Fundamentals of Cancer Prevention

David S. Alberts
Lisa M. Hess
Editors

Fourth Edition

Springer

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David S. Alberts, MD

In my 44th year as a faculty member at the University of Arizona Cancer Center, I want to thank my research colleagues and the administration for giving me so many outstanding opportunities to express my adventuresome academic spirit for so many years. The University of Arizona Cancer Center has been an exciting and inspirational place to work!

First and foremost, I would like to pay tribute to Lisa Hess, Ph.D., who is a brilliant cancer prevention researcher with a wide breadth of detailed knowledge in cancer chemoprevention, healthcare outcomes, and clinical trial design and management. I have benefitted greatly from her wisdom, vision, and outstanding editing capability over the past 25 years.

I also want to thank all of the "Friends of the Cancer Center," who have made seminal donations and continuous personal efforts to our life-saving and health-promoting laboratory-based cancer prevention research programs. These kind and giving individuals

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I continue to thank my daughter, Rachael, who every day teaches me the value of health and motivates me to dedicate my work to improve cancer prevention and care.

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Introduction to Cancer Prevention

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The reduction in cancer observed in the United States (US) is primarily due to advances in and improved access to cancer detection and prevention efforts, resulting in less exposure to risk factors such as tobacco (Jemal et al. 2010). As a result, an estimated 767,100 cancer deaths have been averted over the past two decades (Jemal et al. 2010). These averted deaths are largely driven by reductions in lung cancer (reduction in tobacco use), breast cancer and colorectal cancer (due to improved screening and treatment modalities), cervical cancer (Pap testing and the HPV vaccine), as well as lymphoma, leukemia, and testicular cancer (due to new treatments). Unfortunately, these efforts to reduce the burden of cancer have not been distributed equitably around the world. For example, the incidence of cervical cancer is increasing in some areas (e.g., Zimbabwe, Uganda, Eastern Europe),

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perhaps due to lack of access to vaccination, increasing HPV infection rates, and gaps in screening programs (Torre et al. 2016).

Other cancers have increased in the US and Western Europe, such as liver cancer in part due to increasing hepatitis C infection rates, while liver cancer has decreased in China and Japan, where public health programs have decreased the rate of hepatitis C infection (Torre et al. 2016).

Despite the reduction in incidence and mortality rates, particularly in high-income countries, cancer remains a significant public health burden. Cancer is the second leading cause of mortality in the US, where cancer causes approximately 609,640 deaths per year and is responsible for 8.2 million deaths worldwide each year (Siegel et al. 2018; Torre et al. 2016).

1.1 Introduction

The concept of cancer prevention has changed with a greater understanding of the genetic and molecular basis of carcinogenesis. Certainly, it is understood that a person with cancer is not well one day and the next day diagnosed with cancer. It is estimated that there is an average lag of at least 20 years between the development of the first cancer cell and the onset of end-stage metastatic disease for a broad range of solid tumors. In that there are an estimated 14.1 million new cancer cases diagnosed worldwide each year (Torre et al. 2016) and given the 20+-year lag time, it is estimated that up to 280 million "healthy" adults currently harbor ultimately deadly cancers, many of which may be fully preventable. Beyond reducing cancer incidence, it is also estimated that between one-third and one-half of all cancer deaths could be avoided with a combination of primary prevention, early detection, and access to effective treatment; with our current knowledge, approximately three million cancer deaths could be avoided each year through cancer prevention and control programs (Stewart and Wild 2014).

Cancer prevention strategies may represent effective and cost-effective opportunities to dramatically reduce cancer mortality in the next decades. The World Health Organization (WHO) estimates that the cost of cancer will reach US$458 billion per year by 2030 and that implementing a basic package of cancer prevention initiatives to address tobacco use, alcohol consumption, dietary behaviors, and physical inactivity would only cost US$2 billion per year (Stewart and Wild 2014). However, it is important to consider that in addition to these healthcare costs, there are considerable human costs of cancer that cannot be quantified in economic units. The physical suffering and psychosocial burden associated with cancer diagnosis, treatment, and end-of-life care are inestimable. Globally, it is expected that there will be 22 million new cases of cancer diagnosed annually by 2030, with the greatest risk among low- and middle-income nations. It is crucial to ensure that public health and national priorities focus on cancer prevention efforts that address inequalities in healthcare access and delivery (Bray et al. 2015).

1.2 Overview of Cancer Prevention

Cancer is a global term for a variety of diseases that share some similar characteristics, such as uncontrolled cellular growth, enhanced angiogenesis, tissue invasion and metastases, genomic instability, and/or reduced programmed cell death (Hanahan and Weinberg 2000). The site of origin of the disease is used to define general categories of disease (e.g., breast cancer, skin cancer); however, the site of disease alone masks the significant heterogeneity of histological and pathological subtypes within cancers. Cancer prevention research works to identify molecular and cellular changes and to develop interventions as early as possible to reduce the risk of their progression to cancer. Inherent to the challenges of prevention research is the biologic complexity in the multitude of potential cancer-causing mutations even within a single tumor. For example, over 33,300 and 22,900 somatic mutations have been identified in melanoma and non-small cell lung cancer, respectively (Stewart and Wild 2014).

It is estimated that there are over 14.1 million cases of cancer diagnosed and 8.2 million deaths each year worldwide (Torre et al. 2016). The five most common worldwide cancers among men, excluding nonmelanoma skin cancer, include lung, prostate, colorectal, stomach, and liver cancer, whereas for women the most common cancers are breast, colorectal, lung, cervix, and stomach (Table 1.1). It is estimated that 80% of the burden of cancer is found in low- and middle-income countries (Bray et al. 2012). As population and economic changes occur, infection-related cancers (e.g., cervical, stomach) are decreasing whereas cancers associated

Table 1.1 Worldwide annual cancer incidence and mortality of selected common cancers (Stewart and Wild 2014)

	Number of new cases each year	Number of deaths each year
Males		
All cancers	7,427,148	4,653,132
Lung	1,241,601	1,098,606
Prostate	1,111,689	307,471
Colorectum	746,298	373,631
Stomach	631,293	468,931
Liver	554,369	521,031
Bladder	330,360	123,043
Esophagus	323,008	281,212
Females		
All cancers	6,663,001	3,547,898
Breast	1,676,633	521,817
Colorectum	614,304	320,250
Lung	583,100	491,194
Cervix	527,624	265,653
Stomach	320,301	254,096
Uterine	319,905	217,680
Ovary	225,500	140,200

with modifiable behaviors such as dietary factors are increasing (e.g., breast, prostate, and colorectal cancers) (Bray et al. 2012). Not only do cancer sites vary by region due to differences in exposure to infection and varying activity and dietary patterns, but the type of cancers as well. Esophageal cancers occur most commonly in Malawi, South Africa, and Iran. In these high-risk areas, squamous cell carcinoma is most common, possibly due to nutritional status and dietary patterns, whereas in Western countries, adenocarcinomas are more common. The risk factors associated with esophageal adenocarcinoma include smoking and gastrointestinal reflux disease, which are more common in overweight or obese adults (Bray et al. 2012). Therefore, not only are the patterns of cancer incidence and mortality associated with regional variation, but the histological subtype as well.

As the world increasingly adopts behaviors that are associated with risk factors of Western countries (e.g., increased body weight, reduced physical activity), the rates of breast and colorectal cancers are increasing in parallel. Globally, obesity rates doubled from 1980 to 2008 and continue to increase (Stevens et al. 2012). As this trend continues, global cancer incidence rates will also continue to rise.

Contributing to the challenges faced by cancer prevention and early detection efforts is the lack of access to health care due to either a lack of health insurance (e.g., US) or a lack of healthcare services (rural or remote regions and many developing nations). Access to screening programs and improved healthcare programs are essential to prevent cancer or to detect a cancer while it may still be curable. For example, breast cancer rates have been increasing worldwide; however, the mortality due to breast cancer has been decreasing in higher income nations, such as the US, Denmark, and Australia, likely due to improved screening/early detection and access to more effective cancer treatment agents (Stewart and Wild 2014). Similarly, among nations with organized cervical cancer screening programs, the risk of cervical cancer morbidity and mortality has been continuously declining (e.g., Sweden, Finland, and France have all seen cervical cancer decrease by greater than 4% per year since the initiation of cervical cancer screening programs). However, among nations that lack these programs, cervical cancer remains a major health risk for all women (e.g., Slovakia and Slovenia have seen annual increases in cervical cancer without these programs) (Mackay et al. 2006). Currently, more than 70% of the burden of cervical cancer occurs in low- to middle-income nations, and is the leading cause of death in more than 40 countries (primarily in Africa and South America) (Stewart and Wild 2014).

Countries that have organized tobacco control policies have shown decreases in youth tobacco use. While a World Health Organization survey reports that 92% of the 176 countries reported to have tobacco control programs in place, only 69% also have a funded/operational tobacco policy (Stewart and Wild 2014). Even among nations that have established public health policies, individuals must have access to these programs for them to be effective. The US has the highest per capita healthcare expenditures in the world at approximately US$9237 per person per year in 2015 (Dieleman et al. 2017), which is expected to reach nearly US$16,000 per person by 2025 (Keehan et al. 2017). There is a great deal of variability worldwide. High-income nations spend an average of US$5221 per person (range: 853–9237),

upper middle-income nations spend $914 per person (range: 228–1980), lower middle-income nations expend an average of $267 (range: 92–791), and low-income nations spend $120 per capita (range: 33–347) (Dieleman et al. 2017). Despite the investment in healthcare costs in the US, approximately 14.6% of the population does not have health insurance (National Center for Health Statistics 2017). This is an improvement from the nearly 20% of the population that did not have insurance only 5 years earlier. Healthcare policies, such as the Affordable Care Act, have had an impact on access to health insurance in several groups, particularly among young adults. Due to the provision to require insurers to cover children through the age of 26, gaps in insurance coverage have been reduced from 34% in 2010 to 16% in 2015 (National Center for Health Statistics 2017). Certainly more work must be done to ensure that no individual in any country lacks access to affordable health care. Lack of access to health care has been demonstrated to result in late cancer diagnosis (e.g., at an advanced stage) when costs are greater and outcomes are poor, more cancer treatment delays, and ultimately higher mortality (ACS 2008). Even when patients without insurance are diagnosed at the same stage as patients with insurance, they still have a significantly increased risk of death (e.g., patients without insurance have a 30–50% higher rate of death from colorectal or breast cancer than patients with insurance) (IOM 2002).

The goal of cancer prevention is to reduce the morbidity and mortality from cancer by reducing the incidence of cancer due to these modifiable factors as well as to reduce the impact of unmodifiable factors contributing to cancer. The development of effective cancer prevention strategies has the potential to impact a significant portion of the cancer-related deaths each year worldwide (Jemal et al. 2011). Therefore, cancer prevention is the best approach possible to reduce the burden of cancer worldwide. Cancer prevention research takes a three-pronged approach to target different aspects reducing cancer morbidity and mortality: primary, secondary, and tertiary prevention.

1.3 Primary Prevention

The goal of primary prevention is to prevent a cancer from beginning to develop. Primary prevention involves a reduction of the impact of carcinogens on changes that occur at the cellular level, such as through administration of a chemopreventive agent or the removal of environmental carcinogens, or through changes in the tumor microenvironment that can be influenced by lifestyle modification (e.g., reduction in obesity to influence hormonal exposure). Primary prevention methods are best suited for those cancers in which the causes are known. There are many factors known to reduce overall cancer incidence, such as minimizing exposure to carcinogens (e.g., avoiding tobacco), dietary modification, reducing body weight, increasing physical activity, avoiding infection, or through medical intervention (surgery and/or chemoprevention). Among high-income nations, the leading risk factors for cancer include an unhealthy diet, obesity, and tobacco use (together accounting for 40% of cases), whereas among developing nations poor diet/nutrition is the leading

risk factor in 20% of all cancer cases, and infection accounts for another 26% of all cancer cases.

Tobacco use, which represents the greatest preventable cause of cancer death, is the direct cause of more than 20% of all cancer deaths worldwide each year (primarily lung cancer, but smoking also increases the risk of cancers of the larynx, oral cavity, lip, nasal cavity, esophagus, bladder, kidney, cervix, stomach, liver, and many other sites) (Thun et al. 2010). Tobacco use is the leading cause of smoking-related cancer death among both men and women (80% of all lung cancers among males and 50% among females are directly attributed to tobacco) (Jemal et al. 2011). However, all damage done during smoking is not completely irreversible. Smoking cessation can begin to reverse the risk of cancer. Benefits from quitting smoking begin within the first year of cessation and continue to increase over time. The risk of lung, oral, and laryngeal cancers can be significantly reduced following smoking cessation, with an estimated overall 9-year gain in life expectancy associated with smoking cessation (Jha et al. 2013). The results of tobacco cessation are particularly pronounced if a person quits smoking before the age of 40 (associated with a 90% reduction in premature death that is associated with smoking in midlife) (Jha et al. 2013). Primary tobacco prevention efforts include cessation support programs (behavioral and pharmacologic), public awareness and education, smoke-free public policies, increased tobacco pricing through taxation, and very importantly efforts to reduce the initiation of the use of any form of burnt and smokeless tobacco, all of which are carcinogenic and deadly (Thun et al. 2010; Jemal et al. 2011).

Many cancers are directly attributable to viral or bacterial infections (e.g., human papillomavirus, HPV, infection is a necessary factor in the development of cervical cancer; *Helicobacter pylori* is an initiator and promoter for gastric cancer). Advances in vaccination research led to the development of HPV vaccines that are available to young adults. If these vaccines would be used and available worldwide, nearly all cervical cancers could be prevented. In the US, where the vaccine is widely available but no public health policy exists, approximately 50% of all young women and 38% of young men are vaccinated (Walker et al. 2017). As a result, half of the US population remains at risk for cervical cancer. The adoption of HPV vaccination is highly variable worldwide. In the UK, where a national coverage for HPV vaccination exists, nearly 90% of all young adults have received all courses of the HPV vaccine (Sipp et al. 2018). In Japan the public health recommendation for vaccination was withdrawn, leading to a drop in vaccination rates from 70% to less than 1% (Sipp et al. 2018). The role of public health policy and national coverage policies to ensuring the health of nations cannot be understated.

Despite this known need primary prevention research and efforts continue to remain underfunded. The National Institutes of Health, the government-funded health research organization in the US, dedicated US$5894 million (approximately 18% of the program budget) to cancer research in 2017 (HHS 2016). Of this cancer-specific budget, only 5.5% is dedicated to cancer prevention and control (NCI 2018). This lack of prioritization results in delays in improving and delivering early detection and prevention strategies that have the potential to save millions of lives.

1.4 Secondary Prevention

Secondary prevention refers to screening efforts for early detection and diagnosis. The goal of secondary prevention efforts is to identify abnormal cells or lesions before they develop into a malignant tumor. Secondary prevention efforts are most effective where there is a known precursor lesion to cancer (e.g., mammogram to identify and remove ductal carcinoma in situ, colonoscopy to remove adenomas). By identifying abnormal changes before they become cancerous, the precancer can be removed before it becomes malignant. In some cases, secondary prevention can involve the treatment of precancerous lesions in an attempt to reverse carcinogenesis (e.g., such as topical therapies for nonmelanoma skin cancers, which cause the lesion to regress). Secondary prevention is described in more detail specific to each disease site in this book. Secondary prevention efforts are not possible for all cancers until accurate and effective screening strategies are developed. Ovarian cancer, for example, has no known precursor lesion and no testing strategy has been found to be effective to apply to a broad population. Efforts have been underway by many organizations (e.g., Gynecologic Oncology Group/NRG, UK Collaboration) to identify a strategy using existing approaches such as transvaginal ultrasound and serum CA-125. The high rate of false-positive and false-negative results, invasiveness of testing, and lack of cost-effectiveness even among the highest risk populations have precluded any national screening efforts for ovarian cancer (Menon et al. 2017; Skates et al. 2017). Other diseases, such as stomach cancer, are relatively rare in Western countries, limiting the value of screening programs in those regions. However, Asia has higher incidence rates of stomach cancer (e.g., Japan, Korea, and China account for 60% of the world's stomach cancer cases). The implementation of population-based screening programs has led to earlier stage diagnosis and improved survival outcomes (Balakrishnan et al. 2017). Five-year survival from stomach cancer is nearing 70% in Japan and Korea whereas the 5-year survival is only 31% in the US (Balakrishnan et al. 2017; Noone et al. 2018).

1.5 Tertiary Prevention

Tertiary prevention involves the care of established disease and the prevention of disease recurrence as well as the prevention of disease-related complications. Tertiary prevention efforts also encompass the care of patients at high risk of developing a second primary cancer. Tertiary prevention may involve a variety of aspects of survivorship, such as quality of life, maintenance therapies, surgical intervention, palliative care, or diet and physical activity. Emerging evidence suggests that physical activity may have a greater impact on reducing cancer risk than nutritional interventions to reduce the risk of disease recurrence and to prolong survival in early-stage breast cancer. In a prospective study of women with early-stage breast cancer (George et al. 2011), women with any physical activity and better quality diets had a lower risk of death from breast cancer than those who had poor nutrition and exercise; nutrition alone did not demonstrate any differences between groups (Fig. 1.1). These findings are hypothesis generating rather than confirmatory due to

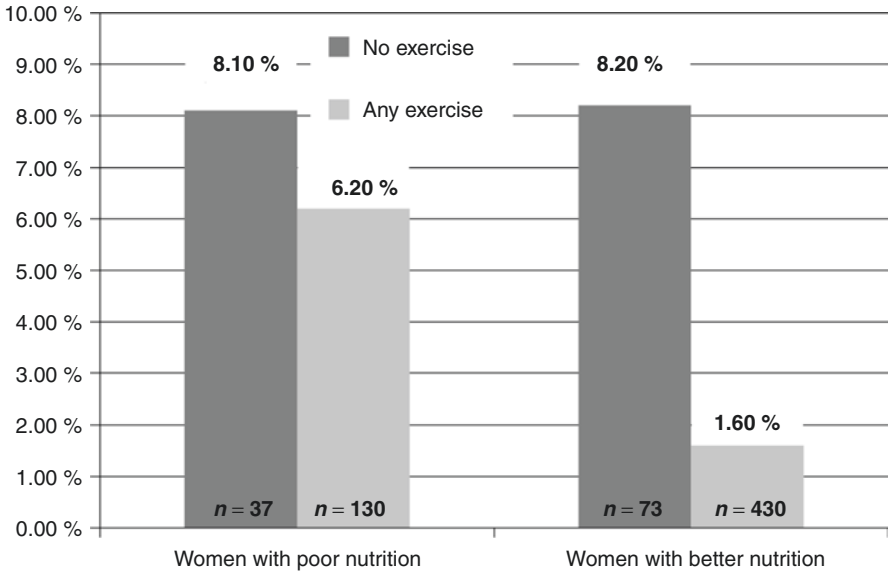

Fig. 1.1 Percentage of deaths due to breast cancer in patients with early-stage disease according to the amount of exercise and nutrition after diagnosis (George et al. 2011)

the self-reported diet and activities and non-randomized study design. Additional research is ongoing to explore this hypothesis in breast cancer and a variety of other tumor types, such as ovarian cancer in GOG-225 (the LIVES Study) (Thomson et al. 2016). In the LIVES Study (Lifestyle Intervention for Ovarian Cancer Enhanced Survival), 1200 women who have completed primary treatment for stage II–IV ovarian cancer are randomized to a plant-based, high-fiber, low-fat diet (similar to that used in the Women's Health Initiative that was associated with the 40% reduction in the risk of ovarian cancer) plus physical activity or to usual care. This study is nearing completion of enrollment in 2018, and will be the largest lifestyle-based intervention in a randomized trial of ovarian cancer survivors to date.

1.6 Molecular Approach to Carcinogenesis

Cancer prevention research has been evolving from an initial understanding of the process of cancer initiation and the steps to progression of disease. Carcinogenesis refers to the process of genetic alterations that cause a normal cell to become malignant and can take many years to develop (Fig. 1.2). For example, in the case of colorectal cancer, it may take up to 35 years from the first initiated colonic mucosal cell to an adenomatous polyp to develop invasive cancer. The same is true for prostate cancer, which progresses over as many as 40–50 years from mild to moderate, then severe intraepithelial neoplasia, to latent or invasive cancer.

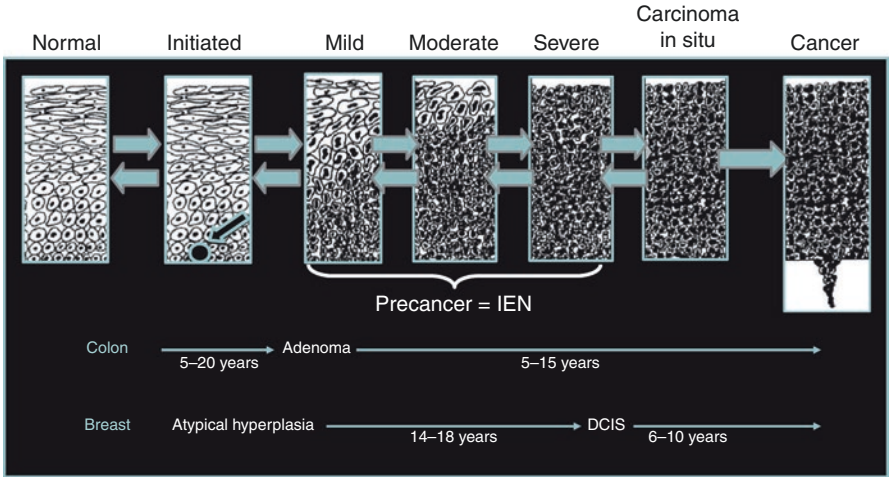

Fig. 1.2 Progression of precancer to cancer in humans is a multiyear process (adapted from O'Shaughnessy et al. 2002)

The process of carcinogenesis involves multiple molecular events over many years to evolve to the earliest dysplastic lesion. This multiyear process provides numerous opportunities to intervene with screening, early detection, surgical procedures, and chemoprevention (i.e., the use of specific nutrients and/or chemicals to treat precancerous lesions and/or delay their development) (Sporn 1976). The understanding of molecular pathways in carcinogenesis has grown rapidly in recent years, fostering novel targeted approaches to cancer prevention research. The hallmarks of cancer (e.g., cellular proliferation, lack of growth suppression, cellular immortality and resistance of cellular death, cellular replication, inflammation, angiogenesis, invasion, and metastasis) can further target prevention efforts to intervene at multiple steps in the path of carcinogenesis (Gupta et al. 2018; Hanahan et al. 2011).

Advances in the field of immunotherapy for cancer may provide valuable insights into further targets for chemoprevention by targeting pathways of immune response to block carcinogenesis. Premalignant cells are found in an inflammatory state that has been found to promote cellular growth and proliferation (Hanahan et al. 2011). The cellular microenvironment can be prevented from becoming immunosuppressive through vaccination for hepatitis B and C (hepatocellular carcinoma) or for HPV (cervical carcinoma). However, cancer usually begins with a precancerous lesion, not always an infection, and the challenge remains to ensure detection at an early enough stage for a vaccine to be effective (Morrison et al. 2018). While the development of primary prevention vaccines is a promising strategy, additional work is needed to identify appropriate biomarkers and to ensure that sufficient patient populations are available for prevention clinical trials.

1.7 Cancer Prevention Clinical Trials

The importance of conducting and participating in clinical trials cannot be understated. Every person is at risk of genetic mutations that may lead to cancer. Due to endogenous or exogenous factors, every human body has undergone genetic alterations. For many individuals, these initiating factors are the early steps in the development of cancer. The time period from the first initiated cell to malignancy is estimated to be approximately 20 years for several cancers that are associated with lifestyle and behavioral choices (e.g., tobacco, obesity, diet). As described earlier, the early steps towards cancer occur over time, which means that millions of individuals worldwide are currently in some phase of undetected cancer progression that will ultimately result in their death without early detection and prevention (Wattenberg 1993). However, there is a need for improved strategies to effectively prevent these untimely cancer deaths.

Cancer prevention trials are research studies designed to evaluate the safety and effectiveness of new methods of cancer prevention or screening. The focus of cancer prevention research can involve chemoprevention (including vaccination), screening, genetics, and/or lifestyle changes (e.g., diet, exercise, tobacco cessation). Cancer chemoprevention research differs from treatment research in several important ways as shown in Table 1.2. Cancer chemoprevention trials generally are performed in relatively healthy volunteers who have well-documented precursor lesions (e.g., colorectal adenomas, bladder papillomas, breast ductal carcinoma in situ, actinic keratosis in the skin) or are at increased risk due to genetic or other factors. These trials are usually double blind (i.e., both physician and participant do not know the assigned treatment) and placebo controlled and involve a few thousand to tens of thousands of randomized participants. As opposed to cancer treatment phase III trials that rarely extend beyond 5 years in duration, cancer chemoprevention trials often take many years to complete and are extremely costly. The high cost of cancer prevention trials and the need to develop reliable and meaningful intermediate endpoints are significant barriers that must be overcome. Cancer prevention clinical trials take between 5 and 10 years (or more) to complete and require thousands of participants. The cost to complete large-scale trials (10,000 participants or more) can exceed US$100–200 million range and, of course, may not always result in the discovery of an effective prevention strategy.

Research on developing and implementing effective cancer prevention and control interventions lags in funding relative to its potential impact on reducing the cancer burden. Despite the known cancer-causing effects of tobacco use, few non-nicotine medications are currently approved by the US Food and Drug Administration (FDA) for smoking cessation, though others are in the pipeline, and these existing medications achieve smoking cessation quit rates that are 25% at best. Since many healthcare organizations do not include smoking cessation medications as a covered benefit, the incentive for pharmaceutical companies to prioritize the development of smoking cessation medications is not high—thus fostering a negative feedback loop that disincentivizes healthcare organizations from covering medications because the effectiveness of those medications is low. Similarly, pharmaceutical companies have

Table 1.2 Cancer chemoprevention versus cancer treatment phase III trials

Characteristic	Cancer chemoprevention trials	Cancer treatment trials
Participants	Relatively healthy volunteers with precancerous lesions or who are at moderate/high risk	Patients diagnosed with invasive cancer
Trial design	Commonly double blind, placebo controlled	Often unblinded to both patient and investigator
Dosage	Minimize dose, emphasize safety	Maximize dose, emphasize efficacy
Toxicity	Toxicity is unacceptable, concern for long-term use of agent	Moderate toxicity acceptable due to severity of disease
Adherence	Concern for "drop-ins" due to media or hype	Concern for "dropouts" due to toxicity
Endpoint	Surrogate biomarkers; cancer incidence	Mortality; disease progression
Sample size	A few thousand to many thousands of participants	A few hundred to a thousand participants
Trial duration	Usually 5–10+ years	Several months to several years

Revised from Alberts et al. (2004)

traditionally been unwilling to invest in the development of chemopreventive agents because of the required length of time, size, and cost of registration trials. Furthermore, companies are concerned about the unexpected, life-threatening toxicities that may be observed with the long-term exposure required for many cancer prevention intervention strategies. The majority of FDA-approved medications have been studied for shorter treatment periods in trials of active disease, and the long-term safety profile is unknown. Unexpected toxicity associated with long-term use of a drug can have an extremely negative impact on approved products. This occurred with the investigation of selective cyclooxygenase-2 (COX-2) inhibitors for the prevention of colorectal and prostate cancers. There are substantial preclinical data suggesting that the COX-2/prostaglandin E2 (PGE_2) pathway has a pivotal role in carcinogenesis (Menter et al. 2010). COX overexpression was identified in several precursor lesions, including cervical intraepithelial neoplasia, Barrett's esophagus, colorectal adenomas, actinic keratosis, and atypical adenomatous hyperplasia of the lung (Subbaramaiah and Dannenberg 2003). Based on a growing body of evidence, inhibition of COX-2, resulting in the inhibition of PGE2 production in the microenvironment, was hypothesized to reduce the risk of a variety of cancers. A number of chemoprevention clinical trials were initiated that randomized patients to COX-2 inhibitors, such as GOG-207 (14–18 weeks of celecoxib versus placebo for cervical intraepithelial neoplasia, Clinicaltrials.gov: NCT00081263), the APPROVe trial (156 weeks of rofecoxib versus placebo for adenomatous colorectal polyps, Clinicaltrials.gov: NCT00282386), the ViP Trial (6 years of rofecoxib versus placebo among men with high PSA levels, Clinicaltrials.gov: NCT00060476), and celecoxib versus placebo (6 months of treatment for lung cancer incidence/recurrence in heavy smokers, Clinicaltrials.gov: NCT00055978). In the midst of recruitment to these chemoprevention trials, the APPROVe study identified a statistically significant

increased risk of cardiovascular events after 18 months of cumulative administration of rofecoxib (Bresalier et al. 2005). This led not only to the early termination of many studies evaluating COX-2 inhibitors, but also to the withdrawal of rofecoxib from the market. This experience highlights the need for long-term safety data for chemoprevention trials that may involve treatment for longer durations of time. In addition to lower tolerance for safety risk in prevention trials, there is a concern with unnecessary drug treatment of otherwise healthy adults, as not all adults at risk of cancer will ultimately be diagnosed with the disease. The anticipated risk-benefit profile of any chemopreventive agent must be thoroughly evaluated prior to initiating a cancer prevention clinical trial, as minimizing risk is paramount.

The stages of investigation in cancer prevention research trials include a series of phases of clinical trials. Phase I trials take place after an agent has demonstrated activity with low toxicity in preclinical models. Phase I chemoprevention trials are relatively brief (i.e., 1–3 months), preliminary research studies in healthy humans to determine dose and safety of an agent. Phase II trials can be categorized into IIa (non-randomized) and phase IIb (randomized) trials. Phase II studies are of longer duration (i.e., 6–12 months), and typically include a surrogate efficacy endpoint, such as a biomarker, to provide evidence regarding the effectiveness of the intervention while continuing to evaluate safety. Phase III trials generally are large, double-blind, multiple-year, placebo-controlled randomized trials to evaluate the efficacy and safety of an agent in a sample of the target population. Often, cancer incidence is the primary endpoint in phase III prevention studies. For a chemopreventive agent to be used in a phase III research setting, it must meet several criteria. The agent must have strong data supporting its mechanistic activity, and there must be preclinical efficacy data from appropriate animal models. If the chemopreventive agent is a nutrient, there must be strong epidemiologic data supporting its potential effectiveness, and it must have demonstrated safety and activity in phase II trials. Phase III trials of novel chemopreventive agents should not be performed in the absence of a fundamental understanding of their mechanism of action. Phase IV trials are focused on the utilization, effectiveness, and safety of an intervention in a real-world setting. Inadequate funding and insufficient attention have been given for these vitally important dissemination studies, leading to underutilization of effective chemoprevention strategies, such as tamoxifen or raloxifene to prevent the development of breast cancer in postmenopausal women (Fisher et al. 1998). These trials are typically single-arm long-term observational studies that evaluate a population that receives the chemopreventive agent. Many phase IV studies are conducted due to regulatory requirements to ensure that the risk/benefit profile remains favorable in an uncontrolled setting after approval of the intervention (Biganzoli and Cesana 2018). Pragmatic trials are a type of post-approval research; however it combines aspects of both phase III designs (i.e., randomization) and phase IV features (e.g., observational/uncontrolled). Pragmatic trials randomize a study participant to the chemoprevention agent versus control. In this case, the control may be anything the patient and provider might normally consider, and is not mandated by the trial. After randomization, the study is much like an observational trial, where the intervention timing, outcome assessments, and other factors are not mandated

by the trial (Thorpe et al. 2009). This type of design basically provides balance on baseline factors to conduct comparative effectiveness and safety research of a chemoprevention agent.

Increasingly, health service research relies on administrative and clinical databases (e.g., claims or electronic health records), to conduct retrospective observational research to evaluate real-world effectiveness of cancer prevention strategies. These studies have the advantage of being less costly and of shorter duration than prospective research. While these studies are also used to provide supporting evidence for the development of cancer prevention interventions, the quality of real-world data sources and the development of improved statistical methods to account for heterogeneity and imbalance between cohorts have led to the increased use of observational research to evaluate effectiveness after the completion of phase III trials (e.g., propensity score methods, marginal structural models, use of an instrumental variable, sensitivity analyses) (Nørgaard et al. 2017; Streeter et al. 2017).

When the mechanism of action of a putative chemoprevention agent has not been previously explored in the setting of broad, real-world populations, the results of phase III trials can be alarming. Two examples of this include the results of the Finnish Alpha-Tocopherol, Beta-Carotene (ATBC) Trial and the University of Washington Carotene and Retinol Efficacy Trial (CARET). Both of these phase III trials used relatively high doses of beta-carotene as compared to placebo in heavy smokers to reduce the incidence of and mortality from lung cancer (Alberts et al. 1994; Omenn et al. 1996). Unfortunately, both trials found that the beta-carotene intervention was associated with an 18–28% increase in lung cancer incidence and an associated increase in mortality. Perhaps the reason for these unexpected and extremely unfortunate results relates to the fact that at high beta-carotene concentrations in the setting of high partial pressures of oxygen (e.g., as achieved in the lung) and in the presence of heat (e.g., as achieved in the lung with cigarette smoking), beta-carotene can become an autocatalytic prooxidant (versus its usual role as an antioxidant) producing reactive oxygen species and DNA damage (Burton and Ingold 1984).

The design of chemoprevention phase II–III trials must be founded on a hypothesis that is soundly based on the mechanism of action of the agent, epidemiologic data, safety profile, and its preclinical efficacy. The population to be enrolled to a phase III prevention trial must be relatively at high risk, to assure that there will be a sufficient number of events (e.g., precancers or cancers) to compare the treatment to the control group. Phase III prevention trials should include both intermediate (e.g., precancerous lesion regression or biomarker) and long-term (e.g., cancer incidence) endpoint evaluations. Most importantly, the endpoint analyses should be planned in advance, including well-defined and well-powered primary and secondary analyses.

One example of a high-impact phase III chemoprevention trial is the Breast Cancer Prevention Trial with Tamoxifen (BCPT) (Fisher et al. 1998). Healthy women at increased risk of breast cancer were randomized to either tamoxifen (20 mg/day) or placebo for up to 5 years. Tamoxifen was selected for this trial because of its well-documented mechanism of action (i.e., binding to the estrogen

receptor to prevent estrogen's effect on tumor cell proliferation), its strong safety profile in the setting of adjuvant breast cancer therapy, and its extreme activity in the prevention of contralateral breast cancer in patients with stage I/II breast cancer. After 69 months of follow-up, tamoxifen was found to be associated with an overall 49% reduction in the risk of invasive breast cancer (Fisher et al. 1998). The benefit of breast cancer risk must be balanced with its toxicities, which include a greater than twofold increase in early-stage endometrial cancer and an increased incidence of deep vein thrombosis and pulmonary embolism. Since the publication of these results, much discussion has led to the identification of women who would most benefit from treatment with tamoxifen. Certainly, women who are at increased breast cancer risk have already undergone a hysterectomy and who are at lower risk for thrombophlebitis (e.g., due to higher levels of physical activity, lack of obesity) would be good candidates for this intervention. Furthermore, there has been a relative lack of dissemination of this information to both primary care physicians and the population, resulting in limited tamoxifen usage (Freedman et al. 2003). More recently, the results of the phase III Study of Tamoxifen and Raloxifene (STAR) revealed equivalent activity of tamoxifen as compared to raloxifene for the reduction of breast cancer risk among postmenopausal women at moderately increased risk (Vogel et al. 2006). Raloxifene was associated with an improved safety profile (e.g., lower thromboembolic events and cataracts), leading to its approval as a chemopreventive agent with the FDA. Only time will tell if these results will lead to increased chemoprevention utilization. Currently, only a small fraction of eligible women at increased risk of breast cancer are taking advantage of the established efficacy of these chemopreventive strategies.

The translation of research findings to the clinic is the ultimate goal of cancer prevention research. Chemoprevention agents or screening modalities must be acceptable to the target population that would benefit from such interventions. For example, the ideal chemoprevention agent would have a known mechanism of action and would have no or minimal toxicity, have high efficacy, be available orally or topically, have an acceptable treatment regimen, and be inexpensive. Similarly, screening or early detection modalities should be minimally invasive, have high sensitivity and specificity, and be acceptable to the target population. Interventions that fail to maintain adequate adherence or that have high attrition rates during phase III trials will likely also not be acceptable to the patient in clinical practice.

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2 Assessing the Impact of Cancer Prevention on Self-Reported Health and Well-Being

Stephen Joel Coons and Mira J. Patel

Contents

2.1 Introduction to Chapter

Being able to do the things that bring meaning and fulfillment to our lives is a basic human desire. However, cancer and its physical, emotional, and social consequences can profoundly impair our ability to participate in those life-enriching pursuits. Hence, to demonstrate the wisdom of individual, health system, and societal commitment to cancer prevention activities, it is important to quantify, to the extent

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possible, the short- and long-term impact of those activities on self-reported health and well-being.

Cancer and its treatment can lead to significant burden on patients and their families. It has been shown that cancer is the cause of more years of life lost than all other causes of death (National Cancer Institute [NCI] 2017) and that being a cancer survivor is associated with decreased physical health-related quality of life (Reeve et al. 2009; Weaver et al. 2012), increased psychological distress (Hoffman et al. 2009), changes in cognitive functioning (Phillips et al. 2011), higher out-of-pocket medical expenditures (Short et al. 2011), employment challenges (Short et al. 2005), and greater risk for personal bankruptcy (Ramsey et al. 2011). Hence, the avoidance of cancer and its consequences is paramount; where real change is possible in regard to known modifiable behavioral, environmental, and policy/regulatory risk factors for cancer, there is no doubt that "prevention is the cure" (Mukherjee 2010).

As will be described in much more detail in subsequent chapters, cancer prevention takes many forms. At the individual level, virtually all prevention activities involve (1) engaging in particular behaviors or interventions (e.g., following screening and immunization recommendations, taking tamoxifen for secondary prevention of breast cancer), (2) avoiding particular behaviors (e.g., sunbathing, smoking), or (3) changing particular behaviors once they have become habitual or routine (e.g., quitting smoking, lowering dietary fat). Each of these prevention behaviors, or the lack of them, can have short- and long-term impacts on health and well-being.

Therefore, it is important to discuss the value of cancer prevention activities and the personal impact they can have on individuals who carry them out. The purpose of this chapter is to provide an overview of the assessment of outcomes of cancer prevention strategies in terms of self-reported health and well-being. However, it must be recognized that most of the published literature in this field has focused on individuals who already have a cancer diagnosis and are being treated. Hence, a huge body of evidence exists regarding the impact of cancer and its treatment on patient-reported functioning and well-being that provides a compelling case for preventing cancer from occurring in the first place. On the other hand, much less empirical evidence exists regarding the implications of cancer prevention activities or interventions themselves on self-reported functioning and well-being.

2.2 Outcome Assessment

In order to discuss the impact of cancer and the substantial benefits of preventing it, it is necessary to define *outcomes*. Death can be an outcome of cancer; however, "death rates alone do not provide a complete picture of the burden that deaths impose on the population" (NCI 2017). A more meaningful metric for measuring the impact of death (and the value of preventing it) is *person years of life lost* (PYLL). PYLL are the expected years of life lost due to premature death from a specific cause. Hence, PYLL can help to illustrate the magnitude of cancer's impact on shortening the length of lives. In 2012, each person who died in the United States (US) as a result of

cancer lost, on average, an estimated 15.7 years of life (NCI 2017). Overall, cancer-related deaths in the US resulted in over 9.2 million PYLL in 2012, which suggests that significant reductions in the number of life years lost to cancer can result from prevention. It was projected that almost 610,000 people in the US will die of cancer in 2018 (Siegel et al. 2018). Fortunately, death is not the only, nor most likely, outcome of cancer. It was estimated that there were 15.5 million cancer survivors in the US at the beginning of 2016 (American Cancer Society 2016) and the number is projected to increase to almost 18 million by 2022 (Siegel et al. 2012).

A conceptual framework articulated by Kozma and colleagues places outcomes into three categories: economic, clinical, and humanistic (Kozma et al. 1993). Economic outcomes are changes in the consumption and production of resources caused by disease or intervention, such as cancer prevention. The changes may be direct (e.g., cost of a medication) or indirect (e.g., early retirement due to reduced productivity). Clinical outcomes are the medical events that occur as a result of the condition or its treatment as measured in the clinical setting. This includes death, which will not be addressed further in this section. Humanistic, or patient-reported, outcomes include condition or intervention-related symptoms and side effects, treatment satisfaction, health status, and self-assessed function and well-being, or health-related quality of life. It is important to recognize that *progression-free survival*, which is the most commonly used measure of treatment benefit in cancer clinical trials, does not necessarily translate into quality-of-life improvements (Brettschneider et al. 2011).

The major cancer clinical trial cooperative groups in North America and Europe have recognized the importance of this outcome triad in evaluating and improving the net benefit of cancer therapy (Bruner et al. 2004). Humanistic outcomes (e.g., self-reported health and well-being), which are the focus of this chapter, are increasingly being incorporated into clinical trials (Lipscomb et al. 2004). In addition, the importance of outcome assessment in cancer was reinforced with NCI's establishment of its Outcomes Research Branch in 1999 (Lipscomb and Snyder 2002) and the Cancer Outcomes Measurement Working Group in 2001 (Lipscomb et al. 2005). According to the NCI, "outcomes research describes, interprets, and predicts the impact of various influences, especially (but not exclusively) interventions on 'final' endpoints that matter to decision makers: patients, providers, private payers, government agencies, accrediting organizations, or society at large" (Lipscomb and Snyder 2002).

2.3 Humanistic Outcomes

As mentioned above, humanistic or patient-reported outcomes (PROs) include a wide range of health-related concepts or constructs. According to the US Food and Drug Administration (2009), a PRO is "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else." PROs are on a continuum from the purely

symptomatic (e.g., pain intensity) to more complex aspects of functioning (e.g., ability to perform activities of daily living) to much more complex concepts (e.g., quality of life). Since many cancer prevention activities are aimed at populations rather than individual patients, the term PRO in the context of this chapter may seem too narrow; however, the intent is to convey the importance of capturing individual's health and healthcare perceptions and experiences through self-report. The PRO that has increasingly garnered the most attention, particularly in regard to drug therapy (Willke et al. 2004; European Medicines Agency 2005), is health-related quality of life or health-related functioning and well-being, which will be a primary focus of this section.

Quality of life is a commonly used term that usually conveys a general feeling rather than a specific state of mind. A person's quality of life, or subjective well-being, is based on personal experience and expectations that affect and can be influenced by many factors, including standard of living, family life, friendships, and job satisfaction (Sirgy et al. 2006). Although health can impact these factors, health care is not directly aimed at enhancing them. Studies of health outcomes use the term *health-related quality of life* to distinguish health effects from the effects of other important personal and environmental factors. There is growing awareness that in certain diseases, such as cancer, or at particular stages of disease, health-related quality of life may be the most important health outcome to consider in assessing the effect of interventions (Staquet et al. 1992).

In much of the empirical literature, explicit definitions of health-related quality of life are rare; readers must deduce its implicit definition from the manner in which its measurement is operationalized. However, some authors have provided definitions. For example, Revicki and colleagues define health-related quality of life as "the subjective assessment of the impact of a disease and treatment across physical, psychological, social, and somatic domains of functioning and well-being" (Revicki et al. 2000). Ferrans (2005) has provided a useful overview of various definitions and conceptual models of health-related quality of life. Definitions may differ in certain respects, but an important conceptual characteristic they share is multidimensionality. Essential dimensions of health-related quality of life include:

- Physical health and functioning
- Psychological health and functioning
- Social and role functioning

In addition, disease- and/or treatment-related symptomatology (e.g., pain), general well-being, and spiritual well-being are sometimes assessed. The latter is more likely to be included in measures developed for conditions that have the potential to impact not only quality of life but length of life as well (e.g., cancer). For example, the four-dimensional model that provides the framework for the cancer-related quality of life questionnaires developed at the City of Hope National Medical Center includes spiritual well-being along with physical, psychological, and social well-being (Grant et al. 2004).

2.4 Measuring Humanistic Outcomes

Although PROs such as health-related quality of life are subjective, they can be quantified (i.e., measured) in a uniform and meaningful way. The quality of the data collection tool is the major determinant of the quality of the results. Psychometrics refers to the measurement of psychological constructs, such as intelligence, attitudes, and well-being. It is a field of study concerned with the proper development and testing of assessment tools (e.g., questionnaires) so that confidence can be placed in the measurements obtained. Two of the most commonly assessed psychometric properties are reliability and validity. Briefly, reliability refers to the consistency, stability, or reproducibility of scores obtained on a measure; validity reflects whether the instrument actually measures what it is purported to be measuring. More thorough discussions of these properties are provided elsewhere (Cappelleri et al. 2014; Streiner et al. 2015). Anyone planning to use PRO measures in cancer prevention research or clinical practice should confirm that there is adequate evidence to support the reliability and validity of the measures chosen.

There are hundreds of PRO instruments currently available (Bowling 1997; McDowell 2006), some of which have been developed for use in people with cancer (Bowling 2001; Donaldson 2004) or for individuals undergoing cancer screening (Mandelblatt and Selby 2005). The Psychosocial Effects of Abnormal Pap Smears Questionnaire (PEAPS-Q) (Bennetts et al. 1995) and the Psychosocial Consequences Questionnaire for abnormal screening mammography (PCQ-DK33) (Broderson et al. 2007) are examples of PRO measures specifically developed for cancer-related clinical preventive screening services. However, the vast majority of available PRO measures were developed for use in people already experiencing disease and/or disability. The value of these measures in the context of cancer prevention is that they provide quantitative evidence of the losses in functioning and well-being that may be avoided by effective prevention strategies. A primary distinction among PRO instruments, particularly measures of health-related functioning and well-being, is whether they are specific or generic.

2.5 Cancer-Specific Measures

The pioneering work of Karnofsky and Burchenal in the 1940s that produced the Karnofsky Performance Scale recognized the need to assess the patient's functional status in the context of cancer chemotherapy (Karnofsky and Burchenal 1949). This tool, which was designed for clinician assessment of observable physical functioning, is still used today. It was one of the first steps in the development of patient-centered and, ultimately, patient-reported outcome measures. Since then, a considerable amount of time and effort has been invested in the development of cancer-specific instruments for use in clinical trials and routine patient monitoring. Another of these instruments is the Q-TWiST (Quality-Adjusted Time Without Symptoms and Toxicity), which

Table 2.1 Domains/dimensions addressed by the FACT-G and EORTC QLQ-C30

EORTC QLQ-C30[a]	FACT-G[b]
Physical functioning	Physical well-being
Role functioning	Social/family well-being
Cognitive functioning	Emotional well-being
Emotional functioning	Functional well-being
Social functioning	
Fatigue	
Global quality of life	
Nausea and vomiting	
Pain	

[a]European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30
[b]Functional Assessment of Cancer Therapy-General

addressed both quality and quantity of time following cancer treatment (Gelber et al. 1993). Other examples are the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) (Aaronson et al. 1993) and the Functional Assessment of Cancer Therapy-General (FACT-G) (Cella et al. 1993). The EORTC has worked extensively in the area of instrument development (www.eortc.be/home/qol). In addition, the developers of the FACT-G have a broad array of cancer-specific instruments available (www.facit.org). Table 2.1 lists the dimensions covered by the EORTC QLQ-C30 and the FACT-G. Each of these instruments was designed to be supplemented with additional modules or scales aimed at specific cancer patient subgroups.

Cancer-specific instruments such as these are intended to provide greater detail concerning particular outcomes, in terms of functioning and well-being, uniquely associated with a condition and/or interventions to treat or prevent it. Disease- or condition-specific instruments may be more sensitive than a generic measure to particular changes in self-reported function and well-being secondary to the disease or its treatment. For example, the FACT subscales, such as the neurotoxicity subscale (FACT-NTX), address specific concerns (e.g., finger numbness, difficulty buttoning), which would not be addressed in a generic instrument. In addition, specific measures may appear to be more clinically relevant to patients and healthcare providers since the instruments address issues directly related to the disease (Guyatt et al. 1993). However, a concern regarding the use of only specific instruments is that by focusing on the specific impact of a disease or its treatment, the general or overall impact on functioning and well-being may be overlooked. Therefore, the use of both a generic and a specific instrument may be the best approach. This was the approach taken by the developers of the UCLA Prostate Cancer Index, which covers both general and disease-specific (e.g., sexual, urinary, and bowel function) concerns (Litwin et al. 1998).

2.6 Generic or General Measures

Since primary cancer prevention involves avoiding the occurrence of disease, general measures may be more applicable in that context. Generic, or general, instruments are designed to be applicable across a wide variety of populations, across all diseases or conditions, and across different medical interventions (Patrick and Deyo 1989). The two main types of generic instruments are health profiles and preference-based measures.

2.6.1 Health Profiles

Health profiles provide multiple outcome scores representing individual dimensions of health status or health-related quality of life. An advantage of a health profile is that it enables clinicians and/or researchers to measure the differential effects of a disease state or its treatment on particular dimensions. A very commonly used generic instrument is the 36-Item Short Form Health Survey (SF-36) (www.sf36.org). The SF-36 includes eight multi-item scales (Table 2.2) which address a wide array of dimensions (Ware and Sherbourne 1992). Each of the scale scores can range from 0 to 100, with higher scores representing better functioning or well-being. It is brief (it takes about 10 min to complete) and its reliability and validity have been documented in many clinical situations and disease states (Ware 2000). A means of aggregating the items into physical (PCS) and mental component summary (MCS) scores is available (Ware et al. 1994). However, the SF-36 does not provide an overall summary or index score, which distinguishes it from the preference-based measures.

2.6.2 Preference-Based Measures

For health-related quality of life scores to be most useful as an outcome in economic analysis, they need to be on a scale anchored by 0.0 (i.e., death) and 1.0 (i.e., perfect health). The values for the health states represented on the scale reflect the relative desirability or preference level for individual health states as judged by population- or patient-based samples. Although one can undertake direct preference measurement, a number of preference-based instruments are already available for which the health state preferences have been derived empirically through population studies. Examples include the Health Utilities Index (HUI) (www.healthutilities.com), the EuroQol Group's EQ-5D (www.euroqol.org), and the SF-6D (www.sheffield.ac.uk/scharr/sections/heds/mvh/sf-6d). The SF-6D was developed to provide a preference-based overall summary or index score for data collected with the SF-36 (Brazier et al. 2002). The domains addressed by each of these instruments are listed in Table 2.2.

Table 2.2 Domains included in selected generic instruments

36-Item Short Form Health Survey (SF-36)	
Physical functioning	
Role limitations due to physical problems	
Bodily pain	
General health perceptions	
Vitality	
Social functioning	
Role limitations due to emotional problems	
Mental health	
Health Utilities Index (HUI)	
HUI2	*HUI3*
Sensation	Vision
Mobility	Hearing
Emotion	Speech
Cognition	Ambulation
Self-care	Dexterity
Pain	Emotion
Fertility	Cognition and pain
EQ-5D	
Mobility	
Self-care	
Usual activity	
Pain/discomfort	
Anxiety/depression	
SF-6D	
Physical functioning	
Role limitation	
Social functioning	
Mental health	
Bodily pain	
Vitality	

2.6.3 Quality-Adjusted Life Years (QALYs)

The preference-based instruments described above are administered to assess respondents' self-reported health status, which is then mapped onto the instrument's multiattribute health status classification system producing a health-related quality of life score on the 0.0–1.0 scale. Scores on this scale, which may represent the health-related consequences of disease or its treatment, can be used to adjust the length of life for its quality resulting in an estimate of quality-adjusted life years (QALYs). QALYs integrate in a single-outcome measure the net health gains or losses, in terms of both quantity and quality of life. The metric of life years saved (LYS) is not sufficient since death is not the only outcome of concern; health-related quality-of-life changes can occur with or without changes in life years. The QALY approach assumes that 1 year in full health is scored 1.0 and death is 0.0. Years of

life in less than full health are scored as less than 1.0 QALY. For example, based on a review by Tengs and Wallace, a year of life with small-cell lung cancer after the disease has progressed is equal to 0.15 QALY (Tengs and Wallace 2000).

QALYs can be a key outcome measure, especially in diseases such as cancer, where the treatment itself can have a major impact on patient functioning and well-being. Although the QALY is the most commonly used health outcome summary measure, it is not the only one (Gold et al. 2002). Other conceptually equivalent outcomes include *years of healthy life* (YHL), *well years* (WYs), *health-adjusted person years* (HAPYs), and *health-adjusted life expectancy* (HALE). As observed by Ubel, without an outcome measure such as QALYs, it would be impossible to compare the relative cost-effectiveness of life-prolonging versus life-enhancing interventions, much less interventions that do both (Ubel 2001). The next chapter discusses how preference-based measures and QALYs are used to evaluate the cost-effectiveness of cancer prevention activities, services, and policies.

2.7 Reviews of Empirical Evidence

Cullen and colleagues, in their review of the short-term quality-of-life impact of cancer prevention and screening activities, addressed ways in which outcomes have been assessed through the use of new and existing measures (Cullen et al. 2004). Since many of the outcomes were exclusively psychological states (e.g., anxiety, relief) or symptoms, they cannot be considered assessments of health-related quality of life. Measures of health-related quality of life should include, at a minimum, the three essential dimensions (i.e., physical, psychological, and social) recognized as comprising it. Nevertheless, the review by Cullen and colleagues and another by Mandelblatt and Selby (2005) provide important insight into the research that has been conducted to assess the short-term patient-reported consequences of clinical preventive services such as chemoprevention, genetic testing and counseling, and screening. Knowledge of these consequences is critical in attempting to understand and act upon the factors that may affect participation in prevention-related activities.

Although it remains an empirical question, it appears that the predominantly transient negative consequences of participating in routine cancer prevention activities would be readily offset by the positive long-term outcomes (e.g., avoidance of quality-of-life losses resulting from future cancer-related morbidity). As asserted by Badia and Herdman (2001), preventive interventions are unlikely to lead to immediate gains in quality of life, but should prevent or delay reductions in quality of life over time. For example, the human papillomavirus (HPV) vaccines marketed in the US for primary prevention of invasive cervical cancer have a record of being safe and well tolerated (Einstein et al. 2009; Muñoz et al. 2009; Centers for Disease Control and Prevention 2018; Stillo et al. 2015), with the most common adverse events being brief and self-limiting occurrences of injection-site reactions, fever, headache, nausea, and vomiting. There is a very low risk of serious adverse reactions with HPV vaccines and accepting transient side effects is a worthwhile investment in prevention for the vast majority of those vaccinated. HPV vaccination along

with HPV-based screening has the potential to significantly decrease the incidence of invasive cervical cancer and the human and economic burden associated with it in the US (Campbell et al. 2012).

However, cancer prevention strategies that involve surgery (e.g., breast or ovary removal) for individuals at high cancer risk have the potential for more serious adverse outcomes. Currently, prophylactic mastectomy is the most common and effective surgical method to reduce the risk of breast cancer in high-risk women (Padamsee et al. 2017). The decision to undergo a prophylactic mastectomy requires careful consideration since the surgery itself can profoundly affect an individual's functioning and well-being.

The BREAST-Q is one example of a PRO measure that assesses the impact of breast surgery (as a preventive surgery) on health-related quality of life and patient satisfaction (Pusic et al. 2009). A systematic review that identified studies focusing on the assessment of quality of life among patients after bilateral prophylactic mastectomies concluded that most patients were satisfied and had positive quality of life after undergoing the surgery (Razdan et al. 2016). While some patients do report psychosocial, sexuality, femininity, and/or body image issues due to breast removal (Brandberg et al. 2008; Frost et al. 2011), most still had positive body image after the surgery. Patients who underwent prophylactic mastectomy with reconstruction reported higher satisfaction and quality of life than those who had the surgery without reconstruction.

Similar to reducing the risk of breast cancer, women may choose to have salpingo-oophorectomy to greatly reduce their risk of ovarian cancer (American Cancer Society 2016). Various generic PRO measures, such as the SF-36 and the symptom checklist created for the National Surgical Breast and Bowel Project, are used in research to evaluate this type of surgery (Fang et al. 2009); however, currently, there are no specific PRO measures that assess the impact of this type of surgical intervention on many of the humanistic outcomes of most importance to patients.

2.8 Conclusion

Although the ultimate success of cancer prevention strategies is judged by the number of cancer cases prevented, the assessment of more proximal outcomes can help enhance our understanding of the willingness of individuals to participate in them. Preventing cancer at some future date is a very worthwhile goal, but it is important to quantify the more immediate impact of cancer prevention services/activities in terms of the self-reported health and well-being of those who receive/undertake them. The purpose of this chapter was to review the types of measures that can be used to assess self-reported function, well-being, and other aspects of health-related quality of life. Much of the existing research in oncology has been conducted with patients who already have cancer, which has provided compelling evidence of the wisdom of preventing it. Some empirical evidence has emerged in the context of cancer prevention, but it is not enough. Many cancer prevention-related behaviors (e.g., wearing sunscreen, eating more fruits and vegetables) have little to no impact