William B. Coleman
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Editors

The Molecular Basis of Human Cancer

Second Edition

Springer

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The information contained in this textbook describes the ever-expanding field of cancer biology and our contemporary understanding of the pathology, pathogenesis, and pathophysiology of the diverse collection of diseases representing human cancer. Hence, this work represents the culmination of innumerable small successes that emerged from the ceaseless pursuit of new knowledge by countless clinical, experimental, and translational cancer biologists working around the world on all aspects of human cancer. Their ingenuity and hard work have dramatically advanced the field of cancer pathobiology over time, and particularly during the last 25 years. This book is a tribute to the dedication, diligence, and perseverance of individual scientists who contributed to the advancement of our understanding of the molecular basis of human cancer, especially graduate students, laboratory technicians, and postdoctoral fellows, whose efforts are so frequently taken for granted, whose accomplishments are so often unrecognized, and whose contributions are so quickly forgotten.

We especially dedicate this book to the loving memory of Chris Helms Austin who passed away far too young on August 17, 2014 after a long battle with breast cancer. Chris was cherished by her family and friends, and was a gifted teacher who made significant impressions on her students, their parents, and her colleagues. She did so much good in her short lifetime and that goodness continues through the lives of her students and everyone else she touched. Chris' journey through breast cancer showed us the realities associated with a cancer diagnosis, treatment, and disease progression. Her obstinate optimism and resolve in the face of an unrelenting disease provides a lesson and example for all of us on how to attack life's challenges no matter how insurmountable the odds of success.

We also remember people we have known and loved, that taught us through example about dignity, positivity, strength, courage, and tenacity in the fight against cancer – Samuel Apostola, Dr. Bobby G. Bell, Jeffery A. Bell, Dr. Sharon Ricketts Betz, Linwood Braswell, Bobbie Coleman Clark, William B. Coleman, Jr., Anne Griffin Clawson, Jewell T. Coleman, George G. Gerding, Evelyn B. Hadden, Shayne Snyder Hall, Dr. Eugene F. Hamer, Jerry S. Harris, Effie H. Helms, Larry Hendley, Joel C. Herren, Jean G. Herren, Kathleen M. Jackson, Jerry W. Kirkman, Gloria Morin, John Panu, Dr. Kathleen Rao,

Dr. Rhonda Simper Ronan, Alexandria Rucho, Peter Rucho, Beverly Clark Tice, Ruth E. Trull, Josephine Caccavallo Vasquez, and W. Kenneth Weatherman. This book is also dedicated to the cancer survivors and those who continue to live with cancer, for their bravery and determination, for the inspiration that they provide, and for reminding us that there is far too much left to be done to rest on our accomplishments.

We also dedicate The Molecular Basis of Human Cancer – Second Edition to the many people that have played crucial roles in our successes. We thank our many scientific colleagues, past and present, for their camaraderie, collegiality, and support. We especially thank our scientific mentors for their example of dedication to research excellence. We are truly thankful for the positive working relationships and friendships that we have with our faculty colleagues, for the mentoring we received from our elders and for the opportunity to mentor those that follow us. We also thank our undergraduate students, graduate students, and postdoctoral fellows for teaching us more than we might have taught them. We thank our parents for believing in higher education, for encouragement through the years, and for helping make dreams into reality. We thank our brothers and sisters, and extended families, for the many years of love, friendship, and tolerance. We thank our wives, Monty and Nancy, for their unqualified love, unselfish support of our endeavors, understanding of our work ethic, and appreciation for what we do. Lastly, we give special thanks to our children, Tess, Sophie, Pete, and Zoe. Their achievements and successes as young adults are a greater source of pride for us than our own accomplishments. As when they were children, we thank them for providing an unwavering bright spot in our lives, for their unbridled enthusiasm and boundless energy, and for giving us a million reasons to take an occasional day off from work just to have fun.

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Preface

The practice of medical oncology has been in a period of sustained significant positive change over the last two decades that is primarily due to advances in the basic science of cancer biology. In recent years, developments in molecular biology techniques have substantially increased our ability to detect and characterize genetic defects in human cells, resulting in significant increases in our understanding of the normal molecular mechanisms controlling cellular proliferation and differentiation. The advancement of our comprehension of these basic molecular mechanisms has been paralleled by comparable increases in our understanding of the molecular basis of the processes involved in neoplastic transformation and tumorigenesis. Information gleaned from studies conducted in basic molecular research laboratories is being applied with unprecedented speed to the development of new molecular tests for cancer detection, diagnosis, and prediction of clinical outcomes, as well as to the development of new strategies for cancer prevention and treatment through therapies that target specific molecular pathways in the cancer cell. Basic scientists, clinical scientists, and physicians have a need for a source of information on the current state-of-the-art of the molecular biology of human neoplastic diseases. In this Second Edition of *The Molecular Basis of Human Cancer* we attempt to provide such a source of current information, as well as providing a look to the future of the discipline and the potential impact of scientific advances on the practice of medical oncology. This book is directed primarily to advanced graduate students and medical students, postdoctoral trainees, and established investigators having basic research interests in the molecular basis of human neoplastic disease. However, this book is also well suited for the non-expert with similar interests since it provides a broad overview of general themes in the molecular biology of cancer. To be sure, our understanding of the many processes of neoplasia and their molecular basis is far from complete, but numerous areas of thematic or conceptual consensus have developed. We have made an effort to integrate accepted principles with broader theoretic concepts in an attempt to present a current and comprehensive view of the molecular basis of human cancer. We hope that this book will accomplish its purpose of providing students and researchers who already possess strong but diverse basic science backgrounds with unifying concepts, so as to stimulate new research aimed at furthering our understanding of the array of diseases that represent human cancer.

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Cancer Epidemiology: Incidence and Etiology of Human Neoplasms

1

William B. Coleman and Gregory J. Tsongalis

1.1 Introduction

Cancer does not represent a single disease. Rather, cancer is a myriad collection of diseases with as many different manifestations as there are tissues and cell types in the human body, involving innumerable endogenous or exogenous carcinogenic agents, and various etiological mechanisms. What all of these disease states share in common are certain biological properties of the cells that compose the cancer, including unregulated (clonal) cellular growth, impaired cellular differentiation, invasiveness, and metastatic potential. It is now recognized that cancer, in its simplest form, is a genetic disease, or more precisely, a disease of abnormal gene expression. Recent research efforts have revealed that different forms of cancer share common molecular mechanisms governing uncontrolled cellular proliferation, involving loss, mutation, or dysregulation of genes that positively and negatively regulate cell proliferation, migration, and differentiation (generally classified as proto-oncogenes and tumor suppressor genes). Essential to any discussion of the molecular mechanisms that govern disease pathogenesis for specific cancers is an appreciation for the distribution of these diseases among world populations, with consideration of specific risk factors and etiologic agents involved in disease causation. This introduction will describe cancer incidence and mortality for the major forms of human cancer, and will briefly review some of the known risk factors and/or causes of these cancers for specific at-risk populations.

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1.2 Cancer Incidence and Mortality

Cancer is an important public health concern in the USA and worldwide. Due to the lack of nationwide cancer registries for all countries, the exact numbers of the various forms of cancer occurring in the world populations are unknown. Nevertheless, estimations of cancer incidence and mortality are generated on an annual basis by several domestic and world organizations. Estimations of cancer incidence and mortality for the USA are provided annually by the American Cancer Society (ACS—www.cancer.org) and the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program (http://seer.cancer.gov/data/). Global cancer statistics are provided by the International Agency for Research on Cancer (IARC—http://globocan.iarc.fr/), the World Health Organization (WHO—http://www.who.int/en/), and Cancer Research UK (http://info.cancerresearchuk.org/cancerstats/world/). Monitoring of long-range trends in cancer incidence and mortality among different populations is important for investigations of cancer etiology. Given the long latency for formation of a clinically detectable neoplasm (up to 20–30 years) following initiation of the carcinogenic process (exposure to carcinogenic agent), current trends in cancer incidence probably reflect exposures that occurred many years (and possibly decades) before. Thus, correlative analysis of current trends in cancer incidence with recent trends in occupational, habitual, and environmental exposures to known or suspect carcinogens can provide clues to cancer etiology. Other factors that influence cancer incidence include the size and average age of the affected population. The average age at the time of cancer diagnosis for all tumor sites is approximately 65 years [1, 2]. As a higher percentage of the population reaches age 60, the general incidence of cancer will increase proportionally. Thus, as the life expectancy of the human population increases due to reductions in other causes of premature death (due to infectious and cardiovascular diseases), the average risk of developing cancer will increase.

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1.3 Cancer Incidence and Mortality in the USA

1.3.1 General Trends in Cancer Incidence

The American Cancer Society estimates that 1,658,370 new cases of invasive cancer were diagnosed in the USA in 2015 [3]. This number of new cancer cases reflects 848,200 male cancer cases (51 %) and 810,170 female cancer cases (49 %). The estimate of total new cases of invasive cancer does not include carcinoma in situ occurring at any site other than in the urinary bladder, and does not include basal and squamous cell carcinomas of the skin. In fact, basal and squamous cell carcinomas of the skin represent the most frequently occurring neoplasms in the USA, with an estimated occurrence of >1 million total cases in 2015 [3]. Likewise, carcinoma in situ represents a significant number of new cancer cases in 2015 with 60,290 newly diagnosed breast carcinomas in situ and 63,440 new cases of melanoma carcinoma in situ [3].

Estimated site-specific cancer incidence for both sexes combined is shown in Fig. 1.1. Cancers of the reproductive organs represent the largest group of newly diagnosed cancers in 2015 with 329,330 new cases [3]. This group of cancers includes prostate (220,800 new cases), uterine corpus (54,870 new cases), ovary (21,290 new cases), and uterine cervix (12,900 new cases), in addition to other organs of the genital system (vulva, vagina, and other female genital organs; testis, penis, and other male genital organs). The next most frequently occurring cancers originated in the digestive tract (291,150 new cases), respiratory system (240,390 new cases), and breast (234,190 new cases). The majority of digestive system cancers involved colon (93,090 new cases), rectum (39,610 new cases), pancreas (48,960 new cases), stomach (24,590 new cases), liver and intrahepatic bile duct (35,660 new cases), and esophagus (16,980 new cases), in addition to the other digestive system organs (small intestine, gallbladder, and others). Most new cases of cancer involving the respiratory system affected the lung and bronchus (221,200 new cases), with the remaining cases affecting the larynx or other components of the respiratory system. Other sites with significant cancer burden include the urinary system (138,710 new cases), lymphomas (80,900 new cases), melanoma of the skin (80,100 new cases), leukemias (54,270 new cases), and the oral cavity and pharynx (45,780 new cases).

Estimated cancer incidence by cancer site for males and females are shown in Fig. 1.2. Among men, cancers of the prostate, respiratory system (lung and bronchus), and digestive system (colon and rectum) occur most frequently. Together, these cancers account for 61 % of all cancers diagnosed in men. Prostate is the leading site, accounting for 220,800 new cases and 26 % of cancers diagnosed in men (Fig. 1.3). Among women, cancers of the breast, respiratory system (lung and bronchus), and digestive system (colon and rectum) occur most frequently. Cancers at these sites

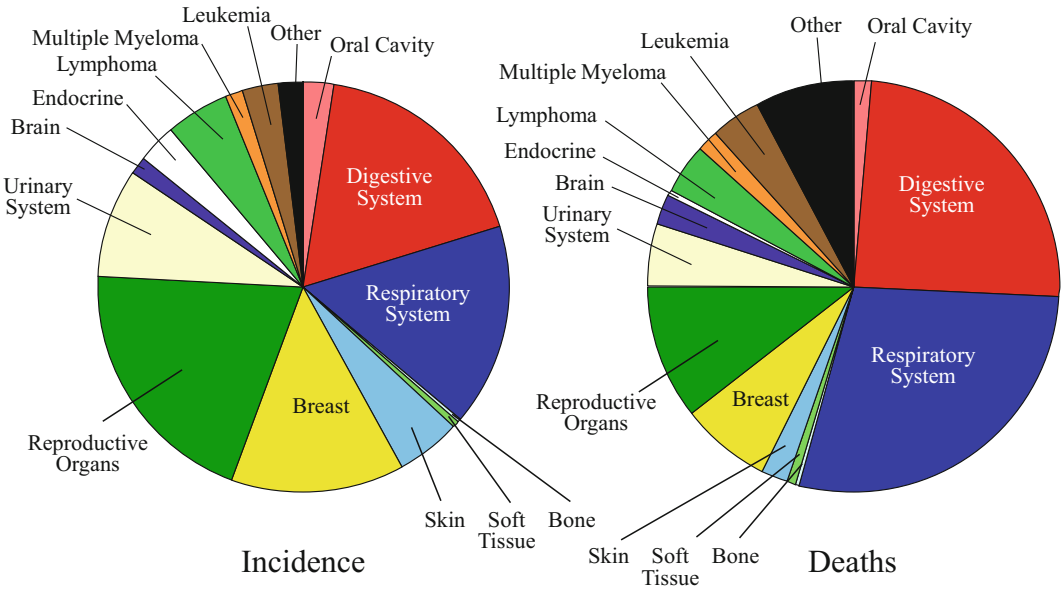

Fig. 1.1 Cancer incidence and mortality by site for both sexes (USA, 2015). The relative contributions of the major forms of cancer to overall cancer incidence and cancer-related mortality (both sexes combined) were calculated from data provided by Siegel et al. [3]. Cancers of the reproductive organs include those affecting the prostate, uterine corpus, ovary, uterine cervix, vulva, vagina, testis, penis, and other organs of the male and female genital systems. Cancers of the digestive system include those affecting esophagus, stomach, small intestine, colon, rectum, anus, liver, gallbladder, pancreas, and other digestive organs. Cancers of the respiratory system include those affecting lung, bronchus, larynx, and other respiratory organs.

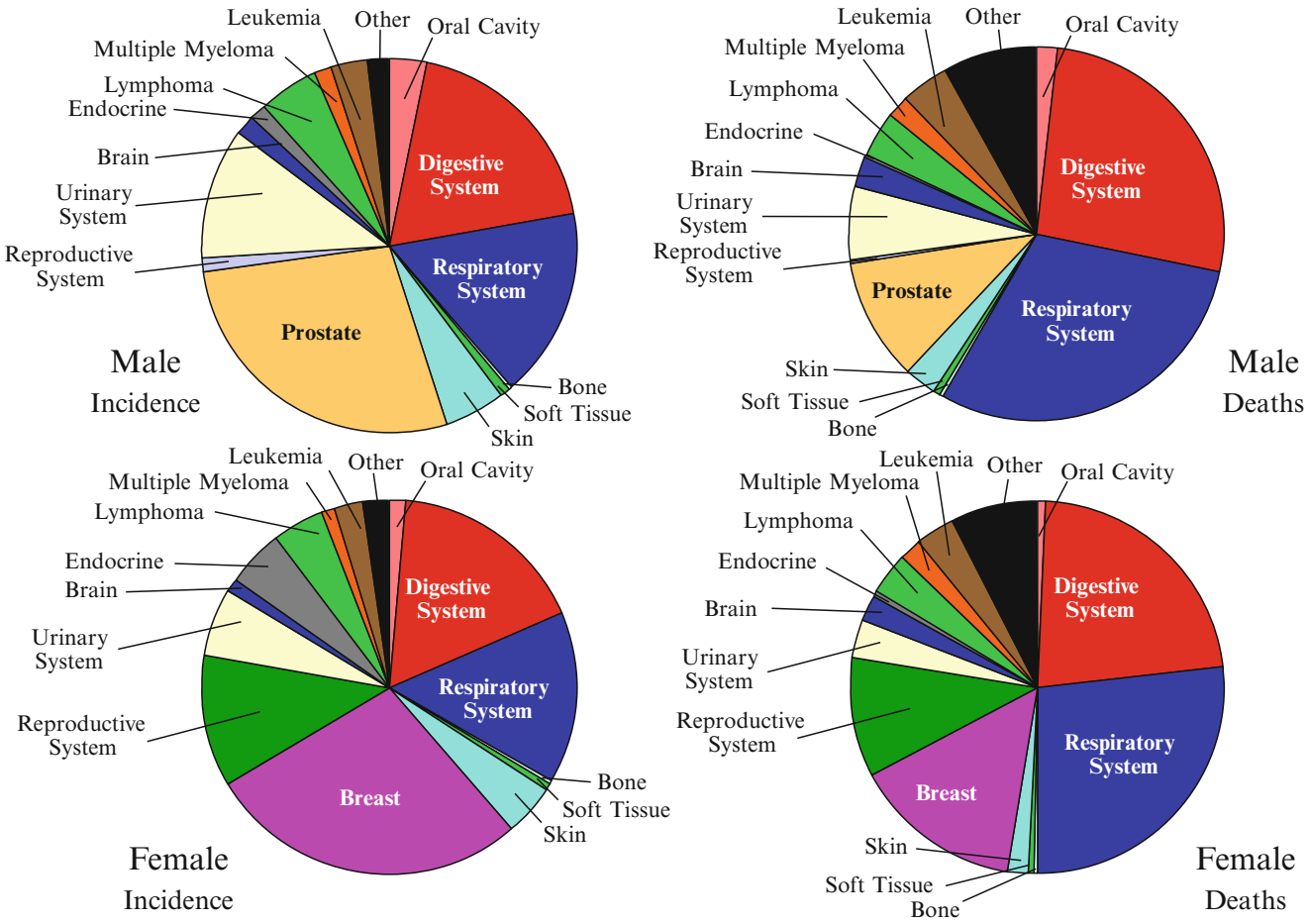

Fig. 1.2 Cancer incidence and mortality by site (USA, 2015). The relative contributions of the major forms of cancer to overall cancer incidence and cancer-related mortality for males and females were calculated from data provided by Siegel et al. [3]. Cancers of the male reproductive organs include testis, penis, and other organs of the male genital system. Cancers of the female reproductive organs include those affecting the uterine corpus, ovary, uterine cervix, vulva, vagina, and other organs of the female genital systems. Cancers of the digestive system include those affecting esophagus, stomach, small intestine, colon, rectum, anus, liver, gallbladder, pancreas, and other digestive organs. Cancers of the respiratory system include those affecting lung, bronchus, larynx, and other respiratory organs.

combine to account for 58 % of all cancers diagnosed in women. Breast is the leading site for cancers affecting women, accounting for 231,840 new cases and 29 % of all cancers diagnosed in women (Fig. 1.3).

1.3.2 General Trends in Cancer Mortality in the USA

Mortality attributable to invasive cancers produced 589,430 cancer deaths in 2015. This reflects 312,150 male cancer deaths (53 % of total) and 277,280 female cancer deaths (47 % of total). Estimated numbers of cancer deaths by site for both sexes are shown in Fig. 1.1. The leading cause of cancer death involves tumors of the respiratory system (162,460 deaths), the majority of which are neoplasms of the lung and bronchus (158,040 deaths). The second leading cause of cancer deaths involve tumors of the digestive system (149,300 deaths), most of which are tumors of the colorectum (49,700 deaths), pancreas (40,560 deaths), stomach (10,720 deaths), liver and intrahepatic bile duct (24,550 deaths), and esophagus (15,590 deaths). Together, cancers of the respiratory and digestive systems account for 53 % of cancer-associated death.

Trends in cancer mortality among men and women mirror in large part cancer incidence (Fig. 1.2). Cancers of the prostate, lung and bronchus, and colorectum represent the three leading sites for cancer incidence and cancer mortality among men (Fig. 1.3). In a similar fashion, cancers of the breast, lung and bronchus, and colorectum represent the leading sites for cancer incidence and mortality among women (Fig. 1.3). While cancers of the prostate and breast represent the leading sites for new cancer diagnoses among men and women (respectively), the majority of cancer deaths in both sexes are related to cancers of the lung and bronchus (Fig. 1.3). Cancers of the lung and bronchus are responsible

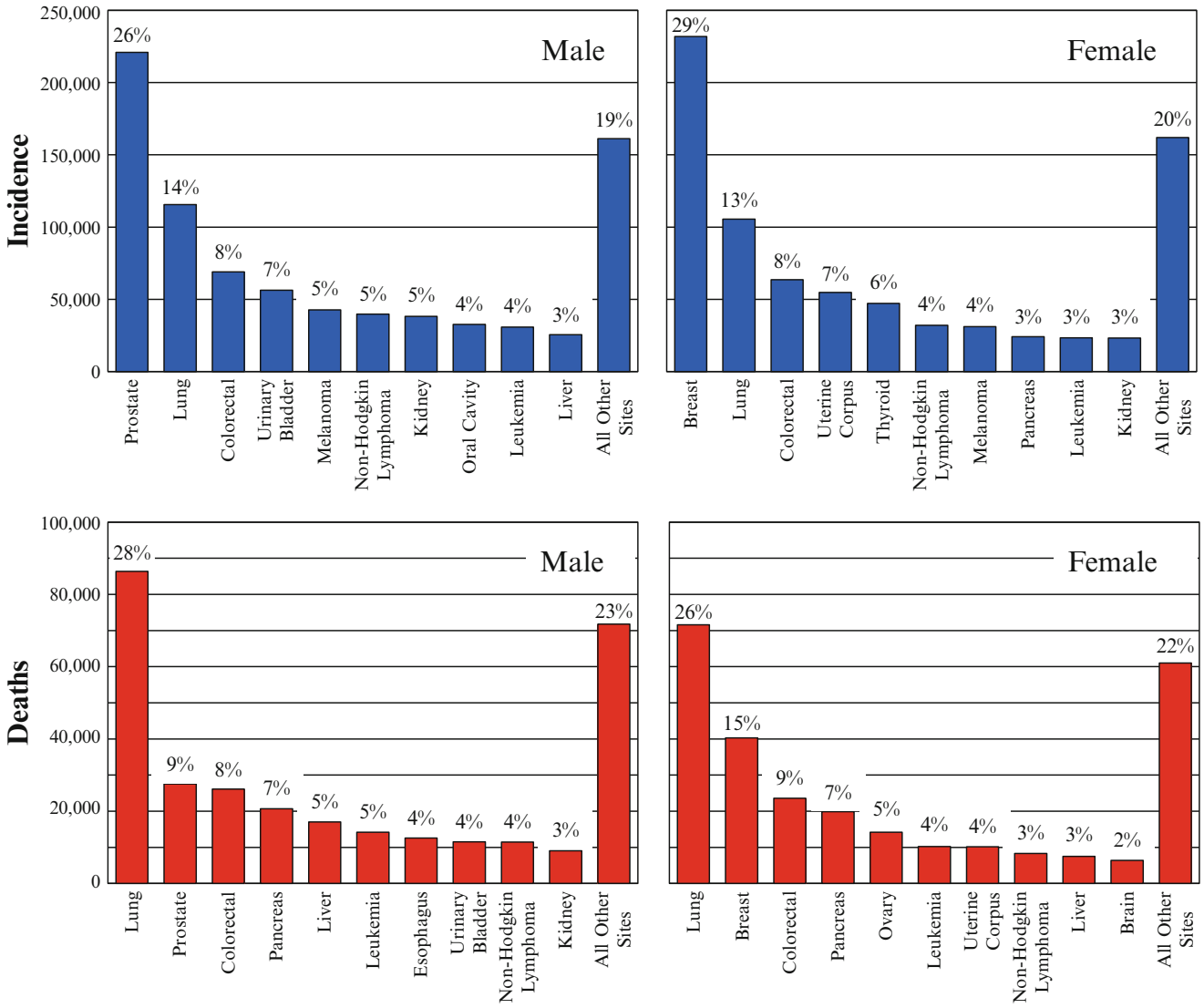

Fig. 1.3 Cancer incidence and mortality by leading site (USA, 2015). The numbers of cancers (and percentage of total cancers) and numbers of cancer-related deaths (and percentages of cancer-related deaths) for the leading sites for males and females were calculated from data provided by Seigel et al. [3]. The numbers provided for lung include tumors of the lung and bronchus, and numbers for colorectal cancer include tumors of the colon and rectum.

for 28 % of all cancer deaths among men and 26 % of all cancer deaths among women (Fig. 1.3). The age-adjusted death rate for lung cancer among men increased dramatically during the six decades between 1930 and 1990, while the death rates for other cancers (like prostate and colorectal) remained relatively stable (Fig. 1.4). However, since 1990, the age-adjusted death rate for lung cancer among men has decreased, although it remains very high compared to all other cancers. The lung cancer death rate for women increased in an equally dramatic fashion since about 1960, becoming the leading cause of female cancer death in the mid-1980s after surpassing the death rate for breast cancer (Fig. 1.4).

1.4 Global Cancer Incidence and Mortality

1.4.1 Current Trends in Cancer Incidence and Mortality Worldwide

The IARC estimates that 12,667,500 new cancer cases were diagnosed worldwide in 2008 [4]. This number of new cases represents 6,629,100 male cancer cases (52 %) and 6,038,400 female cancer cases (48 %). Mortality attributed to cancer for the same year produced 7,571,500 deaths worldwide [4]. This reflects 4,225,700 male cancer deaths (56 %) and

3,345,800 female cancer deaths (44 %). The leading sites for cancer incidence worldwide in 2008 included cancers of the lung (1,609,000 new cases), breast (1,383,500 new cases), colorectum (1,233,700 new cases), stomach (989,600 new cases), and prostate (903,500 new cases; Fig. 1.5). The leading sites for cancer mortality worldwide in 2008 included cancers of the lung (1,378,400 deaths), stomach (738,000 deaths), liver (695,900 deaths), colorectum (608,700 deaths), and breast (458,400 deaths; Fig. 1.5). As can be seen, lung cancer accounted for the most new cancer cases and the most cancer deaths among men and women combined during this period of time (Fig. 1.5). The leading sites for cancer incidence among males worldwide included cancers of the lung (1,095,200 new cases), prostate (903,500 new cases), colorectum (663,600 new cases), stomach (640,600 new cases), and liver (522,400 new cases). Combined, cancers at these five sites account for nearly 48 % of all cancer cases among men [4]. The leading causes of cancer death among men included tumors of the lung (951,000 deaths), liver (478,300 deaths), stomach (464,400 deaths), colorectum (320,600 deaths), and esophagus (276,100 deaths). Deaths from these cancers account for 59 % of all male cancer deaths [4]. The leading sites for cancer incidence among females included breast (1,383,500 new cases), colorectum (570,100 new cases), cervix uteri (529,800 new cases), lung (513,600 new cases), and stomach (349,000 new cases). The leading causes of cancer death among females directly mirrors the leading causes of cancer incidence: breast (458,400 deaths), lung (427,400 deaths), colorectum (288,100 deaths), cervix uteri (275,100 deaths), and stomach (230,000 deaths). Combined, these five cancer sites accounted for approximately 55 % of all female cancer cases and 51 % of female cancer deaths [4].

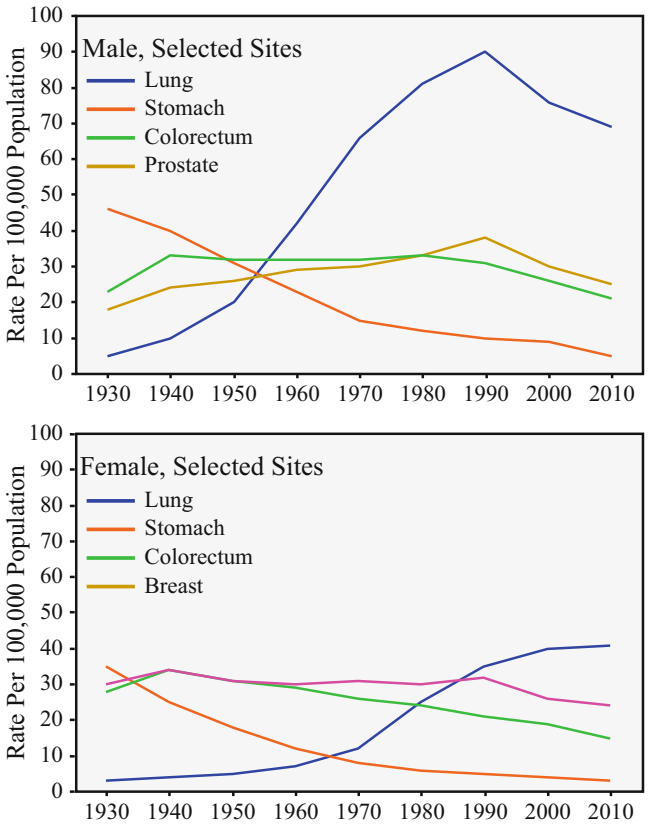

Fig. 1.4 Age-adjusted cancer mortality by site. The age-adjusted death rates for males and females for selected sites were adapted from the data provided by Seigel et al. [3]. Death rates are per 100,000 population and are age-adjusted to the 2000 standard population of the USA.

1.4.2 Geographic Differences in Cancer Incidence and Mortality

Cancer incidence and mortality differs between developed and developing countries [4]. In 2008, developed countries accounted for 43.9 % of new cancers (5,560,000 cases) and 36.3 % of cancer deaths (2,751,400 deaths), whereas developing countries accounted for 56.1 % of new cancers (7,107,600 cases) and 63.7 % of cancer deaths (4,820,100 deaths). The leading sites for cancer occurrence among men from developed countries include prostate (648,400 new cases), lung (482,600 new cases), and colorectum

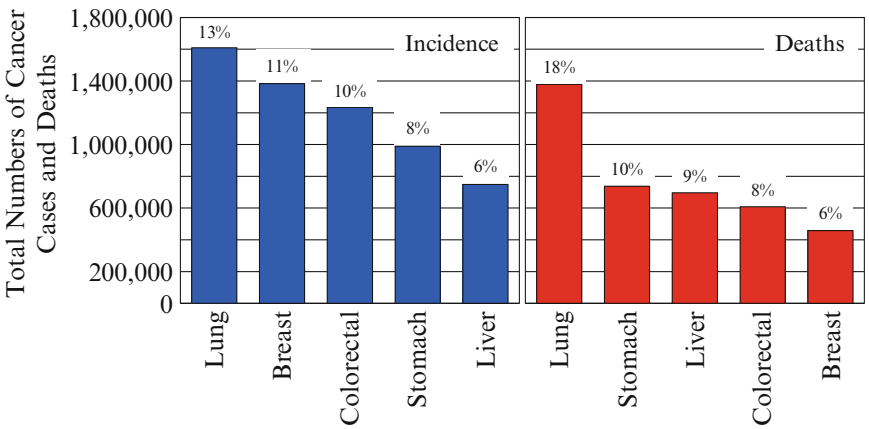

Fig. 1.5 Worldwide cancer incidence and mortality by leading site. The numbers of cancers (and percentage of total cancers) and numbers of cancer-related deaths (and percentages of cancer-related deaths) for the leading sites worldwide were calculated from data provided by Jemal et al. [4]. The numbers provided for lung include tumors of the lung and bronchus and the numbers for colorectal cancer include tumors of the colon and rectum.

(389,700 new cases). In contrast, the leading sites for cancer occurrence among men from developing countries include lung (612,500 new cases), stomach (466,900 new cases), and liver (440,700 new cases). The incidence of prostate cancer and liver cancer provide excellent examples of differences in incidence between men from developed and developing countries. In 2008, prostate cancer affected 648,400 men in developed countries (ranked first for cancer incidence in this cohort) compared to 255,000 men in developing countries (ranked sixth for cancer incidence in this cohort). Likewise, in 2008, liver cancer affected 440,700 men in developing countries (ranked third for cancer incidence in this cohort) compared to 81,700 men in developed countries (ranked tenth for cancer incidence in this cohort). While incidence rates vary, lung cancer represents the most frequent cause of cancer death among men from both developed and developing countries. Among women, breast cancer is the most frequent site of cancer in both developed (692,200 new cases) and developing countries (691,300 new cases) in 2008. Likewise, lung cancer occurs frequently in both groups—241,700 new cases in developed countries (ranked third for cancer incidence) and 272,000 new cases in developing countries (ranked third for cancer incidence). However, significant differences in cancer incidence among women from developed and developing countries can be seen for cancer of the cervix. Women from developing countries develop cervical cancer frequently (453,300 new cases, ranked second for cancer incidence), while women in developed countries develop cervical cancer less often (76,500 new cases, ranked tenth for cancer incidence).

New cancer incidence and cancer-related mortality can differ tremendously from world area to world area, country to country, and even from region to region within a single country. The leading world areas for new cancer cases includes Eastern Asia/China (17.3 % of new cases), North America (14.9 % of new cases), South Central Asia (11.6 % of new cases), Eastern Europe (10.4 % of new cases), and Western Europe (8.3 % of new cases). Collectively, Asia accounted for approximately 40 % of all new cancer cases worldwide in 1990 [5]. Recognizing the significant contribution of the population density of China and other regions of Asia to these numbers of cancers, it is appropriate to consider the cancer burden of these countries after correction for population. The numbers of cases/deaths and the incidence/mortality rates for these world regions in 1999 are given in Fig. 1.6. It is evident from the data contained in Fig. 1.6 that there is a marked disparity between total numbers of cancer cases/deaths and the incidence/mortality rate for specific world regions [5]. In 2012, men from Australia/New Zealand exhibit the highest cancer incidence rate worldwide (365 cases per 100,000 population), followed closely by men from North America (344 cases per 100,000 population) and

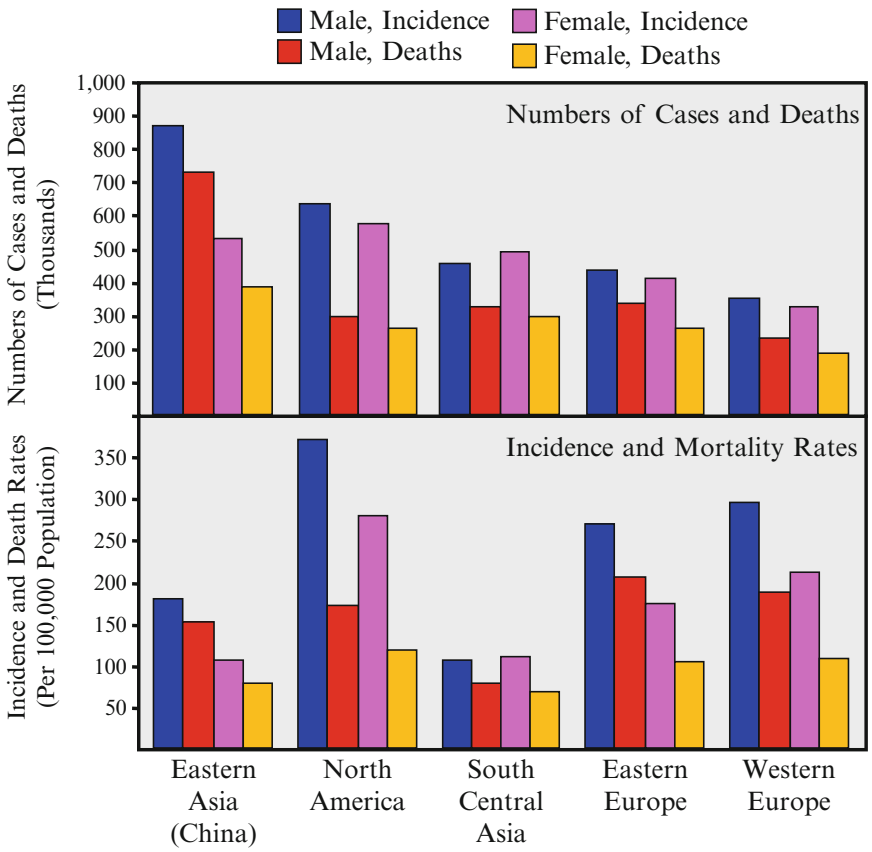

Fig. 1.6 Worldwide cancer incidence and mortality for both sexes by world region. The total numbers of cancers and cancer-related deaths, and the total incidence of cancer and cancer-related mortality rates for selected world regions were calculated from data provided by Parkin et al. [5].

Western Europe (344 cases per 100,000 population), while the lowest cancer incidence rate is found among men from Western Africa (79 cases per 100,000 population) [6]. While demonstrating the highest cancer incidence rate worldwide, the male populations of Australia/New Zealand, North America, and Western Europe rank 13th, 9th, and 5th (respectively) for cancer mortality rate, possibly reflecting the relative quality and availability of healthcare and treatment options among the various world regions [6]. The highest cancer mortality rate for men is found in Central/Eastern Europe (173 deaths per 100,000 population), followed by Eastern Asia (159 deaths per 100,000 population), Southern Europe (138 deaths per 100,000 population), Southern Africa (137 deaths per 100,000 population), and Western Europe (131 deaths per 100,000 population), while the lowest mortality rate is found among men from West Africa (69 deaths per 100,000 population) [6]. The North American female population shows the highest cancer incidence rate worldwide (295 cases per 100,000 population), followed by Australia/New Zealand (278 cases per 100,000 population), Northern Europe (264 cases per 100,000 population), and Western Europe (264 cases per 100,000 population), while the lowest incidence rate is found among women from South/Central Asia (103 cases per 100,000 population) [6]. The highest mortality rate for females worldwide is found in Melanesia (119 deaths per 100,000 population), followed by Eastern Africa (111 deaths per 100,000 population), Southern Africa (99 deaths per 100,000 population), Northern Europe (94 deaths per 100,000 population), and Polynesia (93 deaths per 100,000 population), while the lowest mortality rate is found among women from Micronesia (56 deaths per 100,000 population) [6].

1.5 Population Factors Contributing to Cancer Incidence and Mortality

1.5.1 Age-Dependence of Cancer Incidence and Mortality

Cancer is predominantly a disease of old age. Most malignant neoplasms are diagnosed in patients over the age of 65, making age the most important risk factor for development of many types of cancer [7, 8]. The age-specific incidence and death rates for cancers of the prostate, breast (female), lung (both sexes combined), and colorectum (both sexes combined) for the period of 1992–2012 [2] are shown in Fig. 1.7. The trends depicted in this figure clearly show that

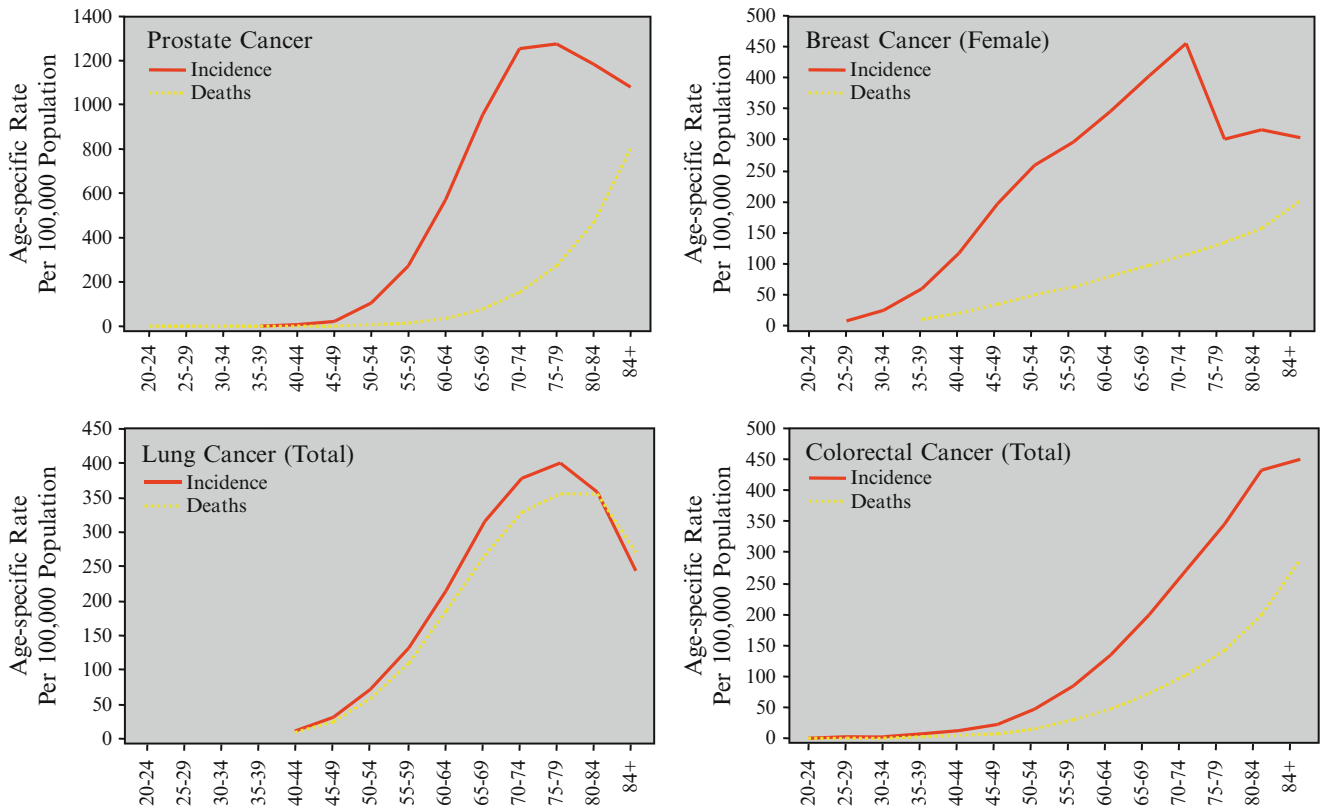

Fig. 1.7 Age-specific incidence and mortality rates for selected sites, 1992–2012. The age-specific rates for breast cancer incidence and mortality are for females only. The age-specific rates for lung cancer and colorectal cancer are combined for both sexes. These data were adapted from Howlander et al. [2]. Rates are per 100,000 population and are age-adjusted to the 2000 standard population of the USA.

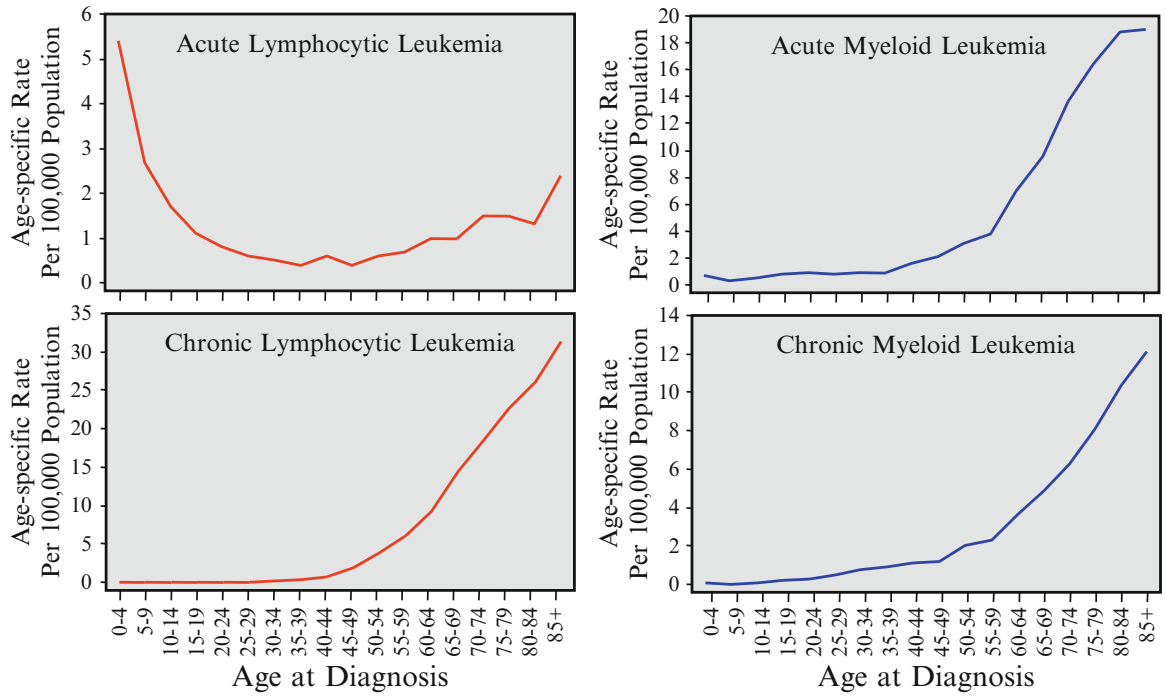

Fig. 1.8 Age-specific incidence rates for acute and chronic leukemias, 1992–2012. The age-specific rates for incidence and mortality for the major forms of leukemia are combined for both sexes. These data were adapted from Howlander et al. [2]. Rates are per 100,000 population and are age-adjusted to the 2000 standard population of the USA.

the majority of each of these cancer types occur in individuals of advanced age. In the case of prostate cancer, 86 % of all cases occur in men over the age of 65, and 99.5 % occur in men over the age of 50. Likewise, 97 % of prostate cancer deaths occur in men over the age of 65 (Fig. 1.7). In contrast, female breast cancer occurs much more frequently in younger individuals. Nonetheless, 63 % of cases occur in women over the age of 65, and 88 % of cases occur in women over the age of 50 (Fig. 1.7). A notable exception to this relationship between advanced age and cancer incidence involves some forms of leukemia and other cancers of childhood. Acute lymphocytic leukemia (ALL) occurs with a bimodal distribution, with highest incidence among individuals less than 20 years of age, and a second peak of increased incidence among individuals of advanced age (Fig. 1.8). The majority of ALL cases are diagnosed in children, with 40 % of cases diagnosed in children under the age of 15, and 45 % of cases occurring in individuals under the age of 20. Despite the prevalence of this disease in childhood, a significant number of adults are affected. In fact, 32 % of ALL cases are diagnosed in individuals over the age of 65 years of age. In contrast to ALL, the other major forms of leukemia demonstrate the usual pattern of age-dependence observed with solid tumors, with large numbers of cases in older segments of the population (Fig. 1.8). Among 54,270 new cases of leukemia in 2015, 88 % (48,020 new cases) represent forms of leukemia that primarily affect older individuals (acute myeloid leukemia, chronic myeloid leukemia, or chronic lymphocytic leukemia), with the remainder (6250 new cases) reflecting childhood ALL.

1.5.2 Cancer Incidence and Mortality by Race and Ethnicity

Cancer incidence and mortality can vary tremendously with race and ethnicity [9]. In the USA, African Americans and Caucasians are more likely to develop cancer than individuals of other races or ethnicities (Fig. 1.9). African Americans demonstrated a cancer incidence for all sites combined of approximately 443 cases per 100,000 population, and Caucasians exhibited a cancer incidence rate of 403 cases per 100,000 population. In contrast, American Indians showed the lowest cancer incidence among populations of the USA with 153 cases per 100,000 population for all sites combined. Mortality due to cancer also differs among patients depending upon their race or ethnicity. Similar to the cancer incidence rates, mortality due to cancer is higher among African Americans (223 per 100,000 population) and Caucasians (167 deaths per 100,000 population) than other populations, including Asian/Pacific Islanders, American Indians, and Hispanics (Fig. 1.9). For both cancer incidence and mortality, racial and ethnic variations for all sites combined differ from those for individual cancer sites. African