

Review

Cancer Survivors in the United States: A Review of the Literature and a Call to Action

Manuel Valdivieso^{1,2✉}, Ann M. Kujawa², Tisha Jones³, Laurence H. Baker¹

1. Division of Hematology/Oncology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA.
2. Office of the Medical and Administrative Director, ProMedica Cancer Institute, Toledo, OH, USA.
3. Department of Research Grants and Contracts, ProMedica Cancer Institute, Toledo, OH, USA.

✉ Corresponding author: Manuel Valdivieso, M.D., M.S., C.P.E., Division of Hematology/ Oncology, Department of Internal Medicine, University of Michigan, 24 Frank Lloyd Wright, Ste. A3400, P.O. Box 483, Ann Arbor, Michigan 48106. Telephone: 734-998-7130; Fax: 734-998-7118; e-mail: manuelva@med.umich.edu

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Abstract

Background: The number of cancer survivors in the U.S. has increased from 3 million in 1971, when the National Cancer Act was enacted, to over 12 million today. Over 70% of children affected by cancer survive more than 10 years, and most are cured. Most cancer survivors are adults, with two-thirds of them 65 years of age or older and two-thirds alive at five years. The most common cancer diagnoses among survivors include breast, prostate and colorectal cancers. This review was conducted to better appreciate the challenges associated with cancer survivors and the opportunities healthcare providers have in making a difference for these patients.

Methods: Comprehensive review of literature based on PubMed searches on topics related to cancer survivorship, and associated physical, cognitive, socio-economic, sexual/behavioral and legal issues.

Results: At least 50% of cancer survivors suffer from late treatment-related side effects, often including physical, psychosocial, cognitive and sexual abnormalities, as well as concerns regarding recurrence and/or the development of new malignancies. Many are chronic in nature and some are severe and even life-threatening. Survivors also face issues involving lack of appropriate health maintenance counseling, increased unemployment rate and workplace discrimination.

Conclusions: Advances in the diagnosis and treatment of cancer will lead to more survivors and better quality of life. However, tools to recognize potentially serious long-lasting side effects of cancer therapy earlier in order to treat and/or prevent them must be developed. It is incumbent upon our health care delivery systems to make meeting these patients' needs a priority.

Key words: Cancer survivorship, detection of treatment complications, side effects of therapy, secondary malignancies, socioeconomic/legal/healthcare policy issues.

Introduction

Cancer remains a major public health problem. The American Cancer Society projected over 1.5 million new cancer cases would be diagnosed in 2010, with an estimated over half a million deaths from this

disease [1]. It is estimated that the aging of America will contribute to a 45% increase in cancer incidence by 2030 [2]. Cancer continues as the second most common cause of death (22.8%) following heart dis-

eases (26.6%) [3]. The comparison of new diagnoses and mortality from cancer in 1971, when the National Cancer Act was enacted as a U.S. federal law, and 2010 indicates that although the number of cancer diagnoses increased, the mortality proportion over those years declined (Table 1). This accounts for the increase in cancer survivors from 3 million in 1971 to nearly 12 million in 2007 [4]. Of those, it is estimated that 328,652 are survivors of childhood cancer [5].

Table 1. Cancer in the U.S.^a

	1971	2010
New Diagnosis	563,000	1,529,560
Deaths	335,000	569,490
Percent Mortality	53	37
Survivors (millions)	3	12

^aAmerican Cancer Society comparison.

The expected survivorship from cancer in the U.S. is summarized in Table 2. Almost 80% of children and 60% of adult cancer patients are expected to survive at least five years from diagnosis and many of them are, in fact, cured from cancer. As expected, most cancer survivors are adults 65 years of age or older.

Table 2. Survival Information from the National Cancer Institute and Centers for Disease Control and Prevention.

* 79% of childhood cancer survivors will be living five years after diagnosis and nearly 75% will be living 10 years following diagnosis.

* 64% of adults whose cancer is diagnosed today can expect to be alive in five years.

* 61% of cancer survivors are age 65 and older.

* An estimated one of every six persons over the age of 65 is a cancer survivor.

* Breast cancer survivors make up the largest group of cancer survivors (22%) followed by prostate cancer survivors (17%) and colorectal cancer survivors (11%).

The most common diagnoses include breast, prostate and colorectal cancers [6]. Similar trends have been reported from other countries but with appreciable regional differences. In a study of three common and one less common cancers (breast, colorectal, lung and ovary) in Australia, Canada, Denmark, Norway, Sweden and the United Kingdom, the survival of patients improved between 1995 and 2007, though survival was consistently higher in Australia, Canada, Sweden, intermediate in Norway, and lower in Denmark, England, Northern Ireland and Wales

[7]. The majority of cancer survivors have been treated with aggressive medical, radiation and surgical therapies administered either at a time when a patient's organs were still developing, leading to complications later in life, or when the patient was already suffering from underlying degenerative processes where the side effects of therapy represent insult over injury. As a result, long-term follow-up of cancer survivors reveals significant concern for cancer recurrence or development of a new primary cancers, as well as physical, cognitive, socioeconomic, sexual and legal issues. This review highlights some of these problems and brings to the attention of healthcare institutions, medical providers, health policy makers and society in general the urgent need to address these issues.

Chronic and Late-Effect Health Conditions in Adult Survivors of Childhood Cancer

The treatment of childhood cancer has been associated with risk for developing several chronic conditions that appear later in life, including physical, psychological, cognitive abnormalities - some of which are severe and debilitating. In addition, survivors from childhood cancer are at risk for developing secondary malignancies [8].

The frequency and severity of post-cancer-treatment chronic conditions have been reviewed by Oeffinger et al. [9]. Among participants of the Childhood Cancer Survivor Study cohort, comparative data were reported on the experiences of 10,397 survivors and of 3,034 siblings. A chronic condition was more common among survivors than their siblings (62.3% vs. 36.8%, respectively). Chronic sequelae of treatments was frequently multiple. Among patients with three or more chronic conditions, they were more common among survivors than in their siblings (23.8% vs. 5.4%, respectively). The cumulative incidence of chronic conditions increased with time; 66.8% at 25 years and 73.4% at 30 years.

The severity of post-treatment chronic conditions varies substantially, but could be severe and even life threatening. Serious conditions were also more common among survivors than in their siblings (27.5% vs. 5.2%) and were usually associated with chemo-radiation regimens and/or with those containing Doxorubicin and alkylating agents. The relative risk of the five most common serious conditions were major joint replacement at 54.0; congestive heart failure at 15.1; secondary malignant neoplasm at 14.8; severe cognitive dysfunction at 10.5; and coronary artery disease at 10.4.

Cognitive impairment is associated with brain irradiation and can impact academic achievement. The most common cognitive late-effect of moder-

ate-to-high dose whole brain radiation is diminished intellectual capacity [10]. Central nervous system (CNS) and acute lymphoblastic leukemia (ALL) survivors are at risk for educational deficits [11]. The Children's Cancer Group investigated the impact of treatment on scholastic performance of 593 adult survivors of ALL in comparison with 409 sibling controls [11]. Survivors treated with 24 Gy of cranial irradiation were more likely to enter special education or learning disability programs. Survivors were as likely to finish high school and enter college as controls, but those treated with 24 Gy or treated before the age of six years were less likely to enter college.

Significant psychosocial distress has been reported in survivors of childhood sarcoma treated with combined modality therapy [13]. The majority, 77%, had abnormalities in the Brief Symptom Inventory test that demonstrates severity scores for nine psychiatric symptoms. Twelve percent of patients met diagnostic criteria for Post-traumatic Stress Disorder. Psychological distress usually consisted of intrusive thoughts, avoidant behaviors and health well-being concerns.

Adult Cancer Survivors: Cardiac and Pulmonary Late-Effects

The late cardiac and pulmonary effects of therapy on cancer survivors have recently been reviewed [14]. The estimated aggregate incidence of radiation-induced cardiac disease is 10% - 30%, occurring 5 to 10 years from treatment. Radiation pneumonitis is reported in 5% - 15% of lung cancer patients, with a smaller percent developing progressive pulmonary fibrosis. However, in patients with severe underlying chronic obstructive pulmonary disease before radiation therapy or chemoradiation therapy the outcomes are substantially worse.

Valdivieso et al. reported an increase in pulmonary and infection morbidity during induction chemoradiation therapy, including mitomycin C, etoposide and cisplatin, in 43 patients with stage IIIB non-small cell lung cancer compared to a group of 41 stage IV non-small cell lung cancer patients receiving the same chemotherapy but without chest irradiation. The frequency of these complications was greater according to the pre-treatment severity of underlying small airway disease measured by forced expiratory flow (FEF₂₅₋₇₅). In the group who received chemoradiation therapy, there were 14/24, 4/8 and 0/11 episodes of pneumonia in patients with severe, moderate or normal FEF₂₅₋₇₅, respectively (p 0.005) [15]. Brooks et al. also reported on the increase in pulmonary toxicity of 80 small cell lung cancer patients receiving combined chemoradiation versus chemotherapy

alone for limited disease (p 0.017). Bilateral pulmonary infiltrates beyond the radiation therapy port were found in 28% of patients compared to 5% in those receiving chemotherapy alone. Eight of 13 patients died from pulmonary complications with no clinical evidence of tumor in five. Pretreatment pulmonary function tests (PFT) revealed a significantly lower forced vital capacity (FVC) (p 0.03) and forced expiratory volume in 1 second (FEV-1) (p 0.04) in patients with subsequent pulmonary complications [16].

Theuws reported results of pulmonary function evaluations of 69 breast cancer patients and 41 lymphoma patients before and after radiation therapy alone or combined with chemotherapy, including combinations of mechlorethamine, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, vinblastine, cyclophosphamide, epidoxorubicin, fluorouracil, thiotepa, carboplatin and methotrexate. After an initial reduction in PFTs at 3 months, significant recovery took place at 18 months for all patients. Thereafter, no further improvement could be documented [17]. Thus, pretreatment pulmonary abnormalities have a significant impact on the pulmonary complications from radiation therapy as they could be mild and transient or more severe and long lasting.

Because of the increased risk associated with cancer treatment administered at a young age, adult survivors of pediatric cancer who received mediastinal radiation (most commonly patients with Hodgkin's disease) have a reported increase in the incidence of coronary artery disease, fatal myocardial infarction and other cardiac complications. Hodgkin's disease patients receiving mediastinal radiation have up to a 7.2 higher risk for fatal cardiovascular events than age and sex matched general population controls [18-20].

Doxorubicin-induced cardiomyopathy is the most frequent and most studied chemotherapy-induced cardiotoxicity. The risk of developing cardiotoxicity is mainly related to the cumulative dose of doxorubicin (1% to 5% up to 550 mg/M², 30% at 600 mg/M², and 50% at 1 g/M² with individual variation) [21]. Other anthracyclines are also cardiotoxic. Cardiac abnormalities are likely to be observed in survivors from childhood cancer and in adults undergoing long-term follow-up. A higher risk population is described as those in the extremes of age, higher cumulative dose, mediastinal radiation and female sex. An overall 9% incidence of doxorubicin-related cardiac abnormalities in asymptomatic survivors that required treatment and close follow-up has been reported [22]. An abnormality of systolic function (abnormal wall stress, hypertrophy, contractility) was reported in 65 (43%) of 151 patients.

The cardiotoxicity of breast cancer therapy among survivors has recently been reviewed [23]. Patients with doxorubicin-induced congestive heart failure (CHF) had an 87% improvement with cardiac medications; combined treatment with β -blockers and ACE inhibitors seemed superior to ACE inhibitors alone [24]. These results contrast with retrospective reviews that reported mortality rates of 43% to 59% in similar patients [25].

Epirubicin appears less cardiotoxic than doxorubicin at equimolar doses, due to a lower level of secondary alcohol metabolites produced from epirubicin [26]. Cumulative epirubicin doses of >950 mg/m² are associated with an exponential increase in CHF risk [27]. Little cardiotoxicity was observed with a cumulative epirubicin dose of 300 mg/m² [28].

Dexrazone is the sole cardioprotective agent proved to decrease anthracycline-induced cardiomyopathy. However, some suggest that it may interfere with anthracycline chemotherapy because anthracyclines enhance DNA cleavage by topoisomerase II, but the closed ring form of dexrazone stabilizes DNA-topoisomerase II complexes [29].

Taxanes, particularly paclitaxel, have shown evidence of cardiotoxicity. In contrast to previous reports, a large database has shown that only 0.1% of patients have serious bradycardia and could not confirm that taxanes increased the frequency of ventricular tachycardia or myocardial infarction [30]. Taxanes interfere with the metabolism and excretion of anthracyclines and potentiate anthracycline-induced cardiotoxicity, especially at high cumulative anthracycline doses. When combined with paclitaxel, the cumulative doxorubicin dose should not exceed 360 mg/m², and doxorubicin should be given before paclitaxel [31]. Combination treatments with epirubicin and taxanes may be less cardiotoxic. A cumulative epirubicin dose limit of 990 mg/m² in combination treatments with paclitaxel has been proposed [32].

Recently, interest regarding the potential cardiac toxicity of trastuzumab has developed. Trastuzumab is a humanized monoclonal antibody that binds to the extracellular portion of the receptor HER2, a product of the HER2/neu gene. Although the exact mechanism of cardiotoxicity of trastuzumab is unknown, HER2 is required for cardiac development. Single agent trastuzumab is toxic to rat myocytes *in-vitro* because it induces activation of the mitochondrial apoptosis pathway and the caspase cascade. Neuroregulin, a cardiac stress peptide, may have a role in this problem [33]. The cardiotoxicity of trastuzumab has been recognized when given in combination with doxorubicin (A) and cyclophosphamide (C). The combination produces a 16% incidence of NYHA

(New York Heart Association) classes III and IV relative to 3% with AC alone. Trastuzumab-related cardiac dysfunction differs from anthracycline-induced myocardial damage in that it rarely causes death, is not dose related, and, in most instances, is reversible with improvement in cardiac function when the drug is discontinued and/or the patient is treated with cardiac medications.

Detection and Monitoring for Cardiac Toxicity

The present detection of cardiac abnormalities in asymptomatic patients is suboptimal. Left ventricular ejection fraction (LVEF) is the most widely used measure in the monitoring of cardiac toxicity. Patients with a healthy LVEF might experience subclinical changes, such as diastolic dysfunction, therefore, underestimating possible cardiac damage. Echocardiography and multiple gated acquisition (MUGA) scintigraphy are the gold standard to measure LVEF. Echocardiography, however, provides more information about the structure and function of the heart, including assessment of diastolic dysfunction and, thus, offers greater potential for the monitoring of cardiac function during and after cancer treatment. Several biomarkers, such as troponins and natriuretic peptides, have shown promising results and they should be studied prospectively and in conjunction with echocardiography to detect subclinical signs of cardiac dysfunction [34].

There is growing evidence of the importance for measuring global cardiac strain by Doppler imaging technology to identify heart damage in asymptomatic patients and in patients where standard echocardiogram is normal. Promising results using this technique have been reported in patients with silent coronary ischemia, ventricular failure, wall motion abnormalities, amyloidosis [35-38] and cancer chemotherapy [39]. Sawaya and coworkers reported a decrease in longitudinal strain measured by echocardiography in 43 patients at 3 months predicted cardiotoxicity of anthracycline and trastuzumab treatment ($p = 0.01$) before any other test measuring LVEF. In addition, troponin 1 also significantly predicted cardiotoxicity at 6 months ($p = 0.006$) [40].

Subsequent Neoplasms in Cancer Survivors

One of the most serious complications of cancer and its therapy is the development of additional malignancies (Table 3). The reported incidence of second malignancies in cancer survivors varies considerably, but according to the NCI Surveillance, Epidemiology,

and End Results (SEER) Program, they account for 16% of all cancers [41]. The development of these malignancies can be attributed to a number of factors, including prior chemotherapy and/or radiation therapy, lifestyle choices, the genetics of the individual, environmental exposures and their interactions. Second cancers and beyond have been well described in survivors of childhood and adult-onset cancers, particularly in patients with Hodgkin's disease, as well as in patients with a history of prior cancer of the breast, prostate, testis, lung and cervix [42]. In general, the most commonly occurring second malignancies in adults are represented by the most common cancers overall (i.e., breast, prostate, lung and colorectal), although leukemia has also been described [43-52].

Among children, Meadows et al reported on a long-term follow up of 14,358 childhood cancer survivors that were part of the Childhood Cancer Survivor Study Cohort [53]. At 30 years, the cumulative incidence of secondary malignant neoplasms was 9.3%, and that of non-melanoma skin cancer was 6.9%. By multivariate analysis, greater risk was described for those receiving radiation therapy, older age at diagnosis, female sex, family history of cancer and primary childhood cancer. Female survivors from Hodgkin's disease or sarcoma and those who received radiation therapy were at increased risk. Compared to the general population, the largest risk excesses were

found for breast cancer, bone cancers and thyroid cancers.

Over the years, greater emphasis has been placed on long-term surveillance of patients with Hodgkin's disease. It has been recognized since the 1970's that these patients are at greater risk for second malignancies because of the type of chemotherapy, radiation therapy or combination therapy administered to them. Among 18,862 5-year survivors from Hodgkin's disease, Hodgson reported a 30-year cumulative risk for second malignancies of 18% and 26% for men and women respectively [54]. Metayer et al. described 195 second cancers among 5,925 patients with Hodgkin's disease who were diagnosed before the age of 21 years in the US, Europe and Canada. Eighty-one percent of second cancers were solid tumors from different sites that occurred at an average of 16 years after diagnosis of Hodgkin's disease. Twenty-year survivors experienced significantly increased risks of cancers of the female breast, thyroid, digestive tract, lung, uterine cervix, bone and connective tissue [55]. A British study of 5,519 patients identified 322 second malignancies among Hodgkin's disease patients treated between 1963 and 1993. They found a significant increase in relative risk for gastrointestinal, lung, breast, bone and soft tissue cancers and leukemia among younger patients at first treatment. Absolute excess risks and cumulative risks of solid tumors and leukemia were greater at older ages [56].

Table 3. Subsequent Malignancies among Cancer Survivors.

Author	No. Patients	Diagnosis	New Cancers
Ng & Travis [42]	1,319	Hodgkin's Disease	189 (14.3%)
Hodgson, et al. [54]	18,862	Hodgkin's disease	Men (18%) Women (26%)
Metayer, et al. [55]	5,925	Hodgkin's Disease	195 (3.2%)
Swerdlow, et al. [56]	5,519	Hodgkin's Disease	322 (5.8%)
Okines [48]	3,764	Malignant Lymphoma	68 (1.9%)
Heyne, et al. [59]	47	Small Cell Lung Cancer	14 (30%)
van der Gaast, et al. [45]	81	Small Cell lung cancer	5 (6.1%)
Takigawa, et al. [47]	90	Stage III Non-Small Cell Lung Cancer	7 (7.8%)
Raymond & Hogue [46]	332,014	Breast Cancer	4/19 (21%) long-term Survivors 40,068 (12%)
Kirova, et al. [50]	16,705	Breast Cancer	709 (4.2%)
Gianni, et al. [51]	1,035	Breast Cancer	55 (5.3%)
Travis, et al. [43]	40,576	Testicular cancer	2,285 (5.6%)
Stava, et al. [44]	968	Malignant Melanoma	111 (11.4%)
Fernebro, et al. [49]	818	Soft Tissue Sarcoma	113 (13.8%)
Chaturvedi, et al. [52]	85,109	Squamous Cell Ca. Cervix	10,559 (12.4%)
	10,280	Adenocarcinoma of Cervix	920 (8.9%)

Among patients with Hodgkin's disease, Ng reported on the risk of developing multiple malignancies in 1,319 survivors; 181 patients developed a second malignancy and 18 developed a third malignancy [57]. The median time between the second and the third malignancy was 34 months. Similar experiences have been described in survivors from childhood cancer and in adult cancer survivors who developed up to five subsequent malignancies [46, 58].

In a data base of consecutive small cell lung cancer patients entering clinical trials at MD Anderson Cancer Center, Heyne et al. reported the development of second cancers in fourteen of forty-seven (30%) survivors of two-years or more. Second cancers continued to develop during follow-up with an actuarial risk of 9.1%, 26.8% and 50% at 3, 5 and 8 years survival, respectively. The most common second cancers were non-small cell lung, with others being bladder, esophagus, breast, bone, rectum and multiple primaries. The study demonstrates that careful and long-term follow-up of small cell lung cancer survivors reveals a very high incidence of second malignancies [59]. The development of second malignancies in small and non-small cell lung cancers has been reported to be lower by others, in the range of 6.1% to 21% [45,47].

Matesich reported that adjuvant chemotherapy for breast cancer is not associated with an increased risk for development of other solid tumors beyond what is expected with normal aging. However, alkylating agents, such as cyclophosphamide and topoisomerase II inhibitors, are associated with two types of cytogenetically distinct leukemias. The risk of developing leukemia, however, is significantly lower than the survival benefit from adjuvant chemotherapy. Tamoxifen, on the other hand, is associated with a two- to threefold increase in the risk of developing endometrial cancer that is equivalent to approximately 80 excess cases per 10,000 treated women at 10 years [60].

Quality of Life in Survivors

Several studies have addressed quality of life issues in cancer survivors. Among young adults survivors of childhood cancer, Langeveld et al. reported that many survivors, except those with bone tumors, reported being in good health and that most were functioning well psychologically. It was also reported that survivors had lower rates of marriage and parenthood [11]. The same authors reported that, in a sample of 400 long-term survivors of childhood cancer, predictors of a diminished quality life included female gender, unemployment, severe late ef-

fects/health problems and low self-esteem. Additionally, it was found that female survivors had more cancer-specific concerns than males survivors [61]. Factors associated with serious psychological distress in long-term survivors of adult-onset cancer include age younger than 65 years, being unmarried or not living with a partner, having less than high school education, being uninsured, having co-morbidities, or having difficulty performing activities of daily living [62]. Among adult long-term survivors of breast, prostate, colorectal cancer and lymphoma (5-10 years post-diagnosis), older respondents expressed better quality of life ($p = 0.004$), mental health ($p < 0.001$), but worse physical health ($p = 0.04$) [63]. Physical functioning was worse among those reporting low income ($p = 0.02$) and co-morbidities ($p = 0.003$). The evaluation of the impact of cancer score demonstrated that higher positive scores were associated with better mental health ($p = 0.0004$) and better overall quality of life ($p = 0.005$).

Sexual disturbances are common among adult survivors and they are often not addressed. Physical abnormalities and low hormone levels resulting from gonadal injury from cancer therapy contribute to lower self-esteem, depression, less desire for sexual activity and lower libido. This is particularly significant for younger women undergoing breast cancer therapy and for those recovering from gynecologic malignancies [64-66].

In breast cancer patients, ovarian abnormalities from chemotherapy are related to a number of factors including the direct damage of ovarian follicles, the ovarian function at the time chemotherapy begins and the specific chemotherapeutic agent employed particularly alkylating agents such as cyclophosphamide [67]. Transient or permanent amenorrhea develops with associated symptoms of treatment induced ovarian suppression such as hot flashes and osteoporosis [68]. These abnormalities will also have a negative effect on fertility.

Even though most cancer patients suffer from some degree of sexual dysfunction, patients with gynecologic malignancies, much like men with treated prostate cancer, develop early reduction in sexual activity that for some could be permanent [66, 69-71]. In addition, gynecologic patients have been found to have higher levels of depressive symptoms than patients with breast, gastrointestinal and urologic cancer survivors [72].

Great progress has taken place in our knowledge of reproductive physiology to assure the existence of fertility preservation options for patients interested in having children after cancer therapy. These methods

include reducing the impact of chemotherapy on gonadal function, removing and preserving ovarian tissue before starting chemotherapy, sperm banking and methods designed to produce mature oocytes or fertilized embryos for use in the future [67]. Cancer treatment choices and age have been considered in the development of an algorithm to influence fertility preservation [73].

Sexual dysfunction abnormalities are frequent among cancer survivors regardless of gender and deserve close attention by care providers.

Counseling Health Behaviors among Cancer Survivors

It has been reported that cancer survivors receive less counseling by their primary care physicians on three important health behaviors: diet, exercise and smoking [74]. Utilizing the 2000 National Health Interview Survey, 1,600 cancer survivors and 24,636 adults without cancer or non-melanomatous skin cancer history (controls) were studied. Among cancer survivors, 96% were diagnosed after the age of 18, there was a slight predominance of women (56% vs. 44%) and the majority was Caucasian (82%). Few survivors reported having discussions with their health care providers related to diet (30% survivors vs. 23% controls; $p < .0001$), exercise (26% of survivors vs. 23% of controls; $p < .005$), or smoking cessation (42% of survivors vs. 41% of controls; $p = .41$). Survivors reporting discussion with their physicians on all three health behaviors were even less (10% of survivors and 9% of controls). Colorectal cancer survivors were less likely than controls of similar age range to report exercise recommendations (16% vs. 27%; $p < .003$) or smoking cessation (31% vs. 41%; $p < .05$), and cervical cancer survivors were more likely than controls of similar age range to have discussions regarding smoking (58% vs. 43%; $p < .001$). Thus, many providers are missing the opportunity to counsel their cancer survivors on modification of important health behaviors.

Survivors and Unemployment, Health Insurance and Legal Issues

Since the approval of the National Cancer Act of 1971, many changes have occurred, including a greater understanding of cancer and its biology, better methods for early detection, improved treatment outcomes and a larger number of cancer survivors in the U.S. The attitudes of patients and the public have also changed. Patients are less likely to be considered victims, their expectation of surviving is greater and so are their prospects with regard to employment,

health insurance and preservation of their human rights [75-76].

Many survivors are ready to maintain or seek employment, though there are concerns because of employer and co-worker misconceptions regarding their ability to successfully return to work after therapy. To address this issue, there are several federal and state laws in place to protect survivors from discrimination. These include the Americans with Disability Act (ADA), Federal Rehabilitation Act, Family and Medical Leave Act (FMLA) and Employment Retirement and Income Security Act (ERISA) [75]. There is also increasing concern among patients and their families regarding employer's discrimination based on genetic history. Several federal laws provide limited protection to cancer survivors: the Genetic Privacy Act, Genetic Privacy and Nondiscrimination Act, the ADA, and the Health Insurance Portability and Accountability Act. More than 30 states have genetic non-discrimination laws. The levels of protection provided by these laws vary considerably [75].

Survivors report problems with job discrimination and obtaining health and life insurance [11]. A meta-analysis and meta-regression study of 20,366 long-term cancer survivors, all with cancer diagnosis beyond the age of 18, has identified a higher percent of unemployment among cancer survivors than a healthy control population of 157,603, 33.8% vs. 15.2%, respectively [77]. Specifically, unemployment was higher among survivors from breast cancer, gastrointestinal cancers and cancers of the female reproductive tract. Overall, survivors in the U.S. were 1.5 times more likely to be unemployed than their counterparts in Europe. Given the present poor status of our economy, it is likely that this figure will increase.

Park et al. studied the prevalence and predictors of health insurance coverage in 12,358 5-year survivors of childhood cancer and 3,553 sibling controls participating in the Childhood Cancer Survivor Study [78]. Health insurance coverage was reported by 83.9% of adult survivors and 88.3% of siblings. Twenty-nine percent of survivors reported difficulty obtaining health insurance coverage, compared to 3% of siblings ($p < .01$). Additionally, survivors were more likely to report exclusions or restrictions on their policies. Among survivors 18 years of age or older, factors associated with being uninsured included being diagnosed with cancer before the age of 15, male gender, lower level of attained education, income less than \$20,000, marital status, smoking status and treatment that included cranial radiation. Other factors include prior diagnosis of leukemia, second malignancy and recurrence of original cancer.

Clinical Research in Cancer Survivors

There is significant interest in the understanding of the many problems cancer survivors face as a result of their disease process and or their treatment. The Children's Oncology Group has pioneered the careful follow up of these patients resulting in carefully developed guidelines of care for survivors from childhood cancers and the study of some of their problems such as psychosocial, cognitive and academic achievement, and developmental issues. The guidelines of care for adults are more limited. Ongoing research in adults focuses on symptom control, sexual dysfunction, obesity-nutrition-exercise, prevention of recurrence and of second malignancies. Examples of these studies by the SWOG cancer research cooperative group, for instance, include: a. A feasibility study of physical activity and dietary change weight loss intervention in breast and colorectal cancer survivors; b. A Phase IIb randomized controlled biomarker modulation study of Vitamin D in premenopausal women at high risk for breast cancer; c. A randomized placebo controlled trial of Omega-3-fatty acid for the control of Aromatase inhibitor induced musculoskeletal pain in women with early breast cancer; d. A randomized placebo-controlled trial of Acetyl L-Carnitine for the prevention of Taxane induced neuropathy and; e. Phase III trial of LHRH Analog administration during chemotherapy to reduce ovarian failure following chemotherapy in early stage hormone-receptor negative breast cancer. What is needed, however, are studies aimed at the early detection and treatment of organ toxicity by the use of new and promising technologies, such as those focusing in the cardiopulmonary system.

Conclusion

It is clear that surviving cancer today is associated with significant risk for cancer recurrence and/or the development of a new cancer plus physical, cognitive, social, legal and economic problems. Although it is anticipated that modern cancer therapies will alleviate some of these problems, they will not prevent worsening of already existing degenerative processes in adults, since it has been demonstrated that treatments hasten the development of future cardiac and pulmonary problems. Nor will they lessen the socioeconomic issues experienced by cancer survivors either. The interactions between the individual's genetics, prior cancer therapy, environment and lifestyle choices will continue. While the genetic underpinnings of these interactions are unknown today, they represent a fruitful source of research in the future.

Healthcare organizations, members of the medical profession and advocacy groups need to heighten public awareness of these patients' problems to assure that comprehensive programs are developed to attend to the many issues described here.

Prospective sets of guidelines of care and supportive services need to be established taking into account the needs of children, adolescents and adults. A comprehensive multidisciplinary program or clinic that includes pediatric and adult hematologists and medical oncologists, primary care and internal medicine physicians, as well as other medical and surgical specialists, social services, geneticists, legal and financial counselors, would be necessary to better understand and optimally assist these patients. The amount of physical and staff resources necessary for these types of efforts are beyond what most community settings or even academic cancer centers would be able to afford.

A good alternative to comprehensive multidisciplinary survivor clinics is the expanded oncology clinics, provided there is the appropriate physician and patient support systems to deliver cost-effective care under circumstances where most survivor programs generate limited revenue. Thus, oncology trained physician extenders and nurse clinicians could staff these clinics under the guidance of a physician interested in survivor issues. Together, they will implement survivorship guidelines into an overall survivor healthcare plan; they will refer patients to specialty clinics for specific problems requiring that type of expertise; and will work collaboratively with primary care physicians, or other home physicians, to assure patients get the appropriate health maintenance programs at home. Social services support will be required in these clinics. An excellent level of verbal and written communication among healthcare providers will be essential for these programs to succeed.

Cancer survivors need all members of the healthcare team to assist them in coping with many evolving challenges, and to live with dignity and respect. We learn from them after they conquer cancer and, as providers, we join them at a new level of team approach that is ever-inspiring.

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Conflict of Interest

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References

- American Cancer Society. Cancer Facts & Figures 2010. Atlanta: American Cancer Society. 2010.
- Smith BD, Smith GL, Hurria A, et al. Future of cancer incidence in the United States: burdens upon an aging, changing nation. *J Clin Oncol* 2009;27(17):2758-2765.
- Heron M. Deaths: Leading causes for 2006; National vital statistics reports Vol 58. Hyattsville, MD: National Center for Health Statistics; 2010.
- [Internet] Altekruse SF, Kosary CL, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2007; based on November 2009 SEER data submission, posted to the SEER web site, 2010. http://seer.cancer.gov/csr/1975_2007/.
- Mariotto AB, Rowland JH, Yabroff KR, et al. Long-term survivors of childhood cancers in the United States. *Cancer Epidemiol Biomarkers Prev* 2009;18(4):1033-1040.
- Centers for Disease Control and Prevention (CDC). Cancer survivorship--United States, 1971-2001. *MMWR Morb Mortal Wkly Rep* 2004;53(24):526-529.
- Coleman MP, Forman D, Bryant H, et al. and the ICBP Module 1 Working Group. *Lancet* 2011; 377 (9760): 127-138.
- Oeffinger KC, Hudson MM. Long-term complications following childhood and adolescent cancer: foundations for providing risk-based health care for survivors. *CA Cancer J Clin* 2004;54(4):208-236.
- Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med* 2006;355(15):1572-1582.
- Mulhern RK, Palmer SL. Neurocognitive late effects in pediatric cancer. *Curr Probl Cancer* 2003;27(4):177-197.
- Langeveld NE, Stam H, Grootenhuis MA, et al. Quality of life in young adult survivors of childhood cancer. *Support Care Cancer* 2002;10(8):579-600.
- Haupt R, Fears TR, Robison LL, et al. Educational attainment in long-term survivors of childhood acute lymphoblastic leukemia. *JAMA* 1994;272(18):1427-1432.
- Wiener L, Battles H, Bernstein D, et al. Persistent Psychological Distress in Long-Term Survivors of Pediatric Sarcoma: The Experience at a Single Institution. *Psychooncology*, 2006; 15 (10): 898-910.
- Carver JR, Shapiro CL, Ng A, et al. American Society of Clinical Oncology clinical evidence review on the ongoing care of adult cancer survivors: cardiac and pulmonary late effects. *J Clin Oncol* 2007;25(25):3991-4008.
- Valdivieso M, Kraut M, Lattin P, et al. Pulmonary functions tests predict for pulmonary toxicity in non-small cell lung cancer patients receiving chemotherapy and radiotherapy. *Proc AACR*. 1992; 33:226.
- Brooks BJ, Jr., Seifter EJ, Walsh TE, et al. Pulmonary toxicity with combined modality therapy for limited stage small-cell lung cancer. *J Clin Oncol* 1986;4(2):200-209.
- Theuvs JC, Muller SH, Seppenwoolde Y, et al. Effect of radiotherapy and chemotherapy on pulmonary function after treatment for breast cancer and lymphoma: A follow-up study. *J Clin Oncol* 1999;17(10):3091-3100.
- Hancock SL, Tucker MA, Hoppe RT. Factors affecting late mortality from heart disease after treatment of Hodgkin's disease. *JAMA* 1993;270(16):1949-1955.
- Lee CK, Aeppli D, Nierengarten ME. The need for long-term surveillance for patients treated with curative radiotherapy for Hodgkin's disease: University of Minnesota experience. *Int J Radiat Oncol Biol Phys* 2000;48(1):169-179.
- Mauch PM, Kalish LA, Marcus KC, et al. Long-term survival in Hodgkin's disease relative impact of mortality, second tumors, infection, and cardiovascular disease. *Cancer J Sci Am* 1995;1(1):33-42.
- Lipshultz SE, Lipsitz SR, Mone SM, et al. Female sex and drug dose as risk factors for late cardiotoxic effects of doxorubicin therapy for childhood cancer. *N Engl J Med* 1995;332(26):1738-1743.
- Pein F, Sakiroglu O, Dahan M, et al. Cardiac abnormalities 15 years and more after adriamycin therapy in 229 childhood survivors of a solid tumour at the Institut Gustave Roussy. *Br J Cancer* 2004;91(1):37-44.
- Bird BR, Swain SM. Cardiac toxicity in breast cancer survivors: review of potential cardiac problems. *Clin Cancer Res* 2008;14(1):14-24.
- Tallaj JA, Franco V, Rayburn BK, et al. Response of doxorubicin-induced cardiomyopathy to the current management strategy of heart failure. *J Heart Lung Transplant* 2005;24(12):2196-2201.
- Von Hoff DD, Layard MW, Basa P, et al. Risk factors for doxorubicin-induced congestive heart failure. *Ann Intern Med* 1979;91(5):710-717.
- Minotti G, Licata S, Saponiero A, et al. Anthracycline metabolism and toxicity in human myocardium: comparisons between doxorubicin, epirubicin, and a novel disaccharide analogue with a reduced level of formation and [4Fe-4S] reactivity of its secondary alcohol metabolite. *Chem Res Toxicol* 2000;13(12):1336-1341.
- Ryberg M, Nielsen D, Skovsgaard T, et al. Epirubicin cardiotoxicity: an analysis of 469 patients with metastatic breast cancer. *J Clin Oncol* 1998;16(11):3502-3508.
- Roche H, Fumoleau P, Spielmann M, et al. Five years analysis of PACS 01 trial: 6 cycles of FEC 100 vs 3 cycles of FEC 100 followed by 3 cycles of docetaxel (D) for the adjuvant treatment of node-positive breast cancer. *Breast Cancer Res Treat* 2004;88:S16-S16.
- Sehested M, Jensen PB. Mapping of DNA topoisomerase II poisons (etoposide, clerocidin) and catalytic inhibitors (aclerubicin, ICRF-187) to four distinct steps in the topoisomerase II catalytic cycle. *Biochem Pharmacol* 1996;51(7):879-886.
- Arbuck SG, Strauss H, Rowinsky E, et al. A reassessment of cardiac toxicity associated with Taxol. *J Natl Cancer Inst Monogr* 1993; (15):117-130.
- Giordano SH, Booser DJ, Murray JL, et al. A detailed evaluation of cardiac toxicity: a phase II study of doxorubicin and one- or three-hour-infusion paclitaxel in patients with metastatic breast cancer. *Clin Cancer Res* 2002;8(11):3360-3368.
- Gennari A, Salvadori B, Donati S, et al. Cardiotoxicity of epirubicin/paclitaxel-containing regimens: role of cardiac risk factors. *J Clin Oncol* 1999;17(11):3596-3602.
- Sawyer DB, Zuppinger C, Miller TA, et al. Modulation of anthracycline-induced myofibrillar disarray in rat ventricular myocytes by neuregulin-1beta and anti-erbB2: potential mechanism for trastuzumab-induced cardiotoxicity. *Circulation* 2002;105(13):1551-1554.
- Altena R, Perik PJ, van Veldhuisen DJ, et al. Cardiovascular toxicity caused by cancer treatment: strategies for early detection. *Lancet Oncol* 2009;10(4):391-399.

35. Lafitte S. Do we need new echocardiographic prognosticators for the management of heart failure patients? *J Am Coll Cardiol* 2009;54(7):625-627.
36. Cho GY, Marwick TH, Kim HS, et al. Global 2-dimensional strain as a new prognosticator in patients with heart failure. *J Am Coll Cardiol* 2009;54(7):618-624.
37. Koyama J, Falk RH. Prognostic significance of strain Doppler imaging in light-chain amyloidosis. *JACC Cardiovasc Imaging* 2010;3(4):333-342.
38. Marwick TH, Raman SV, Carro I, et al. Recent developments in heart failure imaging. *JACC Cardiovasc Imaging* 2010;3(4):429-439.
39. Jassal DS, Han SY, Hans C, et al. Utility of tissue Doppler and strain rate imaging in the early detection of trastuzumab and anthracycline mediated cardiomyopathy. *J Am Soc Echocardiogr* 2009;22(4):418-424.
40. Sawaya H, Sebag I, Plana JC, et al. Early Detection and Prediction of Cardiotoxicity in Chemotherapy-Treated Patients: An Echocardiographic and Biomarker Study. American Society of Echocardiography - 21st Annual Scientific Sessions; San Diego, California. 2010:AbstractP1-42.
41. [Internet] Reis L, Melbert D, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2004, National Cancer Institute. http://seer.cancer.gov/csr/1975_2004/.
42. Ng AK, Travis LB. Subsequent malignant neoplasms in cancer survivors. *Cancer J* 2008;14(6):429-434.
43. Travis LB, Fossa SD, Schonfeld SJ, et al. Second cancers among 40,576 testicular cancer patients: focus on long-term survivors. *J Natl Cancer Inst* 2005;97(18):1354-1365.
44. Stava C, Beck M, Weiss LT, et al. Health profiles of 996 melanoma survivors: the M. D. Anderson experience. *BMC Cancer* 2006;6:95.
45. van der Gaast A, Postmus PE, Burghouts J, et al. Long term survival of small cell lung cancer patients after chemotherapy. *Br J Cancer* 1993;67(4):822-824.
46. Raymond JS, Hogue CJ. Multiple primary tumours in women following breast cancer, 1973-2000. *Br J Cancer* 2006;94(11):1745-1750.
47. Takigawa N, Kiura K, Segawa Y, et al. Second primary cancer in survivors following concurrent chemoradiation for locally advanced non-small-cell lung cancer. *Br J Cancer* 2006;95(9):1142-1144.
48. Okines A, Thomson CS, Radstone CR, et al. Second primary malignancies after treatment for malignant lymphoma. *Br J Cancer* 2005;93(4):418-424.
49. Fernebro J, Bladstrom A, Rydholm A, et al. Increased risk of malignancies in a population-based study of 818 soft-tissue sarcoma patients. *Br J Cancer* 2006;95(8):986-990.
50. Kirova YM, De Rycke Y, Gambotti L, et al. Second malignancies after breast cancer: the impact of different treatment modalities. *Br J Cancer* 2008;98(5):870-874.
51. Gianni L, Gelber S, Ravaoli A, et al. Second non-breast primary cancer following adjuvant therapy for early breast cancer: a report from the International Breast Cancer Study Group. *Eur J Cancer* 2009;45(4):561-571.
52. Chaturvedi AK, Kleinerman RA, Hildesheim A, et al. Second cancers after squamous cell carcinoma and adenocarcinoma of the cervix. *J Clin Oncol* 2009;27(6):967-973.
53. Meadows AT, Friedman DL, Neglia JP, et al. Second Neoplasms in Survivors of Childhood Cancer: Findings From the Childhood Cancer Survivor Study Cohort. *J Clin Oncol* 2009; 27: 2356 - 2362.
54. Hodgson DC, Gilbert ES, Dores GM, et al. Long-term solid cancer risk among 5-year survivors of Hodgkin's lymphoma. *J Clin Oncol* 2007;25(12):1489-1497.
55. Metayer C, Lynch CF, Clarke EA, et al. Second cancers among long-term survivors of Hodgkin's disease diagnosed in childhood and adolescence. *J Clin Oncol* 2000;18(12):2435-2443.
56. Swerdlow AJ, Barber JA, Hudson GV, et al. Risk of second malignancy after Hodgkin's disease in a collaborative British cohort: the relation to age at treatment. *J Clin Oncol* 2000;18(3):498-509.
57. Ng AK, Bernardo MV, Weller E, et al. Second malignancy after Hodgkin disease treated with radiation therapy with or without chemotherapy: long-term risks and risk factors. *Blood* 2002;100(6):1989-1996.
58. Bhatia S, Yasui Y, Robison LL, et al. High risk of subsequent neoplasms continues with extended follow-up of childhood Hodgkin's disease: report from the Late Effects Study Group. *J Clin Oncol* 2003;21(23):4386-4394.
59. Heyne KH, Lippman SM, Lee JJ, et al. The incidence of second primary tumors in long-term survivors of small-cell lung cancer. *J Clin Oncol* 1992;10(10):1519-1524.
60. Matesich SM, Shapiro CL. Second cancers after breast cancer treatment. *Semin Oncol* 2003;30(6):740-748.
61. Langeveld NE, Grootenhuis MA, Voute PA, et al. Quality of life, self-esteem and worries in young adult survivors of childhood cancer. *Psychooncology* 2004;13(12):867-881.
62. Hoffman KE, McCarthy EP, Recklitis CJ, et al. Psychological distress in long-term survivors of adult-onset cancer: results from a national survey. *Arch Intern Med* 2009;169(14):1274-1281.
63. Zebrack BJ, Yi J, Petersen L, et al. The impact of cancer and quality of life for long-term survivors. *Psychooncology* 2008;17(9):891-900.
64. Partridge AH, Gelber S, Peppercorn J, et al. Web-based survey of fertility issues in young women with breast cancer. *J Clin Oncol* 2004; 22: 4174-4183.
65. Thewes B, Meiser B, Taylor A, et al. Fertility- and menopause-related information needs of younger women with a diagnosis of early breast cancer. *J Clin Oncol* 2005; 23: 5155-5165.
66. Carpenter KM, Andersen BL, Fowler JM, et al. Sexual self schema as a moderator of sexual and psychological outcomes for gynecologic cancer survivors. *Arch Sex Rehab* 2009; 38(5): 828-841.
67. Hickey M, Peate M, Saunders CM, et al. Breast cancer in young women and its impact on reproductive function. *Human Reproduction Update*; 2009; 15 (No 3): 323-339.
68. Sverrisdottir A, Fornander T, Jacobsson H, et al. Bone mineral density among premenopausal women with early breast cancer in a randomized trial of adjuvant endocrine therapy. *J Clin Oncol* 2004; 22: 3694-3699.
69. Bertero C. Altered sexual patterns after treatment for prostate cancer. *Cancer Practice* 2001; 9: 245-251.
70. Jenkins R, Schover LR, Fouladi RT, et al. Sexuality and health-related quality of life after prostate cancer in African-American and white men treated for localized disease. *Journal of Sex & Marital Therapy* 2004; 30: 79-93.
71. Gershenson DM, Miller AM, Champion VL, et al. Reproductive and sexual function after platinum-based chemotherapy in long-term ovarian germ cell tumor survivors: A Gynecologic Oncology Group study. *J Clin Oncol* 2007; 25: 2792-2797.
72. Parker PA, Baile WF, De Moor C, et al. Psychosocial and demographic predictors of quality of life in a large sample of cancer patients. *Psycho-Oncology* 2003; 12: 183-193.
73. Sonmezer M, Oktay K. Fertility preservation in young women undergoing breast cancer therapy. *Oncologist* 2006; 11: 422-434.
74. Sabatino SA, Coates RJ, Uhler RJ, et al. Provider counseling about health behaviors among cancer survivors in the United States. *J Clin Oncol* 2007;25(15):2100-2106.
75. Hoffman B. Cancer survivors at work: a generation of progress. *CA Cancer J Clin* 2005;55(5):271-280.

76. Jemal A, Clegg LX, Ward E, et al. Annual report to the nation on the status of cancer, 1975-2001, with a special feature regarding survival. *Cancer* 2004;101(1):3-27.
77. de Boer AG, Taskila T, Ojajarvi A, et al. Cancer survivors and unemployment: a meta-analysis and meta-regression. *JAMA* 2009;301(7):753-762.
78. Park ER, Li FP, Liu Y, et al. Health insurance coverage in survivors of childhood cancer: the Childhood Cancer Survivor Study. *J Clin Oncol* 2005;23(36):9187-9197.