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Review

Why and how to study the fate of cancer survivors: observations from the clinic and the research laboratory

P.A. Ganz*

Division of Cancer Prevention and Control Research, Jonsson Comprehensive Cancer Center, UCLA Schools of Medicine & Public Health, 650 Charles Young Drive South, Rm. A2-125 CHS, Los Angeles, CA 90095-6900, USA

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Abstract

This paper provides a rationale for the importance of studying health outcomes in cancer survivors, including their growing numbers, the need for detailed information on the short and long-term effects of treatment, and the interactions of cancer with other comorbid conditions. However, there are a number of challenges associated with this research. Identification and recruitment of cancer survivors is not always easy, and linking their current health status to details of medical treatment is important, but not always feasible. National surveys and databases are a potential source of information on survivors, but may not provide sufficient details for this type of research. Strategies need to be developed to plan for long-term outcome studies in cancer patients from the very beginning of treatment to obtain the most comprehensive data on the outcomes of survivors.

Keywords: Cancer survivors; Late effects; Registries; Childhood leukaemia

1. Introduction

Advances in the early diagnosis and effective treatment of cancer have led to increasing numbers of individuals who are either cured of their cancer or are living with it as a chronic disease [1–4]. Three decades ago when President Nixon declared a 'war on cancer' in the United States, long-term survival from cancer was seldom expected and patients were often not even told their diagnosis. Much has changed in the ensuing decades. Public figures have begun to reveal their diagnosis of cancer and the need for treatment; more recently, we have even had detailed reports in leading newspapers of how public figures have weighed the options for prostate cancer treatment. Open discussions of cancer diagnosis and treatment are closely linked to the more favourable expectations regarding cancer and its survivability. Importantly, these medical and social changes gave birth to the concept of a cancer survivor [5], and organisations focusing on the needs of concerns of survivors were established (e.g. the National Coalition for Cancer Survivorship (NCCS)). To demonstrate a scientific commitment to study of the special concerns of this patient population, in July 1996, the National Cancer Institute of the US established an Office of Cancer Survivorship, to shepherd and foster scientific research in this field. No doubt, the critical mass of cancer survivors in the US, along with their advocacy efforts, made this come about. With this background in mind, I will provide more justification for why we need to be doing research on health outcomes in cancer survivors, followed by some thoughts on how this type of research should be conducted.

2. Why should we study the fate of cancer survivors?

2.1. The example of childhood leukaemia

Some of the earliest achievements in cancer therapy were noted in the treatment of childhood leukaemia [6]. With the recognition of the central nervous system as a 'sanctuary' and site of first relapse after systemic chemotherapy, clinical investigators began to test treatment strategies, through clinical trials, that could prevent the

* Tel.: +1-310-206-1404; fax: +1-310-206-3566.
E-mail address: pganz@ucla.edu (P.A. Ganz).

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subsequent growth of occult metastases in the leptomeninges. The first approaches used cranial irradiation, which then had intrathecal therapy with methotrexate added to it. These therapies had a dramatic effect on the curability of this disease, and in subsequent decades, long-term relapse-free survival and cure were obtained. However, as these children matured and faced the intellectual challenges of school and work, many behavioural and cognitive deficits were noted. These problems were usually not subtle, although detailed neuropsychological testing often revealed a broader range of deficits. Radiological imaging studies of the brain were performed and these often detected structural changes in the brain thought to be related to the combined toxicities of the two treatment modalities.

Having now achieved a cure, the task for clinicians was to re-evaluate their treatment strategies for the prevention of central nervous relapse. Over a series of clinical trials, it was found that therapeutic efficacy could be maintained with reductions in the cranial radiation dose (or its elimination altogether) with more frequent use of intrathecal chemotherapy alone. There was greater awareness of the age-related susceptibility to central nervous system toxicity (especially in young children and infants), and new treatment strategies were refined to minimise late complications in these patients who were expected to have long-term survival. The treatment of childhood leukaemia has taught us about the clinical tension that exists between intensive curative treatments with higher survival rates versus increases in long-term toxicities that may be unknown until many years later (e.g. congestive heart failure, second malignancies) (for a review see Refs. [7,8]). Furthermore, we can see that it is only when there is a critical mass of long-term survivors that we recognise some of the late effects of treatment, and can then be motivated to modify our therapies to minimise or eliminate the risk of late complications.

2.2. Growing numbers of cancer survivors

In the US today, there are nearly 9 million cancer survivors [9]. Tables 1 and 2 provide current estimates of the prevalence of various cancer sites among these survivors, as well as the current age distribution of cancer survivors. As can be seen, the majority of US cancer survivors are aged 65 years or older. Prevalence estimates for Europe are not as easily available; however, there are several reports that compare the relative survival for various cancers in Europe emanating from the EUROCARE Study (see a Special Issue of the *European Journal of Cancer* [10]). Comparison of survival data from EUROCARE with data from the US suggests that survival rates are better in the US [6,11]. The relative distribution of cancer sites appears similar (e.g. with breast and prostate being the most common) between Europe and North America; however, prevalence data on survivors are currently not available from Europe.

Table 1
Cancer site distribution of US cancer survivors ($N = 9.6$ million) [9][a]

Site	Percentage of survivors
Female breast	22
Prostate	17
Colorectal	11
Gynaecological	10
Other genitourinary (bladder and testis)	7
Haematological (lymphoma, leukaemia)	7
Melanoma	6
Lung	4
Other	16

US, United States; SEER, Surveillance, Epidemiology and End Results.

[a] Prevalence proportions are based on nine US SEER registries and US prevalence counts were estimated by applying SEER prevalence proportions to US populations without adjustment for demographic differences other than age.

Table 2
Estimated number of persons alive in the US diagnosed with cancer in the last 25 years by current age ($N = 8.7$ million survivors) [9][a]

Age group (years)	Percentage of survivors
<19	1
20–39	5
40–64	33
65+	61

[a] US estimated prevalence counts were estimated by applying US populations to SEER 9 limited duration prevalence proportions. Populations from January 2000 were based on the average of the July 1999 and July 2000 population estimates from the US Bureau of Census.

For many individuals whose disease was diagnosed at a very early stage and treated with surgery alone, there may be few if any specific late effects apparent as a result of the cancer diagnosis and treatment. However, multimodal therapies are frequently used to achieve cure (e.g. in the treatments of breast cancer, colon cancer, lymphomas and gynaecological cancers), and there may be late consequences to these treatments. In addition, cancer survivors are often at risk for second malignancies, either related to the biology of the primary cancer (e.g. breast cancer and colorectal cancer) or secondary to treatments. While many cancer survivors have a very short period of primary treatment, i.e. 6–12 months, others may have their disease chronically controlled by medications (e.g. chronic leukaemias and indolent lymphomas). As the populations of North America and Europe continue to age, we will see expanding numbers of newly diagnosed cancer patients

and survivors. Their future needs must now be addressed by designing therapies that have high rates of cure, with a minimisation of the potential for long-term toxicities.

2.3. Late effects of treatments are not known

For most treatments, we have better information on the acute and intermediate effects of therapy, within the first 5 years of treatment, than we do about possible late effects. There are only limited data on serious late effects such as cardiac toxicity from anthracylines [12,13], and this has been primarily in children. Many normal tissues are vulnerable to acute injury from radiation and chemotherapy, and there are limited prospective cohort studies that adequately describe the late effects of these therapies [14]. For most patients, faced with the diagnosis of cancer, aggressive and intensive therapy will be acceptable because of its potential for cure. However, as we diagnose cancer even earlier, e.g. breast cancer, there may be decreasing absolute benefits from adjuvant therapies and late effects may outweigh the proposed benefits [15–17].

2.4. Choosing primary treatments

Having systematic information about the short-term as well as late effects of various cancer treatment strategies can be very important, since patients may have a preference for one set of outcomes or toxicities over another. For example, a man with an early-stage prostate cancer may wish to know about the different late effects of radiotherapy and surgery for prostate cancer [18–21]. His concerns about the late effects of radiation on the rectum and bladder may lead him to choose surgery. A woman with an early-stage breast cancer may be concerned about the late effects of doxorubicin, and so she chooses an alternative, equivalent adjuvant treatment regimen that does not contain doxorubicin. A young woman with Hodgkin's disease requires combination chemotherapy and selects a regimen that has a decreased likelihood of infertility. As these examples illustrate, when different treatment strategies have different late effects, but a similar efficacy, then this information may be useful in deciding upon the primary treatment strategy.

2.5. Morbidity and comorbidity interactions

As limited as our knowledge of late effects is, even less is known about the interaction of cancer treatments with underlying comorbid conditions [22]. Most clinical trials exclude patients with impaired renal or hepatic function, and thus it is difficult to predict both response and toxicity in patients who may have an underlying chronic condition. Late effects may be potentiated or lead to premature death in individuals with specific comorbid conditions [23]. Much more research is required to address this question [22].

2.6. Aging of the population and an increasing number of cancer cases

Perhaps the most significant factor influencing the need to develop more information on the fate of cancer survivors is the expanding population of elderly men and women who will be diagnosed with cancer during the next 50 years [24–29]. These demographic changes will make it even more critical for us to understand the interactions of primary therapies with underlying comorbid conditions, so that we can avert late toxicities in older cancer survivors. A new speciality of geriatric oncology is developing, and we can expect leadership from these clinicians and researchers. In the US, the National Cancer Institute and the National Institute on Aging have recently formed a partnership to fund geriatric programmes in US cancer centres that will begin to address this area as a research priority.

3. How can we study the outcomes in cancer survivors?

3.1. Challenges in the identification of cancer survivors

To study various health outcomes in cancer survivors, it is important to use a defined population for study to make accurate inferences about the effects of treatments on outcomes. We are fortunate that for cancer, unlike some other chronic diseases, there are often population-based cancer registries that track incident cases over time. These registries exist throughout the world, although their primary purpose is the tracking of incidence, survival and mortality trends. Only limited data on specific treatments are available in these registries, although accurate cancer staging is an important strength of cancer registries. In the US, the federally funded Surveillance, Epidemiology and End Results (SEER) programme has been used to identify cohorts of patients for study, with supplemental data being abstracted from medical charts and obtained from patient interviews [30–32].

Clinical treatment trial databases have also been used to recruit survivors for late-effects studies. The Childhood Cancer Survivor Study (CCSS) [33] in the US is an example of a large cohort study of childhood cancer survivors and their siblings who were all treated on clinical treatment trials. Medical records from the treatment of these children have been abstracted, including dosage of drugs and radiation treatments. Assembling this cohort was very expensive, but now that it has been established it is likely to provide substantial information about the late effects of specific treatments.

Finally, some research on cancer survivors has been conducted using a mixture of convenience samples recruited from the community as well as from local hospital tumour registries [34–36]. Using local hospital registries may have some bias, since the treatments and populations are specific to those institutions. Nevertheless, the cancer registry does provide accurate data on basic medical and demographic factors so that respondents can be compared with non-respondents.

In some institutions, there are specialised clinics that care for cancer survivors. While these clinical settings provide an opportunity to study self-selected survivors in more detail, the spectrum of problems or late effects that these survivors experience may not be representative of the general population as a whole. However, studies in these settings can certainly help in hypothesis-generating [37].

3.2. The problem of non-participant bias

In all of the described approaches to recruitment of survivors, non-participation of a substantial number of survivors can bias the assessment of outcomes. Results of late effects studies are most convincing when they are linked to treatment received as part of clinical trials, or when rates of a condition, such as leukaemia, can be compared with standardised rates in the population. Whenever possible, as cohorts are assembled, care should be taken to minimise non-response and to characterise any potential treatment or sociodemographic differences between responders and non-responders.

3.3. Survey information

Another possible source of data on cancer survivors is from various national health surveys [26,38]. To the extent that these surveys sample the general population of a country, outcomes for those individuals who self-identify as having a history of cancer can be compared with those who do not. While these types of data will not have the same precision as studies that use medical records or clinical trial data, they can provide some estimates of the comparative health status and functioning of cancer survivors.

3.4. Biomedical outcomes

One of our most pressing needs is to have detailed biomedical outcome data on long-term survivors of cancer. Having detailed information on cardiac, pulmonary and renal function many years after treatment is critical if we are to understand how frequently serious organ toxicities occur and who might be most susceptible. A limited number of studies have been done in the US due to the cost of medical testing in a setting in which universal health insurance is not available, and detection of an unsuspected medical problem could threaten the ability to retain or obtain new health insurance [39]. These kinds of studies would appear to be more feasible in countries with national health insurance programmes, and this is in fact the setting in which most research on biomedical endpoints has been done [40,41]. In addition to the late medical effects of treatment, there has been growing evidence of the risk for second malignancies among cancer survivors [42–49]. For this reason, developing a comprehensive picture of the type and incidence of late biomedical outcomes in cancer survivors is essential, including surveillance for second malignancies. Healthcare providers and survivors urgently need specific information on the potential for late medical effects of treatments. This type of information, when available, must be disseminated to the general medical community, as the majority of cancer survivors do not have ongoing contact with oncology specialists as they age and survive.

3.5. Many different cancer sites and treatments

A serious challenge to the research of survivors is the fact that there are more than 100 different types of cancer and, even within a cancer site, there can be considerable heterogeneity in treatments. Treatments may vary in intensity by stage or body location, and they vary over time as new drugs and treatment regimens become available. Thus, the problems facing children treated for leukaemia 20 years ago are not the same as for children treated today. For some rarer cancer sites, it may be hard to gather enough cases and survivors to make substantial conclusions about the late effects of treatment. However, for common cancers such as breast, colorectal, lung and prostate cancers, as well as other cancers with high cure rates (e.g. lymphoma and Hodgkin's, testicular cancer), sufficient numbers of survivors are available for rigorous study.

3.6. Evolving treatment strategies

Treatment for cancer is continuously evolving. Thus, it is difficult to know whether or not certain late effects will persist with treatment modifications and/or whether new and unanticipated late effects will result from the addition of new therapies or treatment administration schedules. In diseases where very high survival rates can be anticipated (e.g. early-stage breast cancer), the inclusion of additional health outcomes (e.g. cardiac or cognitive functioning), can provide very important information for future patients and survivors. For example, in some National Surgical Adjuvant Breast and Bowel Project (NSABP) trials, we have included prospective data collection on the development of amenorrhoea, arm dysfunction and oedema, as well as cardiac function. Obtaining more detailed data on non-cancer

causes of death is also an important consideration in patient populations where high survival rates are expected, as cancer treatments may contribute to other causes of death [50].

3.7. Best opportunities for research of cancer survivors

Some of the best opportunities for doing research may be in the linkage of data from cancer registries and administrative data from health registries. This is likely to be more feasible in countries with existing databases in the population (e.g. Nordic countries and Canadian provinces). In the US, there is linkage of data from the SEER cancer registry system and the national health insurance plan for the elderly (Medicare). The SEER-Medicare database [51] provides case identification of cancer cases from SEER, a nationally representative sample of cancer cases in the US, with insurance claim data from Medicare. While not perfect, this resource has been used to look at patterns of care and geographical variations in cancer care in the US. To date, it has not been used to examine the late effects of treatment, and it may be unsuitable for such purposes [52]. Other healthcare databases that may contain complete diagnoses or laboratory data may be more useful for the follow-up of large cohorts of survivors. If feasible, this type of monitoring system would be ideal.

4. Conclusions

In this brief review, I have provided a rationale for considering the late effects of cancer treatment. The growing numbers of cancer survivors demand our attention and we can no longer ignore their sub-clinical complaints or reports of more serious problems. In addition, it may be important for us to consider preventive interventions and surveillance in high-risk survivor groups, for organ toxicities or second malignancies. To the extent that we realise that our care of the cancer survivor does not end after completion of primary treatment, then we can begin to confront the possibility of some untoward effects as the cost of our success. Overall, these late effects are likely to be modest in their extent and severity but, without knowledge of their prevalence, it is hard to prepare the survivors and their healthcare providers as to how best to monitor them. As we accumulate this information, it will be critical to ensure that all members of the healthcare team (primary care physicians, nurses and oncology specialists) incorporate systematic assessment of late effects into their clinical practice. Cancer survivors should be informed about the kinds of treatments that they had and the potential late sequelae from treatments. In turn, clinicians need to review the patient's history and take responsibility for careful follow-up as part of good general medical care. In the ideal setting, specialised programmes at cancer centres might be established to monitor the late effects of cancer treatment, as well as provide care and advance our knowledge; however, funding for such programmes is likely to be limited. Therefore, the shared responsibility between survivor and primary care provider is likely to be the most practical solution to the surveillance needs of cancer survivors.

5. Summary of the article

- There are growing numbers of cancer survivors.
- The ageing of the population over the next few decades will expand the pool of survivors.
- Little is known about the late effects of cancer treatments.
- Challenges associated with research of survivorship are described.
- Strategies are suggested for follow-up and surveillance of survivors.

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