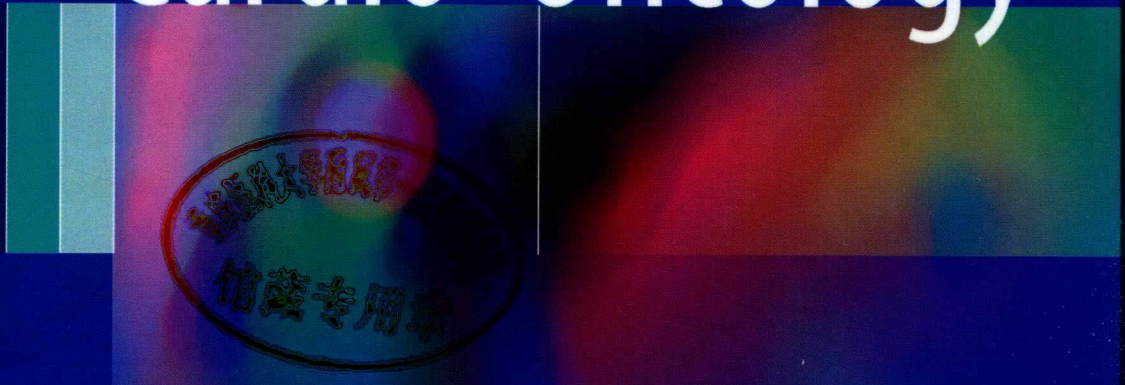
Gretchen G. Kimmick · Daniel J. Lenihan
Douglas B. Sawyer · Erica L. Mayer
Dawn L. Hershman *Editors*

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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Contents

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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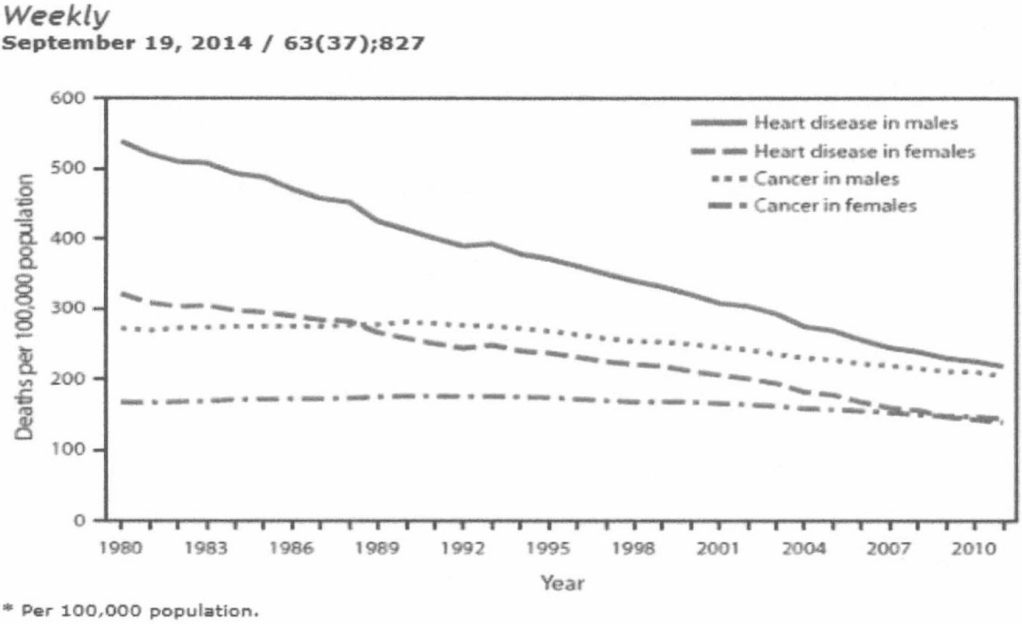

Fig. 1.1 Age-adjusted death rates for heart disease and cancer in the United States, 1980–2011

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].

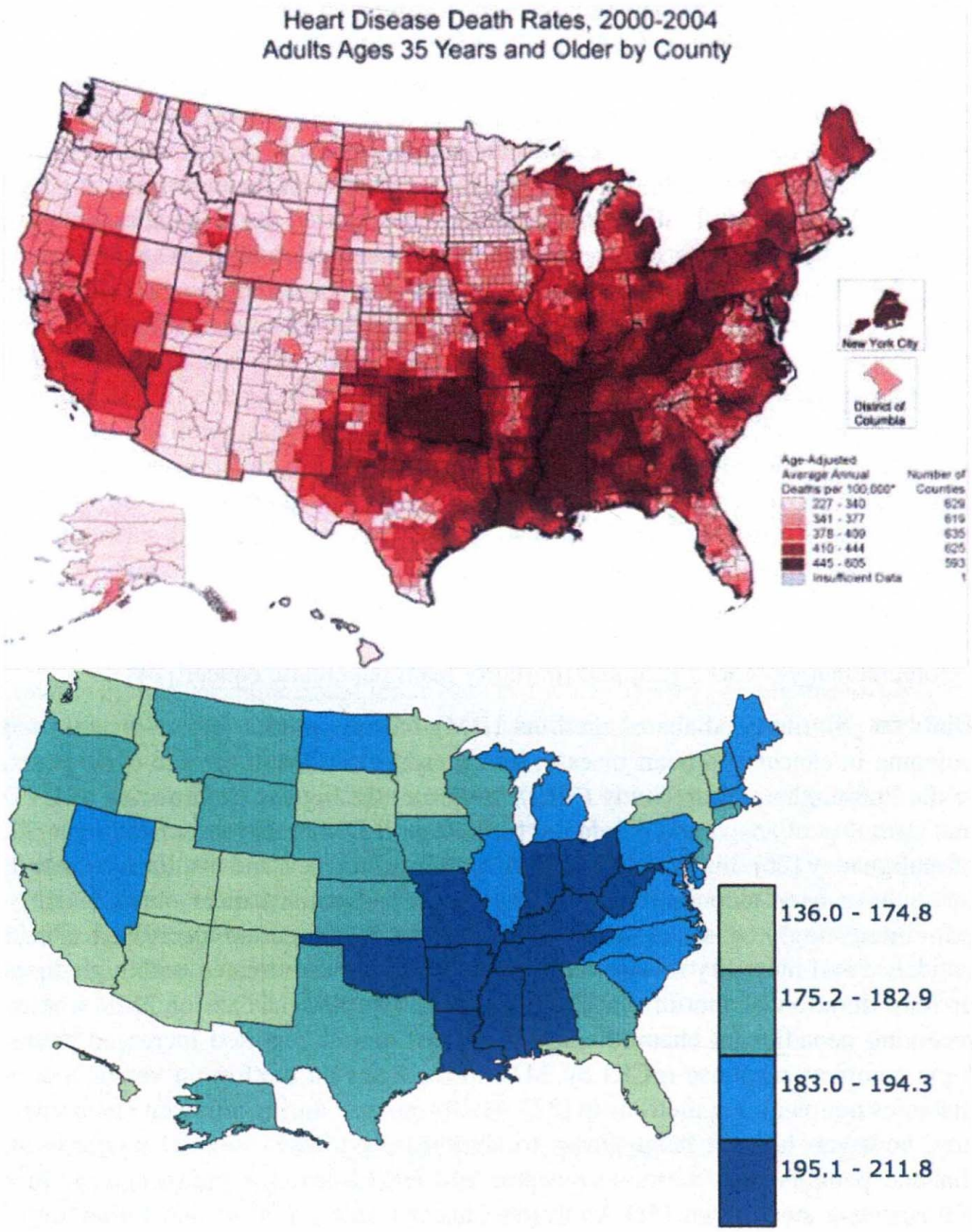

Fig. 1.2 Illustrative example of the overlapping epidemiology of heart disease and cancer, drawn from the US Center for Disease Control and Prevention data

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