support to write this truly collaborative book, we thank our families and loved ones, those for whom we have the honor of providing care, our colleagues/collaborators, mentors, and students.

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Preface

As we see the explosion of new treatment approaches for many diseases, medicine becomes more and more subspecialized, and subsequently there is increased fragmentation. As a result of this progressive partitioning of medical care, close collaboration between medical subspecialties becomes an essential component to effective health care. The emerging medical discipline of cardio-oncology is a prime instance when such cooperation is paramount. In adults, cancer and heart disease have remarkable similarities in epidemiology. These two diseases, cardiovascular disease and cancer, account for at least half of the reasons for death in developed countries. It is no surprise that these diseases may coexist in many patients, emphasizing the need for there to be close collaboration between oncology and cardiology specialists.

With this textbook, we hope to provide a clinically useful volume containing knowledge about cardiac complications of cancer therapy, treatment of cancer in patients with cardiovascular disease, and treatment of cardiovascular disease in patients with cancer for practicing cardiologists, medical and radiation oncologists, and trainees in these fields. The book has been edited by three oncologists and two cardiologists with the purpose of integrating the two medicine subspecialties to be clinically useful to the oncologist and the cardiologist in caring for these patients. Each chapter is coauthored by at least one oncologist and one cardiologist, in order to include the perspective of each discipline and make the text user-friendly and clinically applicable to both specialties as well as others. We believe that this is the first textbook of cardio-oncology to provide this comprehensive coverage from a truly multidisciplinary standpoint. Combined, the chapters provide a clinically relevant overview of the epidemiology, basic science, and clinical knowledge in the ever-expanding space in which cardiology and oncology overlap.

This textbook adds to available learning resources in that it expands the topic from one focused only on heart failure caused by cancer therapies to a more inclusive one, where multiple cardiovascular issues, including coronary artery disease, hypertension, and vascular complications, among others, are thoroughly considered. We also asked the authors to generally include practical management

approaches to common clinical problems in order be a useful guide to clinicians encountering these potentially difficult decisions. We hope that you find this text engaging and informative, but we also recognize this is a rapidly changing discipline. Perhaps by reading this text, a practitioner will be stimulated to contribute to our combined knowledge and advance the research in this invigorating discipline to continuously improve patient care.

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Chapter 1
Epidemiology of Cardio-Oncology

Carrie Geisberg Lenneman, Gretchen G. Kimmick, and Douglas B. Sawyer

Introduction

Heart disease and cancer are the first and second leading causes of death, accounting for 47 % of all mortality in the United States in 2010 [1, 2]. In adults, cancer and heart disease have remarkable similarities in epidemiology, explaining why many adult patients require the care of both oncology and cardiology specialists. This is augmented by the fact that patients with cardiovascular disease (CVD) and cancer are living longer due to improved screening, earlier detection, and increasingly successful treatments, as demonstrated in Fig. 1.1. New insights into the biology of inflammation and senescence may help understand why these have become the dominant diseases of aging. Many breast cancer patients, for instance, have multiple risk factors for cardiac disease, such as cigarette smoking, diabetes, dyslipidemia, alcohol consumption, obesity, and sedentary lifestyle [3–5]. These risk factors also increase the likelihood of adverse cardiovascular effects of some cancer therapies. For a newly diagnosed cancer patient, preexisting cardiovascular

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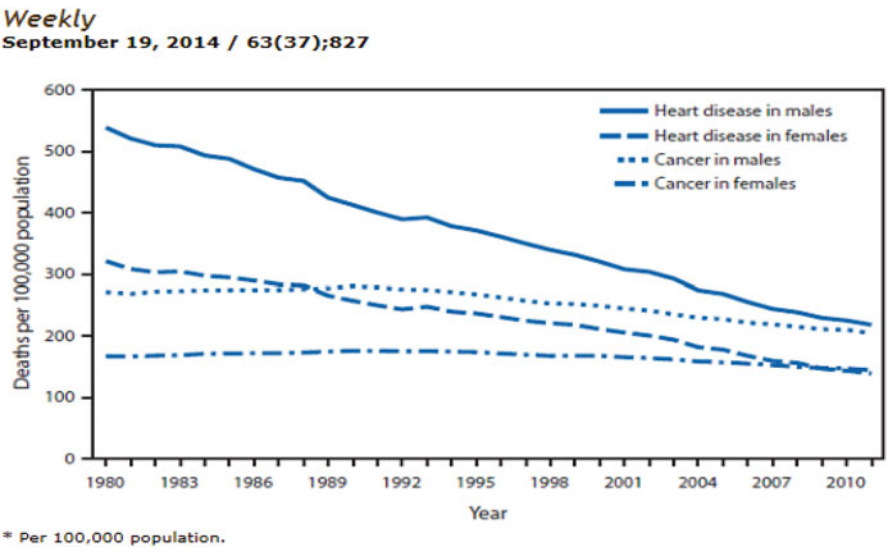

Fig. 1.1 Age-adjusted death rates for heart disease and cancer in the United States, 1980–2011

disease may significantly limit the diagnosis, staging, and therapy offered. This is a particularly common problem in the older patient. The purpose of this chapter is to summarize the current state of knowledge of the shared epidemiology between common cancers and cardiovascular diseases and discuss the potential biological explanations as well as the clinical implications.

Cancer and Cardiovascular Disease: Convergent Epidemiology

Many of the risk factors for cardiovascular disease (e.g., tobacco use) are also well-known risk factors for cancer development. This is demonstrated by the similarity of geographic clustering of heart disease deaths and cancer deaths in the United States (Fig. 1.2). Genetic predisposition and age are strong determinants of risk for both classes of disease, but the majority of cancer and cardiovascular diseases are caused by modifiable risk factors. A multinational study of the epidemiology of heart disease (INTERHEART) revealed that nine risk factors, including abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, physical activity, and consumption of fruits, vegetables, and alcohol, account for 90 % of population attributable risk of myocardial infarction in men and 94 % in women [6]. Similarly, several epidemiologic studies have demonstrated association between these same modifiable risk factors and development of cancer. Lung, breast, prostate, and colon cancers have been linked to obesity, high-fat diets, and smoking [7, 8].

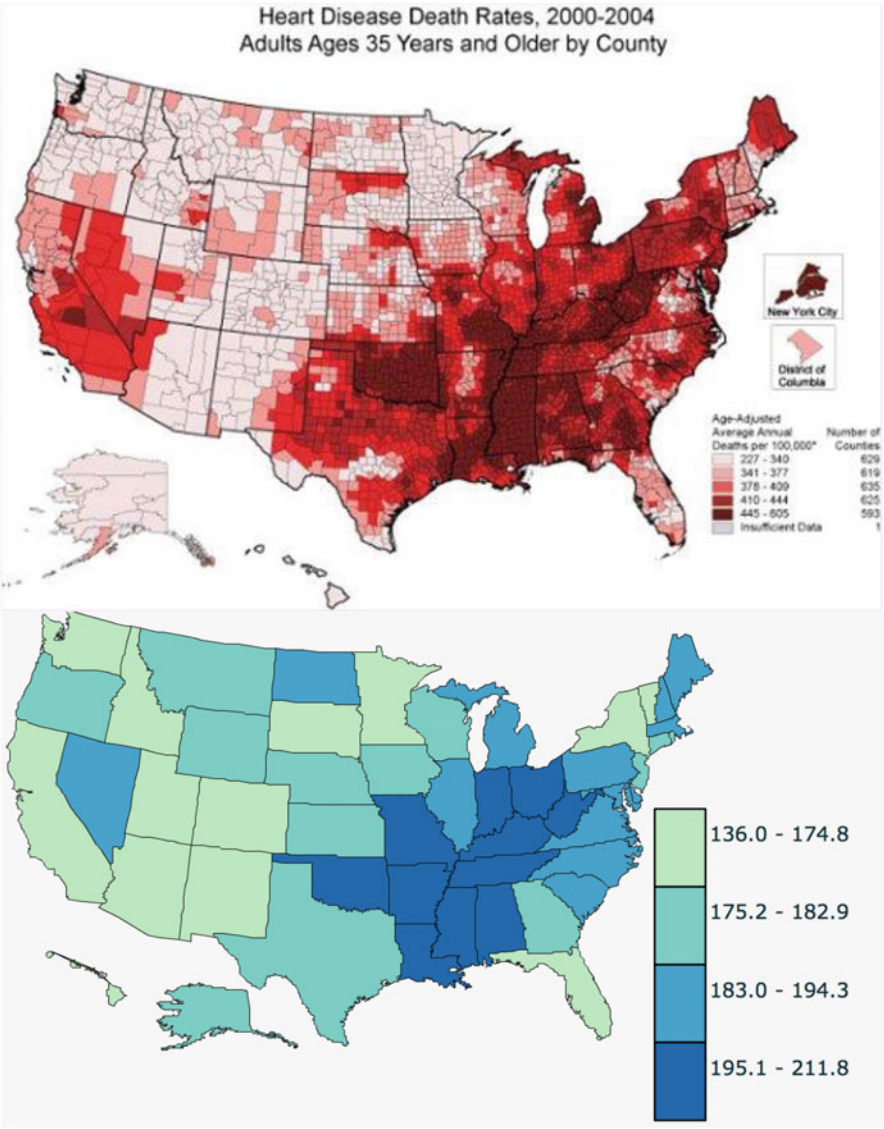

Fig. 1.2 Illustrative example of the overlapping epidemiology of heart disease and cancer, drawn from the US Center for Disease Control and Prevention data

Obesity. Defined as a body mass index (BMI) greater than 30, obesity is a known risk factor for CVD and is now a well-established risk factor for cancer and is highly prevalent with estimates that 35 % of populations in developed countries are obese [9]. In addition to its association with known risk factors for cardiovascular disease, including hypertension and reduced HDL cholesterol, in multivariate analysis,

including traditional risk factors for cardiovascular disease, obesity was significantly and independently predictive of cardiovascular disease [10, 11].

Studies have also shown that obesity is a risk factor for certain cancers and may have an adverse effect on outcome. The data is very strong for the adverse association of breast cancer risk and outcome and obesity. A higher BMI and/or perimenopausal weight gain is consistently associated with increased risk of breast cancer [12–16]. Since 1976, when Abe et al. first reported the association between obesity and breast cancer recurrence, there have been more than 50 studies examining the relationship between body weight and breast cancer prognosis [17, 18]. In a prospective cohort of 14,709 patients, obesity was linked to adverse breast cancer prognosis [8]. Other population-based studies have demonstrated that both premenopausal and postmenopausal women who gained 16 kg and 12.7 kg, respectively, increased risk of breast cancer-related death by at least twofold [19]. Similarly, prostate and colon cancer studies show a positive correlation between body mass index (BMI) and cancer incidence [20, 21]. Visceral adipose tissue which is not reflected by measurements of BMI, waist circumference, and subcutaneous adipose tissue may play an important role in inflammation and oxidative stress [22]. Epidemiologic-based cancer studies have more recently been performed and show similar associations between overall obesity and central obesity and risk of colorectal cancer (CRC) [23] and mortality from pancreatic cancer [24].

Diabetes Similarly, diabetes mellitus (DM) has an adverse effect on risk and outcome in cancer and heart disease. The presence of DM at the age of 50 years, in the Framingham Heart Study (FHS), conferred the highest lifetime risk of CVD and mortality of any single risk factor [25]. Type II DM is also associated with risk of malignancy [26]. In patients with DM, high insulin levels and insulin-like growth factor have been associated with worse breast and colon cancer outcomes [27–30]. Interestingly, a series of observational studies reported decreased cancer incidence and mortality among type 2 diabetics who were treated with high doses or long duration of metformin [31]. Retrospective clinical data of 2529 women receiving neoadjuvant chemotherapy for breast cancer reported increased pathologic complete response (pCR) by 24 % in diabetics on metformin versus 8 % in diabetics not receiving metformin [32]. Metformin use during adjuvant chemotherapy, however, has not been shown to significantly impact survival outcomes in diabetic patients with hormone receptor and HER2-negative breast cancer. In a retrospective study from MD Anderson Cancer Center, at a median follow-up of 62 months, there were no significant differences among diabetics receiving metformin, diabetics not receiving metformin, and nondiabetic patients, with regard to 5-year distant metastasis-free survival (0.73 vs 0.66 vs 0.60; $p = 0.23$), recurrence-free survival (0.65 vs 0.64 vs 0.54; $p = 0.38$), and overall survival (0.67 vs 0.69 vs 0.66; $p = 0.58$) [33]. Higher risk of distant metastases was seen in patients who did not receive metformin (HR, 1.63; 95 % CI 0.87–3.06) and nondiabetic patients (HR, 1.62; 95 % CI 0.97–2.71), compared to diabetic patients taking metformin. Likewise, a phase II study of metformin in 44 men with chemotherapy-naïve castration-resistant prostate cancer found limited evidence of antitumor activity with two

cases of >50 % decrease in serum PSA, although approximately one-half of men showed a prolongation in the PSA doubling time [34]. These observational studies generated a biologically plausible link between breast cancer and insulin receptor activity. For example, insulin receptors are overexpressed in breast cancer cells and can bind insulin and insulin-like growth factors (IGF1 and IGF2). When IGFs bind to the insulin receptors instead of insulin, this predominately activates a proliferative rather than metabolic pathway [35]. Additional phase II studies are underway in men with advanced prostate cancer. In addition, a phase III study is comparing metformin with placebo in men being managed with active surveillance for low-risk prostate cancer (NCT01864096).

Smoking Another common risk factor for heart disease and cancer is smoking. Smoking increases inflammation, thrombosis, and endothelial dysfunction [36, 37]. Tobacco smoking strongly increased the risk of lung cancer for current smokers (4.4 for men and 2.8 for females) compared to never smokers. In a comprehensive meta-analysis, tobacco smoking also increased the risk of colorectal cancer (CRC) incidence and mortality [38]. The mechanism linking smoking to colon cancer remains incomplete; however, animal studies have demonstrated that smoking exposure promoted inflammation-associated adenoma formation with increased expression in 5-lipoxygenase, upregulation of matrix metalloproteinase-2 (MMP-2), and vascular endothelial growth factor (VEGF) [39]. There is also an association between smoking and higher cancer stage at diagnosis [40] and the development of lung metastases [41].

While our understanding of the mechanistic link between tobacco exposure and pathogenesis of atherosclerosis and cancer is incomplete, it is very clear that reducing tobacco consumption has health benefits to individuals and society in general. Former smokers reduce their risk of heart disease and cancer within a year of quitting [42]. Similarly, communities that invest in comprehensive tobacco control programs are experiencing a reduction in smoking and smoking-related health costs due to cancer and cardiovascular disease, as well as pulmonary disease [43].

Mechanistic Theories Regarding the Common Epidemiology of CVD and Cancer

Inflammation is one of the common links between obesity, metabolic syndrome, smoking, diabetes, and the pathogenesis of atherosclerosis, heart failure, and cancer (Fig. 1.3). It has long been known that chronic inflammation from conditions such as hepatitis, inflammatory bowel disease, HPV, and *Helicobacter pylori* can lead to increased risk of cancer [44, 45]. Recent studies also demonstrate increased cytokine levels (TNF-α, IL-2, IL-6) or cytokine genetic alterations can lead to increased risk of breast cancer and a worse prognosis [46]. Similarly, elevated inflammatory biomarkers are associated with coronary disease and heart failure [47, 48]. Increased

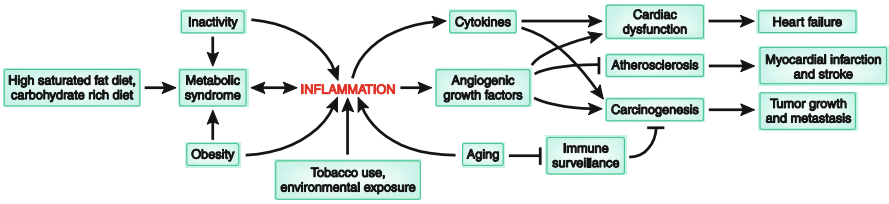

Fig. 1.3 Model for how modifiable risk factors promote development of both cardiovascular disease as well as tumorigenesis

levels of high-sensitivity C-reactive protein (hs-CRP) are associated with cardiovascular events. Elevated plasma levels of CRP are also associated with increased risk of cancer with worse survival [49, 50].

Use of Nonsteroidal Anti-inflammatories Aspirin is recommended for primary and secondary prevention of CVD [51]. It reduces the total morality (RR 0.94, 95 % CI 0.88–1.00) and risk of myocardial infarction (0.80, 0.67–0.96) and stroke (0.95, 0.85–1.06) [52, 53]. The rate of major extracranial bleeding was higher (1.54, 1.30–1.82) [54].

With regard to cancers, the data for a relationship between aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) is strongest for colon cancers [55–64]. Aspirin lowers risk of mortality from colon cancer risk. In a study that combined data from four randomized trials of aspirin versus control (mean duration of scheduled treatment 6.0 years), in which 391 (2.8 %) of 14,033 patients had colorectal cancer during a median follow-up of 18.3 years, risk and mortality of colon cancer were lower in those randomized to aspirin [65]. Allocation to aspirin reduced the 20-year risk of colon cancer incidence (HR 0.76, 0.60–0.96; $p = 0.02$) and mortality (HR 0.65, 0.48–0.88; $p = 0.005$). Randomized trials have also shown reduced incidence of colorectal adenomas and cancer with aspirin use [66, 67], presumed to be through its actions as an inhibitor of the cyclooxygenase-2 (COX-2) pathway, which is overexpressed in 80–85 % of colon cancers. In a study that combined information from the Nurses' Health Study and the Health Professionals Follow-up Study, at a median follow-up of 11.8 years, aspirin users had a significant 29 % (95 % CI, 0.53–0.95) lower cancer-specific mortality and a 21 % (95 % CI, 0.65–0.97) lower overall mortality than nonusers [57]. Reduction in risk was 61 % (95 % CI, 0.20–0.76) in those whose tumors overexpressed COX-2 when aspirin was initiated after diagnosis, but aspirin use was not associated with lower risk in those where COX-2 was not overexpressed (multivariate HR, 1.22; 95 % CI, 0.36–4.18). Studies have also shown that the beneficial effect of aspirin in colon cancer patients may vary by other mutations, including *PIK3CA* (phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha polypeptide) gene status [68, 69], PTGS2 expression [64], BRAF mutations [70], expression of human leukocyte antigen (HLA) class I antigens [61], and potentially other factors that have not yet been determined. The 2013 ASCO guidelines for follow-up care, surveillance, and secondary prevention measures for survivors of CRC do not,

however, endorse the routine use of aspirin or a cyclooxygenase inhibitor [62]. These encouraging reports led to the development of two prospective randomized trials to study aspirin use in colorectal cancer patients: the phase III Alliance trial 80,702 and the Aspirin for Dukes C and High Risk Dukes B Colorectal Cancers (ASCOLT) study.

Regular aspirin use may also decrease risk of breast cancer. In the prospective Women's Health Initiative (WHI) study, which included 80,741 postmenopausal women between 50 and 79 years of age who reported no history of breast cancer or other cancers, regular (two or more tablets/week for 10 or more years) use of aspirin, ibuprofen, and other nonsteroidal anti-inflammatory drugs (NSAIDs) was associated with a 28 % reduction in the incidence of breast cancer (95 % CI, 0.56–0.91) [71]. The estimated risk reduction for long-term use of ibuprofen (RR, 0.51; CI, 0.28–0.96) was greater than for aspirin (RR, 0.79; CI, 0.60–1.03). Other meta-analyses of aspirin use have confirmed the reduced risk of breast cancer [72, 73]. The US Preventive Services Task Force (USPSTF), therefore, recommends that adults 50–69 years of age should take daily low-dose aspirin for at least 10 years to reduce their risk for cardiovascular disease (CVD) and colorectal cancer [74–77].

Changing modifiable lifestyle risk factors, such as weight loss, regular physical exercise, and diet rich in fruits and vegetables, improves prognosis and survival in many patients with cardiovascular disease and lung, breast, prostate, and colon cancers. Age, however, is a nonmodifiable risk factor, which influences both cardiovascular disease and cancer. The longitudinal Physicians' Health Study demonstrated that both cardiovascular disease and cancer rose dramatically in the sixth to seventh decade of life and that commonly both conditions were coexistent in a substantial number of patients [78]. With the rise in an aging population, and the overlap in risk factors between cancer and cardiovascular disease, there is an opportunity that presents itself to physicians and investigators to define common biology, mechanisms, and clinical treatments which optimize cardio-oncology patient outcomes.

Cancer Survivors: Cardiovascular vs Cancer Mortality

In cancer survivors, the risk of death from cardiovascular disease may be greater than the risk of death from cancer. Mortality rates from cancer have declined over the past 30 years, due to more effective methods of early detection and more effective management strategies [79, 80]. As a result, there are a growing number of cancer survivors [81]. According to 2015 estimates, the cancers with the largest differential in incident cases and estimated deaths are breast cancer, with 231,840 new cases and 40,290 deaths; prostate cancer, with 20,800 new cases and 27,540 deaths; and colon and rectal cancer, with 132,700 new cases and 49,700 deaths [82]. From 2014 to 2024, the number of survivors of female breast cancer is estimated to rise from 3,131,400 to 3,951,930, of prostate cancer from 2,975,970

to 4,194,190, and of colon and rectal from 1,246,320 to 1,561,020[83]. In breast cancer survivors, especially those who are elderly, cardiovascular disease is the predominant cause of mortality [84–88]. This is also true of childhood cancer survivors, of whom over 80 % are cured of their cancer and are at risk of cardiovascular death. The Childhood Cancer Survivor Study, which is the largest and most complete cohort study of childhood cancer survivors, showed that childhood cancer survivors suffer from chronic conditions at an alarmingly high rate, and cardiovascular disease is a major cause of morbidity and mortality in this group [89–91].

Adult cancer survivors are at risk for cardiovascular diseases on several levels. First, the diagnosis of cardiovascular disease may predate the cancer diagnosis. In one population-based study of 6439 women, with a mean age of 58.7 years, who were diagnosed with incident breast cancer in 2004, 45.8 % had preexisting cardiovascular disease [92].

Second, coexisting cardiovascular risk factors may lead to the development of cardiovascular disease and/or the manifestation of symptoms of cardiovascular disease after the cancer is diagnosed. This is demonstrated in a study of 2542 breast cancer survivors, in whom 11 % had cardiovascular disease diagnoses before the diagnosis of cancer, and an additional 10 % were diagnosed with cardiovascular disease after diagnosis [4]. Among cardiovascular diagnoses, angina pectoris was the most common, followed by myocardial infarction, stroke, and arterial occlusive disease. Hypertension was also present in 37 % at diagnosis and diagnosed in an additional 12 % after diagnosis.

Interestingly, there may be associations between hypertension or its treatment and cancer outcomes. Epidemiologic studies have described better outcomes in breast cancer patients with hypertension [93]. Beta-blocker use is associated with reduced mortality in cancer patients [94]. Anticancer effects of antihypertensive medications, such as beta-blockers, have been speculated [95–97]. Although beta-blocker use was not associated with reduced mortality in melanoma [98], beta-blockers and angiotensin-converting enzyme inhibitors [99–101] have been linked to reduced breast cancer mortality. In another population-based case-control study of women 65–79 years old, the use of immediate-release calcium channel blockers, thiazide diuretics, and potassium-sparing diuretics was associated with increased risk of breast cancer (OR 1.5, 95 % CI, 1.0–2.1; OR 1.4, 95 % CI, 1.1–1.8; and OR 1.6, 95 % CI, 1.2–2.1, respectively). One large epidemiologic study, however, showed that women with breast cancer were more likely to receive guideline-concordant care [92] leading to better outcomes. Better access to healthcare in general, there, may be a confounder in studies of the relationship between hypertension and cancer outcomes.

Third, cardiotoxicity of cancer therapies, including hypertension, cardiomyopathy, QT prolongation, arrhythmias, thrombosis, and metabolic abnormalities, may lead to cardiovascular disease. Cardiotoxicities of cancer therapies will be covered in greater depth in other chapters of this book.

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