Physical and psychological well-being among long-term cancer survivors

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Publication date:
2007

Document Version
Publisher's PDF, also known as Version of record

Link to publication in Tilburg University Research Portal

Citation for published version (APA):
Mols, F. (2007). *Physical and psychological well-being among long-term cancer survivors*. Universal Press.

PHYSICAL AND PSYCHOLOGICAL WELL-BEING AMONG LONG-TERM CANCER SURVIVORS

FLOORTJE MOLS

Physical and psychological well-being among long-term cancer survivors

Floortje Mols

The research in this report was conducted at the Comprehensive Cancer Centre South, Eindhoven, The Netherlands.

Support for the publication of this thesis has been kindly provided by:
Comprehensive Cancer Centre South, Tilburg University, Bureau Kees Kokke BV, IJsenbrant Project Consultancy BV, Pfizer BV, Eli Lilly Nederland BV and Janssen-Cilag BV.

ISBN 978-90-9021437-5

Cover design: Universal press, Veenendaal
Printed by: Universal press, Veenendaal

Physical and psychological well-being among long-term cancer survivors

Proefschrift

ter verkrijging van de graad van doctor
aan de Universiteit van Tilburg,
op gezag van de rector magnificus,
prof. dr. F.A. van der Duyn Schouten,
in het openbaar te verdedigen ten overstaan van
een door het college voor promoties aangewezen commissie
in de aula van de Universiteit
op vrijdag 2 maart 2007 om 14.15 uur

door

Floortje Mols
geboren op 29 april 1981 te Tilburg

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"What doesn't kill you makes you stronger."

Friedrich Nietzsche
(Twilight of the Idols, 1888)

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General introduction

Increasing numbers of cancer survivors

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]. The number of survivors has also increased due to the growing incidence of cancer and the strong increase in the ageing population. The large number of cancer survivors emphasizes the importance of the possible long-term effects of cancer and its treatment. Studying long-term effects of different treatments provides information on the medical and psychosocial needs of patients and its determinants. This may yield valuable information on current therapies which could help to minimize late complications and thus improve the quality of life (QOL) for cancer survivors.

Quality of life among long-term survivors

For decades, clinical cancer research has focused merely on survival rates; only in the past two decades has more attention been paid to the QOL of cancer patients. The World Health Organization defines health as a state of complete physical, mental and social well-being and not just the absence of sickness and disease. QOL is the individual's perception of his or her position in life, within the context of the cultural and value systems in which he or she lives and in relation to his or her goals, expectations, standards and concerns [2].

A growing number of studies has documented the considerable impact of cancer diagnosis and treatment on QOL in newly diagnosed cancer patients and short-term survivors, but far less attention has been paid to QOL for long-term survivors [3]. According to the definition of the American Cancer Society, a 'long-term survivor' is a cancer patient who is alive 5 years after initial diagnosis [4].

It is likely that short-term survivors deal with other morbidities and QOL than long-term survivors who comprise more patients diagnosed with early stages of the disease and treated with less aggressive treatments. Furthermore, five years or longer after diagnosis, most patients alive may be expected to be disease-free with less fear of recurrence or death. Long-term sequelae of initial treatment then become more important. With this in mind, we started our research on QOL, treatment-related dysfunctions and health care utilisation among long-term cancer survivors.

Setting and background

The studies in this thesis were all conducted at the Comprehensive Cancer Centre South (CCCS). The CCCS has a regional network of clinical specialists and other cancer care providers who aim to improve quality of cancer care by facilitating clinical and psychosocial research and to develop and implement guidelines. One main network function is the existence of specific tumour working groups (such as 'breast cancer'). These working groups are unique networks of involved specialists and researchers of the CCCS who together discuss and evaluate guidelines and research findings but also initiate new research activities. The Eindhoven Cancer Registry (ECR) is part of the CCCS. It has an active data collection directly from patient's medical records, serving a population of 2.3 million in the southern part of the Netherlands. The CCCS region has 10 hospitals, with 18 hospital locations and two large radiotherapy institutes. The present thesis was thus embedded in an environment of expertise, commitment and practical experience with large population studies.

From 2001 to 2004, researchers from the CCCS worked together with the Cancer Watch Committee of the Dutch Cancer Society on the report 'Cancer in the Netherlands' published in November 2004 [5] that reports on trends (incidence, mortality, survival and prevalence), predictions of cancer incidence in the Netherlands and its implications for health care. Chapter 4 of this report ('Prevalence and health care use') concerns the well-being and health care needs of long-term cancer survivors. Therefore, a pilot-study on the influence of breast cancer on well-being and health care utilisation, 10 years after diagnosis, was conducted at the CCCS. The results of this pilot study were in accordance with what was found in other studies. After this pilot study, which was evaluated as being successful by patients, specialists and researchers, other specialists wanted to extend these research activities to cancer survivors of their interest. This thesis reports the results of this project.

Contents of this thesis

To the best of our knowledge, most studies on QOL among long-term cancer survivors focussed on breast cancer patients. Therefore, the existing literature on QOL among long-term breast cancer survivors was systematically reviewed in the first chapter of this thesis (**Chapter 1**). This review showed that the majority of breast cancer survivors experienced a good quality of life. This raised the question of whether patients experienced any *positive* effects of their experience with cancer. In **Chapter 2** we therefore evaluated posttraumatic growth, benefit finding and well-being in long-term breast cancer survivors.

After these two studies of breast cancer patients, we expanded our research on long-term cancer survivors to patients diagnosed with other types of cancer. It was our aim to measure QOL, treatment-related dysfunctions and health care utilisation among long-term cancer survivors and to compare them with general Dutch population norms, if possible. For this purpose, a set of questionnaires was developed. The questionnaire that was, in our opinion, highly suitable for measurement of QOL in long-term cancer survivors was the 'Quality of Life-Cancer Survivor (QOL-CS) questionnaire'. Since this tool was only available in an English and Spanish version, we developed and validated a Dutch version of this instrument (**Chapter 3**).

Using the QOL-CS and other assessment tools, we measured QOL among Dutch prostate cancer survivors 5-10 years after diagnosis and compared them with an age-matched norm group from the general Dutch population (**Chapter 4**). In this same group of patients, we also focussed on bowel, urinary, and sexual problems and we compared these problems with those of an age-matched norm group of Dutch men without a history of prostate cancer (**Chapter 5**).

Furthermore QOL was assessed among long-term endometrial (adeno-)carcinoma survivors (**Chapter 6**). In this study, QOL for long-term survivors of stage I or II endometrial (adeno-)carcinoma treated with surgery alone or with adjuvant radiotherapy was compared with the QOL of an age-matched norm population.

In addition, two of our studies included lymphoma survivors. The first study measured QOL among long-term non-Hodgkin's lymphoma survivors (**Chapter 7**). In the second study, QOL was measured for 10-15 year survivors of Hodgkin's lymphoma and compared with that for 5-9 year survivors (**Chapter 8**).

In all cancer patients in the above-mentioned studies, health care utilisation was assessed. This resulted in two chapters. In **Chapter 9,** the increased health care utilisation among 10-year breast cancer survivors was compared with those of an age- and sex-matched norm population. In **Chapter 10**, health care utilisation among long-term survivors of prostate cancer, endometrial (adeno-)carcinoma, Hodgkin's lymphoma and non-Hodgkin's lymphoma was assessed. We investigated health care utilisation among long-term cancer survivors and compared this to the general Dutch population. We also explored predictors of health care utilisation.

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Quality of life among long-term breast cancer survivors: a systematic review

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Jan Willem W. Coebergh, Lonneke V. van de Poll-Franse

(*European Journal of Cancer,* 2005: **41** (17): 2163-2169)

Abstract

The aim of this study was to review the literature on quality of life (QOL) among long-term survivors of breast cancer and identify the specific aspects of QOL that were affected in these survivors. We also describe predictors of QOL. Published research reports were included if they described the QOL of breast cancer survivors diagnosed at least five years earlier. The methodological quality of the 10 selected studies, conducted between 1997 and 2004, was high according to a list of predefined criteria. Most studies reported that long-term survivors of breast cancer experienced good overall QOL. However almost all studies reported that breast cancer survivors experienced some specific problems (e.g., a thick and painful arm and problems with sexual functioning). The current medical condition, amount of social support and current income level were strong positive predictors of QOL, the use of adjuvant chemotherapy emerged as a negative predictor. More research of the specific medical and psychosocial needs of survivors is needed in order to be able to design appropriate intervention studies. If anything, this review shows that focusing on the long-term effects of breast cancer is important when evaluating the full extent of cancer treatment.

Introduction

Breast cancer is the most prevalent malignancy among women in the industrialized world. One out of every nine women will ultimately be diagnosed with breast cancer in the USA before the age of 85 [1] while this figure is 1 in 11 in Europe. The prevalence of breast cancer rises markedly with age from 3-4% at age 50 to 69 to 6 % of women older than 70 [2]. The number of long-term survivors, defined by the American Cancer Society as every person who is still alive 5 years after diagnosis [1], is increasing rapidly due to the growing rates of detection and incidence, the marked increase in the number and proportion of elderly and the improved survival [2, 3]. This is in part also due to advances in cancer treatment. The relative survival of women with breast cancer five years after initial diagnosis is now 86% [4]. All in all, this has led to increasing numbers of individuals who are either cured for their cancer or are living with it as a chronic disease [5].

The increasing numbers of long-term breast cancer survivors urge to examine the long-term effects of breast cancer and specific treatments. The latter may need to be adapted in case of severe long-term side effects. In addition, specific medical and psychosocial needs of survivors should be assessed to be able to optimize aftercare. The goal of this review was to identify the specific aspects of QOL that were affected in long-term breast cancer survivors, and to identify predictors. We reviewed the literature on well-being of breast cancer survivors in a systematic way.

Methods

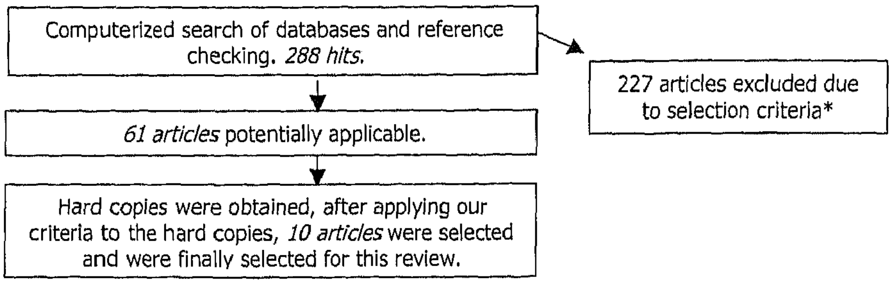
Search strategy

A computerized search of the literature was performed in Pubmed and PsychINFO from 1960 to May 2004. The term 'breast cancer' was used in combination with other key terms: *survivors, long-term, quality of life, QoL, health-related quality of life, HRQoL, well-being.* The reference lists of all identified publications were checked to retrieve other relevant publications, which were not identified by means of the computerized search.

Selection criteria

Studies were included if they described aspects of the QOL in long-term breast cancer survivors. The search was limited to English, German and Dutch language studies. Studies that involved a variety of tumours were excluded. The American Cancer Society's definition of long-term survival was used [1];

Figure 1. Flow diagram of papers accepted and rejected during selection procedure



*Selection criteria:

1. QOL had to be a primary endpoint of the study.
2. Patients had to be alive at least five years after diagnosis.
3. Only breast cancer was selected; Studies of different tumours were excluded.
4. Study had to be published in a peer-reviewed journal.
5. Article had to be in English, German or Dutch language.

studies of survivors of less than five years after initial diagnosis were excluded. QOL had to be measured with a standardized or valid questionnaire. Studies not published in peer-reviewed journals were not taken into account.

The described inclusion criteria were applied to our initial 288 hits. Sixty-one articles met our criteria, but this selection was based on abstracts and titles of reviews and research articles only. The 61 selected studies were conducted between 1989 and 2004. Hard copies were obtained of all studies. After inspection 10 articles fulfilled our selection criteria and were included in this review [6-15]. The flow chart of study selection is shown in Figure 1.

Quality assessment

Two investigators (Mols & Vingerhoets) assessed the methodological quality of each of the ten selected studies using a 14-item standardized checklist of predefined criteria. The checklist was a modified version of an established criteria list for systematic reviews [16-18]. The criteria are presented in Table 1.

Each item of a selected study, which met our criteria, was assigned one point. If an item did not meet our criteria or was described insufficiently or not at all, zero points were assigned. The highest possible score was thus 14. Studies scoring 75% or more of the maximum attainable score (i.e. ≥ 10 points) were, arbitrarily, considered to be of 'high quality'. Studies scoring between

Table 1. Criteria list for assessing the methodological quality of studies on QOL among long-term breast cancer survivors.

	Positive if;
A.	socio-demographic and medical data is described (e.g. age, race, employment status, educational status, tumour stage at diagnosis etc.).
B.	inclusion and/or exclusion criteria are formulated.
C.	the process of data collection is described (e.g. interview or self-report etc.).
D.	the type of cancer treatment is described.
E.	the results are compared between two groups or more (e.g. healthy population, groups with different cancer treatment or age, comparison with time at diagnosis etc.).
F.	mean or median and range or standard deviation of time since diagnosis or treatment is given.
G.	participation and response rates for patient groups have to be described and have to be more than 75 percent.
H.	information is presented about patient/disease characteristics of respondents and non-respondents or if there is no selective response.
I.	a standardized or valid QOL questionnaire is used.
J.	results are not only described for QOL but also for the physical, psychological and social domain.
K.	mean, median, standard deviations or percentages are reported for the most important outcome measures.
L.	an attempt is made to find a set of determinants with the highest prognostic value.
M.	patient signed an informed consent form before study participation.
N.	the degree of selection of the patient sample is described.

50% and 75% were rated as moderate quality. Studies scoring lower than 50% were considered low quality.

Findings were considered consistent if ≥75% of the studies that investigated a factor showed the same direction of the association. In Table 2 we defined five levels of evidence [19].

Results

Study characteristics

In total, 10 studies were included, all published after 1996. All but two [7, 11] were conducted in the USA. The main findings are summarized in Table 3. QOL was a primary endpoint in all studies. Four studies compared the QOL between breast cancer survivors and the general population [6, 7, 10, 11]. Two studies examined the QOL between breast cancer survivors diagnosed at different ages [8, 12]. In addition, one study specifically examined the role of ethnicity [9], one study focused on the impact of primary treatment on survivors [13] and two studies compared the QOL at diagnosis and follow-up [14, 15]. The time since diagnosis ranged between 5 and 23 years, 2169 survivors and 558

Table 2. Levels of evidence

	Levels of evidence
Strong	Consistent findings (≥75%) in at least 2 high quality studies
Moderate	Consistent findings (≥75%) in one high quality study and at least one low quality studies
Weak	Findings of one high quality study or consistent findings (≥75%) in at least 3 or more low quality studies
Inconclusive	Inconsistent findings, or less than 3 low quality studies available
No evidence	No data presented

controls were included and the Rand SF-36 (also known as the MOS-SF 36) was the most frequently used assessment of QOL.

Methodological quality

The evaluation of the methodological quality of the ten studies by the two reviewers yielded the following results. On 8 items there was disagreement between the reviewers, mostly due to differences in interpretation. Item 'L' of Table 1, which represents an attempt to find a set of determinants with the highest prognostic value, yielded the most disagreements. These were solved through discussion in a consensus meeting.

The quality scores are shown in Table 4. They range from 10 to 14 points. The mean quality score was 11.4. All ten studies attained scores above 75% of the maximum score. Methodological shortcomings concerned mainly the response rate and the lack of information on characteristics of non-respondents.

Quality of life

In most studies, breast cancer survivors reported a good QOL [14]. Physical and emotional well-being appeared to be excellent [15]. Scores on the CARES-SF global, physical, medical, psychosocial and marital subscales were all below 1, indicating that there were almost no problems in these areas [9]. In two studies, the QOL of survivors and controls was almost similar [7, 10]. Women who had survived longer after diagnosis of breast cancer reported better overall QOL and better psychological and social well-being than women with fewer years of survival [9].

Table 3. Predictors

	Possible predictors		
	Strong evidence	**Weak evidence**	**Inconclusive evidence**
Chemotherapy	X		
Medical condition	X		
Social support	X		
Income	X		
Employment status		X	
No children under age 18 at home		X	
Ethnicity		X	
Trait anxiety		X	
State anxiety		X	
Health perceptions		X	
Life stress		X	
Belief that the world is controllable		X	
Purpose		X	
Age at diagnosis			X
Current marital status			X
Time since diagnosis			X
Stage of disease			X

Other studies revealed problems in long-term survivors. Long-term survivors reported a lesser physical, psychological and general QOL than the control group [6, 11]. Survivors reported a lesser physical functioning than controls, but this did not affect their daily activities [10]. Survivors also reported a higher prevalence of symptoms of mild to moderate depression than healthy controls; these depression scores predict a lower QOL in all areas except family functioning. Cancer had negative effects on other domains of life as well. Survivors reported arm problems [7] and 51% of survivors still experienced pain [8]. Several studies revealed that sexual functioning was problematic [7, 9, 12-15]. Hormonal changes and menopausal symptoms, such as hot flashes and vaginal dryness, are the main causes of these problems in sexual functioning. One study stated that 29% of breast cancer survivors in their study had reported sexual problems [13]. Another study reported that 69% of women with partners were sexually active, but many of these women reported sexual problems, including lack of desire (56%), difficulty with arousal (46%), less enjoyment (35%), or no orgasm (38%) [14].

Predictors of quality of life

The predictive value of the socio-demographic variables as well as disease and treatment characteristics for QOL was determined. More specifically, demographic (age, education, ethnicity, income, employment), social (social support, marital status, children living at home), psychological (stress, anxiety, belief that the world is controllable, purpose) and disease variables (general health, stage of disease, years since diagnosis, health perceptions, chemotherapy and medical condition) were investigated. Some factors were examined in several studies, others in just one. The levels of evidence are described in Table 2. The predictors of QOL, described below in order of level of evidence, are listed in Table 3.

Strong evidence

Strong evidence was found for the predictive value of chemotherapy, medical condition, social support and income for QOL. Past chemotherapy is a statistically significant predictor of a poor current QOL [15]. Women who received chemotherapy are also at risk for a posttraumatic stress syndrome and thus a lower QOL experience [11]. In contrast, a greater increase in physical QOL since treatment was associated with chemotherapy [14]. Medical condition (i.e. co-morbidity) at the time of the examination also appeared to be a strong predictor of QOL. A patient who suffers from other medical conditions in addition to cancer experiences a lower QOL [9, 14, 15].

A third important predictor of QOL is social support, defined as the number of social contacts and the amount of social involvement with friends and family [15]. A greater increase in QOL in the years after diagnosis was associated with a smaller decrease in emotional support from family and friends in those years [14]. Finally, income emerged as a predictor in two American studies, a higher income being associated with a better QOL [9, 15].

Weak evidence

Weak evidence was found for the predictive value of employment status, no children under age 18 living at home, ethnicity (Euro-American, African American, Latino, Asian or other), trait anxiety, state anxiety, health perceptions, life stress, the 'belief that the world is controllable' and 'purpose'.

Table 4. Overview of studies on QOL among long-term breast cancer survivors.

Study	**Study quality ***	**Participants**	**Age (yrs)**	**Time since diagnosis (yrs)**	**Design**	**Population**	**Quality of Life instruments**	**General conclusions**
Weitzner et al. *(1997)*[6]	10	60 survivors 93 controls	Mean = 53.8 (s.d. 8.8)	>5	Comparison	Selected	Ferrans and Powers QoL index	Survivors exhibited a lower QOL than controls
Dorval et al. (1998)[7]	11	124 survivors 262 controls	18% 30-49 26% 50-59 32% 60-69 25% 70-89	Mean=8.8 (range 7.8-9.3)	Comparison	Unselected	A combination of different questionnaires	QOL of survivors and controls was the same, but survivors reported sexual problems and arm problems
Ferrell et al. (1998)[8]	10	298 survivors	Mean =58 (range 30-93)	Mean = 100 months Median = 75 months	Comparison	Unselected	QoL-breast cancer version	Survivors >60 had a better QOL than younger women.
Ashing-Giwa et al. (1999)[9]	12	117 African-American 161 white	Mean =63.6 (range 32-90)	Mean =7 (range 6-8)	Comparison	Unselected	Rand-SF-36 CARES Ladder of life	Survivors report a good health-related QOL, no ethnical differences.
Ganz et al. (2002)[15]	13	763 survivors	Mean =55.6	Mean =6.3 (range 5.0-9.5)	Follow-up study	Unselected	Rand-SF-36 Cares Ladder of life	High levels of functioning and QOL, systemic adjuvant treatment = lower functioning
Tomich & Helgeson (2002)[10]	10	164 survivors 164 controls	Mean =54.4 (range 33-81)	5.5	Comparison	Selected	MOS-SF-36	QOL of survivors and controls was largely the same

Table 4 Continued. Ove[illegible] of studies on QOL among long-term breast cancer survivors.

Study	**Study quality ***	**Participants**	**Age (yrs)**	**Time since diagnosis (yrs)**	**Design**	**Population**	**Quality of Life instruments**	**General conclusions**
Amir & Ramati (2002)[11]	14	39 survivors 39 controls	Mean =50.42 (range 37-60)	>5	Comparison	Unselected	WHOQOL-Bref	Survivors exhibited a lower QOL than controls
Cimprich et al. (2002)[12]	13	105 survivors	Mean =65.5	Mean=11.5	Cross-sectional study	Unselected	QOL-CS	Age at diagnosis and years of survival are predictors of QOL
Kornblith et al. (2003)[13]	10	153 survivors	Mean =65 (range 41-87)	Mean=18 (range 15-23)	Cross-sectional study	Selected	EORTC-QLQ-C30	Impact on survivor QOL was minimal 20 years after treatment
Bloom et al. (2004)[14]	11	185 survivors	Median 50 At follow-up	5	Follow-up study	Unselected	MOS-SF-36	QOL after 5 years was better than QOL at diagnosis

* The second colum represents 'study quality'. Each item of a selected study, which met our criteria, was assigned one point. If an item did not meet our criteria, was described insufficiently, or not at all, zero points were assigned. The highest possible score was thus 14. Studies scoring 75% or more of the maximum attainable score (i.e., ≥10 points) were arbitrarily considered to be of 'high quality'. Studies scoring between 50% and 75% were rated as moderate quality. Studies scoring lower than 50% were considered as low quality.

These variables were investigated only once in the selected studies, implying that at best only weak evidence was available. At least part-time employment and having no children under age 18 living at home predicted a greater increase in physical QOL [14]. Ethnicity was not a predictor of QOL [9]. Trait anxiety, which represents a long-standing personality feature, was the most consistent predictor of QOL in one study [6] in contrast to state anxiety. Breast cancer survivors with better health perceptions and survivors who experience less life stress reported a better QOL [9]. The 'belief that the world is controllable' predicted physical functioning scores and 'purpose' predicted mental functioning scores on the SF-36 [10].

Inconclusive evidence

Inconclusive evidence was found for age at diagnosis, current marital status, time since diagnosis and stage of disease. Four population-based studies identified age as a predictor of QOL [8, 12, 14, 15], one study found no relation between age and QOL [9]. Age was a predictor of scores on the general health scale of the Rand SF-36 [15]. Young women who survived breast cancer without recurrence and without the development of other forms of cancer improved in both their physical and mental well-being compared to their well-being at diagnosis [14]. Women who were diagnosed at a higher age (>65) reported a lower QOL outcome in the physical domain [12], whereas in another study women over age 60 reported a better physical well-being than younger women [8]. A fifth study found that age was not a predictor of QOL [9].

Evidence about education is also inconclusive. A higher QOL seems to prevail among survivors with a higher educational achievement [9], but educational level was inversely correlated with total QOL scores in another study [12]. In addition, a third study revealed that educational level did not influence ratings of QOL among breast cancer survivors [15].

Current marital status is another inconclusive predictor of QOL. It was found to be associated with better physical well-being [12] and survivors who had a partner and a shared living situation (not living alone) reported a better QOL [9], but a third study failed to find any association between QOL and marital status [15].

Inconclusive evidence also applies with respect to time since diagnosis. Time since diagnosis did not influence QOL in two studies [9, 15], but a third study showed that the number of survival years was significant as a predictor of QOL [12]. Women with more years of survival after diagnosis of breast cancer reported better overall QOL and better psychological and social well-being than women with fewer years of survival [12].

The predictive value of stage of disease was investigated twice in the selected studies. One study found that stage of disease was predictive of QOL in the health/functioning domain. Stage III survivors appeared to have a lower QOL than other survivors [6]. This result can be explained by the fact that these patients are in an advanced stage of disease and thus experience more symptoms. Moreover, it is well known that stage is associated with chemotherapy and past chemotherapy was a statistically significant predictor of a poor current QOL [15]. In contrast, a second study found that women with a low stage of disease were significantly more likely to suffer from a posttraumatic stress syndrome, which by definition is associated with more distress and a lower QOL [11].

Discussion

This systematic review summarized the results of 10 studies on the QOL of long-term survivors of breast cancer (i.e. > 5 years). Most studies reported that long-term survivors of breast cancer experienced good overall QOL. In general it can be concluded that survivors with a high QOL are probably those who did not need chemotherapy, who have no comorbid diseases, who received sufficient emotional support from family and friends and who had a relatively high income. If the survivor is also employed at least part-time, has no children under 18 living at home, enjoys a feeling of good health, experiences little life stress, believes that the world is controllable and that she has a purpose in life, then the chance that she experiences a good QOL gets even better. The role of other variables is less clear. Age, education, marital status, years since diagnosis and stage of disease, for example, predict QOL in some studies but not in others.

In spite of the fact that the QOL for long-term survivors is relatively good, there is no doubt that many survivors still experience substantial complaints as a result of the cancer or its treatment. Most frequently mentioned are sexual problems and a painful/swollen arm. These complaints can be caused by many factors, some of which are known, others are not yet uncovered or are based on weak evidence. With the implementation of new or adjusted treatments, new problematic side-effects can arise [20]. Since the group of breast cancer survivors will only continue to increase over the next few decades due to the demographic age-shift, with populations living longer and many new developments being made in breast cancer therapy [21] it will be necessary to monitor survivors in order to identify possible negative long-term effects.

If we chose to perform more research in this area, it is important that high demands be made on the quality of the new studies. The inclusion of a reference group of equally aged individuals without cancer drawn from the general population is very important. Furthermore, the selection of an appropriate QOL questionnaire is essential. In addition there is the question about the difference between 'real' QOL measures, (such as the WHOQOL), which stress the contentment of the patient with several aspects of her life, and instruments (like the RAND SF-36) which merely focus on functional health status. Moreover, there are both advantages and disadvantages in applying generic measures versus disease specific instruments. Standardization of the use of assessments might be essential for adequate evaluation and mutual comparison of studies. Data on demographical factors and information about health status of survivors should also be collected in order to establish their predictive value. These recommendations seem to be logical but in daily practice it appears that these obvious recommendations for good research are still not always applied.

The results described in this review were partially inconclusive, even though all studies included in this review were of high quality. By the implementation of additional qualitatively good studies, more clarity with respect to the QOL of breast cancer survivors may possibly be achieved. In the mean time we can implement new strategies with the knowledge we have already gained. We know that medical condition (i.e. co-morbidity), chemotherapy, social support and income are important predictors of QOL. Extra attention is therefore warranted for women with a poor medical condition. As far as chemotherapy is concerned this finding might imply that we need to be more reluctant about broadening the indications for this aggressive systemic therapy [20] because of the possible negative side-effects that can last for years. Offering better social support to women with breast cancer can possibly change social support. Psychosocial intervention projects [22] resulted in both short- and long-term good results for breast cancer patients. This not only improved QOL but also reduces health care billings by 24% compared with women who did not attend psychosocial intervention projects. A low income cannot be influenced easily. Generally solutions should be found in broad health care insurance and better access to health care, of course, only in countries where this is a real problem, as in the US.

If anything, this review shows that focusing on the long-term effects of breast cancer is important when evaluating the full extent of cancer treatment.

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2

Well-being, posttraumatic growth and benefit finding in long-term breast cancer survivors

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(Submitted for publication)

Abstract

This study evaluates posttraumatic growth, benefit finding and well-being, and their interaction, in a random sample of disease-free 10-year breast cancer survivors. In October 2003, the population-based Eindhoven Cancer Registry was used to select all women diagnosed with breast cancer in 1993 in six hospitals. One hundred and eighty three (72%) of the 254 breast cancer survivors returned a completed questionnaire. Measures included the Posttraumatic Growth Inventory, the Perceived Disease Impact Scale and the CentERdata Health monitor. Self-reported health status and psychological well-being were similar in survivors compared to general population norms, whereas life satisfaction was significantly higher among survivors. In addition, posttraumatic growth was seen in the following domains: 'relationships with others', 'personal strength' and 'appreciation of life'. The number of patients reporting benefit finding was high (79%, n=145). Benefit finding showed a moderately positive correlation with posttraumatic growth. In addition, women who stated that their satisfaction with life was high reported higher levels of posttraumatic growth in comparison to women who did not. Radiotherapy was negatively associated with posttraumatic growth. Women with a higher tumour stage at diagnosis experienced less benefit finding in comparison to women with a lower tumour stage at diagnosis. The above results can help to identify those patients who will probably experience posttraumatic growth and benefit finding after cancer. However, it is important to be aware that positive effects of cancer on a patient's life do not occur in all cancer patients and all phases of the disease trajectory.

Introduction

There is increasing evidence that many people experience not only negative but also certain positive effects after the confrontation with a traumatic event. Well-known concepts used to define these positive effects are benefit finding and posttraumatic growth. Benefit finding refers to the acquisition of benefit from adversity [1, 2]. Well-documented examples of benefit finding are a positive change in relationships, a greater appreciation of life and a change in life priorities. Posttraumatic growth refers to the success with which individuals coping with the aftermath of trauma reconstruct or strengthen their perceptions of self, others, and the meaning of events [3]. It is also described as "the experience of significant positive change arising from the struggle with a major life crisis" [4]. Recent studies have provided evidence that these processes also take place in chronically ill patients, including individuals suffering from cancer [5-10].

It is not yet clear how the two concepts relate to each other, but where benefit finding may start immediately after diagnosis, posttraumatic growth has been hypothesized to arise as a result of the rumination and restructuring that occurs in the weeks, months, and even years following trauma [11]. Therefore one might expect increasing reports of posttraumatic growth with increasing time since the trauma, because more time is available for cognitive processing [12]. However, the research literature is not unequivocal on this matter.

Until now, adaptation to cancer has been measured mainly by means of questionnaires on well-being or quality of life. Very often, positive effects have been found on quality of life after cancer [12]. However, these effects were generally attributed to the response-shift phenomenon, suggesting that this finding is more or less an artifact due to the fact that patients change their internal standards or redefine their concept of health related quality of life [13].

In this study, we measured well-being, posttraumatic growth, and benefit finding. In accordance with Sears, Stanton and Danoff-Burg (2003) we considered a self-reported positive impact of the disease on a certain life domain as an indication of benefit finding. We included patients who were diagnosed with breast cancer 10 years ago. While the consequences of breast cancer are almost always negative in the immediate aftermath of diagnosis, years later patients appear to become increasingly aware of the positive consequences of their disease. Whereas approximately 30% of breast cancer survivors still report specific complaints [14] , there is also evidence that many long-term survivors experience a good quality of life and benefit finding in the years after diagnosis [5, 12, 15]. A recent review demonstrated that quality of life is acceptable for most long-term breast cancer survivors [12]. Research suggests that the benefits, which survivors of breast cancer derive from their experience with cancer, have only a modest impact on quality of life and that a continued search for meaning in life may even have a negative impact on quality of life [15]. However, finding benefit of breast cancer during the year after diagnosis was shown to predict a better adjustment (e.g. less distress and depression) 5-8 years after diagnosis [5].

The aims of the present study were manifold. First, we wanted to compare health status, satisfaction with life and psychological well-being of breast cancer survivors with age and gender-matched population controls. Second, we assessed whether breast cancer survivors experience posttraumatic growth. Third, we wanted to obtain a better insight into the consequences of cancer for the different aspects of a patient's life. Fourth, we wanted to learn more about the links between benefit finding and posttraumatic growth and the association between benefit finding and posttraumatic growth with subjective well-being. Finally, we investigated the independent associations between patient characteristics and tumour characteristics with posttraumatic growth and benefit finding.

Methods

Setting and Participants

This study was conducted at the Eindhoven Cancer Registry (ECR). The ECR records data on all patients newly diagnosed with cancer in the southern part of the Netherlands, an area with 2.3 million inhabitants, 18 hospital locations and two large radiotherapy institutes [16]. The ECR was used to select all patients diagnosed with invasive breast cancer in 1993, in six community hospitals. Participants older than 75 years at diagnosis were excluded as it was expected that they would have difficulty in completing a self-reported questionnaire without assistance. To exclude all persons who had died before October 2003, our database was linked with the database of the Central Bureau for Genealogy, which collects data on all deceased Dutch citizens via the civil municipal registries.

One hundred and eighty three (72%) of the 254 breast cancer survivors returned a completed questionnaire. Sixty (33%) of the participating women were younger than 50 years when diagnosed; most patients (n=113, 62%) were between 50-69 years old. The majority of the respondents were initially diagnosed with stage I or II disease (87%). Fifty-seven percent of them received breast-conserving therapy and 74 patients (40%) underwent a mastectomy; in almost all cases (97%) the axillary lymph nodes were dissected. Additional chemotherapy was given to 19 women (10%) almost all of whom (n=15) were younger than 50 when diagnosed. Additional hormonal therapy was given to 29 women (16%). The majority of women received additional radiotherapy (n=131, 72%).

A comparison of respondents and non-respondents, by means of chi square statistics, showed that respondents more often received radiotherapy than non-respondents. No differences between respondents and non-respondents were found for age at diagnosis, disease stage at diagnosis, surgical treatments and systemic therapies [14].

Data collection

Specialists sent their (former) patients a letter to inform them about the study together with a questionnaire. The letter explained that by returning the completed questionnaire, the patient agreed to participate and consented with linkage of the outcome of the questionnaire with their disease history as registered in the ECR. Patients were reassured that non-participation would not have any consequence for their follow-up care or treatment. Returned questionnaires only contained a study number which guaranteed anonymity.

Measures

Health status and subjective well-being

Subjective physical and psychological well-being and life satisfaction were determined with the CentERdata Health monitor [17]. This scale includes items to measure health status (8 items), life satisfaction (5 items) and psychological well-being (5 items), all with a 5-point Likert-scale. Higher scores indicate better health status, greater satisfaction with life and better psychological well-being. The CentERdata Health subscales have a high internal consistency (0.88, 0.75, and 0.82) [17]. It is a short, valid and reliable instrument [17, 18]. Norm-scores for this questionnaire are available and are based on 1893 Dutch men and women. For this study we selected an age- and gender-matched normative group (n=149).

Posttraumatic growth

Positive outcomes after cancer were assessed using the Posttraumatic Growth Inventory (PGI) [3]. The scale helps to determine how successful individuals, coping with the aftermath of trauma, are in reconstructing or strengthening their perceptions of self, others, and the meaning of events. The PGI has 21 items on a 6-point Likert scale, ranging from 0 (I did not experience this change as a result of my crisis) to 5 (I experienced this change to a very great degree as a result of my crisis). It contains five subscales; (1) relationships with others; (2) new possibilities; (3) personal strength; (4) spiritual change; and (5) appreciation of life. The scale has good internal consistency and acceptable test-retest reliability [3].

Benefit finding

Benefit finding was assessed using the Perceived Disease Impact Scale (PDIS), a newly developed instrument to measure the influence of the illness on various life domains, including well-being, lifestyle, activities, relationships, work, personality, interests and trust in own body. Its 20 items were based on several sources, such as the Illness Intrusiveness scale [19], a similar instrument to assess the impact of depression [20], and the literature on the effects of cancer [1, 21] and multiple sclerosis [22] on the lives of patients. The response format consisted of a 7-point Likert scale ranging from 'very negatively' (-3) to 'very positively' (+3). The following scores were derived: (1) the grand mean, averaged over all items; and as an index of benefit finding following Sears et al., (2003); (2) the identification of any positive effect (dichotomous coding, 0 = no single positive effect vs. 1 = at least one perceived benefit) and (3) the number of items with a positive, a negative and a neutral score respectively.

Statistical analysis

Health status, satisfaction with life and psychological well-being were compared with age and gender-matched controls from the Dutch population (n=149). Means and standard deviations for the domains of the PGI were calculated. We determined whether PGI scores were significantly different from zero, suggesting posttraumatic growth. For the PDIS, mean scores averaged over all items were calculated. Furthermore, the identification of any positive effect ('benefit finding') was measured and the numbers of items with a positive, a negative and a neutral score respectively, were calculated. Pearson correlations were calculated to examine the association between subjective

Table 1. CentERdata Health monitor scores for disease-free, 10-year breast cancer survivors (n=183) and a control sample of the Dutch female population (n=149).

	Means (SD)		
	Survivors	**Controls §**	**P-value**
Health status (range: 0-40)	31.5 (7.1)	31.5 (5.8)	n.s.
Satisfaction with life (range: 0-25)	21.6 (3.4)	18.1 (3.1)	<0.001
Psychological well-being (range: 0-25)	19.2 (3.9)	19.7 (3.3)	n.s.

§ controls from CentERdata Health monitor [17]
n.s.: not significant

well-being, posttraumatic growth and benefit finding. The ECR routinely collects data on patient characteristics including date of birth and comorbidity at time of diagnosis (a slightly adapted version of the Charlson comorbidity index [23]) and tumour characteristics including stage (Tumour-Node-Metastasis clinical classification [24]) and treatment. Multivariate linear regression analyses were carried out in order to investigate the independent association between patient characteristics (age, comorbidity, health status, life satisfaction, psychological well-being) and tumour characteristics (stage, treatment) with the PGI subscale scores and benefit finding as measured with the PDIS. All statistical analyses were performed using SAS (version 9.1 for Windows, SAS Institute Inc., Cary NC).

Results

Comparison of well-being of long-term breast cancer survivors with norm data revealed that the (former) cancer patients reported similar mean scores on self-reported health status (mean= 31.5 and 31.5, respectively) and psychological well-being (mean= 19.2 and 19.7) compared to the age- and gender-matched normative population (Table 1). In contrast, life satisfaction was significantly higher for breast cancer survivors compared to the normative population (mean=21.6 and 18.1; p<0.001).

Mean scores for the subscales of the Posttraumatic Growth Inventory are shown in Table 2. The scores on the subscales range from 0 (I did not experience this change as a result of my crisis) to 5 (I experienced this change to a very great degree as a result of my crisis). Therefore a subscale score significantly higher than 0 was considered to represent posttraumatic growth. Analyses showed that scores on three of the five subscales ('relationships with

Table 2. Posttraumatic growth scores for disease-free 10-year breast cancer survivors (n=183)

	Means (SD)	**P-value**
Relationships with others (range: 0-35)	19.9 (7.8)	<0.05*
New possibilities (range: 0-25)	9.8 (6.4)	n.s.
Personal strength (range: 0-20)	10.8 (5.0)	<0.05*
Spiritual change (range: 0-10)	2.8 (5.8)	n.s.
Appreciation of life (range: 0-15)	9.6 (3.5)	<0.01*

* Significantly different from zero suggesting posttraumatic growth.

others', 'personal strength' and 'appreciation of life') were significantly higher than zero, suggesting posttraumatic growth in these domains.

Breast cancer patients scored a grand mean, averaged over all items, of 15.6 (SD: 16.8, range: -60 to 60) on the PDIS (Table 3). The percentage of patients experiencing benefit finding (e.g. the identification of at least one positive effect on the PDIS) was 79.2% (n=145). Cancer or cancer treatment reportedly influenced the survivor's family relationships, relations with friends and relatives, other social relations and community and civic involvement in a *positive* way (see percentages in Table 3). Cancer also reportedly had a *positive* influence on the survivor's diet, passive recreation, self-expression/self-improvement, outlook on life, mental health, character and trust in own body. Life style, stress, work, active recreation, financial situation, sex life, relationship with spouse and religious expression did not appear to be influenced by breast cancer or its treatment in the majority of women, ten years after diagnosis. Cancer was held responsible for a negative influence on physical health in 42% of breast cancer survivors. Five percent of the patients indicated that cancer had not influenced their lives in any way. Three percent of patients reportedly had only experienced positive effects and none of the patients reported only negative effects of cancer on their lives. The average number of items (range 0-20) with a negative, neutral or positive score was 2.3, 7.1 and 8.3, respectively.

Pearson correlations for PGI subscales and benefit finding with Health monitor subscales and PGI with benefit finding are presented in Table 4. Benefit finding shows a moderately positive correlation with posttraumatic growth. In addition, women who stated that their satisfaction with life was high reported higher levels of posttraumatic growth than women with a lower satisfaction with life.

Table 3. Negative, neutral and positive influences of breast cancer and treatment on life-domains of the perceived Disease Impact Scale (PDIS) (n=183).

	% of patients			
	Negative effect	**Neutral effect**	**Positive effect**	**Mean (SD)**
Subscales				
Physical health	42	25	33	0.1 (1.7)
Mental health	21	30	49	0.8 (1.6)
Diet	5	39	56	1.2 (1.4)
Life style	9	57	33	0.5 (1.4)
Stress	29	43	28	0.1 (1.4)
Work	16	53	31	0.3 (1.5)
Active recreation	16	43	41	0.5 (1.5)
Passive recreation	1	36	63	1.3 (1.3)
Financial situation	10	55	35	0.6 (1.3)
Sex life	27	57	16	-0.2 (1.5)
Relationship with spouse	9	52	39	0.8 (1.5)
Family relations	2	43	56	1.3 (1.4)
Relations with friends and relatives	2	39	59	1.2 (1.3)
Other social relations	4	36	61	1.3 (1.4)
Self-expression/self-improvement	3	37	60	1.2 (1.3)
Religious expression	10	52	39	0.5 (1.4)
Community and civic involvement	5	29	66	1.2 (1.3)
Outlook on life	9	22	69	1.3 (1.4)
Character	6	37	57	1.2 (1.3)
Trust in your body	17	29	54	0.7 (1.7)
PDIS total score (sumscore)	6	9	84	15.6 (16.8)*
Percentage of patients with <u>only</u> negative, only *neutral or only positive* scores.	0	5	3	

	Mean (SD)		
	Negative score	**Neutral score**	**Positive score**
The average number of items with a negative, a neutral or a positive score (Range 0-20).	2.3 (2.5)	7.1 (6.3)	8.3 (6.3)

Due to rounding errors, the numbers will not always add up to 100.
*the grand mean, averaged over all items

Table 4. Pearson correlations for posttraumatic growth subscales and the perceived disease impact scale with CentERdata Health monitor subscales and benefit finding.

	Posttraumatic growth subscales						
	Relationships with others	**New Possibilities**	**Personal strength**	**Spiritual change**	**Appreciation of life**	**Total score**	**Benefit finding**
Health status	0.01	0.05	-0.09	0.04	-0.06	0.002	0.13
Life satisfaction	0.29***	0.15	0.20*	0.09	0.28***	0.25**	-0.04
Psychological well-being	0.04	0.09	-0.07	0.03	-0.01	0.04	0.10
Benefit finding	0.35***	0.38***	0.41***	0.28***	0.24**	0.42***	-

* p<.05, ** p<.01, *** p<.001

Multivariate linear regression analyses with posttraumatic growth and benefit finding as outcome variables revealed independent associations with the measured tumour and patient characteristics (Table 5). Radiotherapy was negatively and life satisfaction and benefit finding were positively associated with the total posttraumatic growth score. Tumour stage at diagnosis was negatively associated with benefit finding. The other measured tumour and patient characteristics were not strongly associated with posttraumatic growth or benefit finding.

Discussion

The major aim of this study was to obtain a better insight into subjective well-being, posttraumatic growth and benefit finding and their mutual relationships in long-term breast cancer survivors.

Long-term breast cancer survivors had the same self-reported health status and psychological well-being as the healthy general female population of the same age, whereas life satisfaction was higher among survivors. To the best of our knowledge, to date studies have not yet reported findings on subjective health status in breast cancer survivors compared to a norm population. On the other hand, several previous studies have demonstrated that well-being in breast cancer survivors is similar to well-being in age-matched healthy control women [25]. In addition, previous research already demonstrated that breast cancer survivors have a higher life satisfaction than the female norm population; survivors were more satisfied with life than they estimated others to be [26].

Table 5. Multivariate linear regression model evaluating independent variables for posttraumatic growth subscale scores and benefit finding.

	Posttraumatic growth†						
Independent variable	**Relationships with others**	**New possibilities**	**Personal strength**	**Spiritual change**	**Appreciation of life**	**Total score**	**Benefit finding†**
Age	NS	-0.25**	NS	NS	NS	NS	NS
Tumour stage	NS	NS	NS	NS	NS	NS	-0.26**
Radiotherapy	NS	-0.16*	NS	NS	-0.21*	-0.18*	NS
Surgery	NS	NS	NS	NS	NS	NS	NS
Systemic Therapy	NS	NS	NS	NS	0.19*	NS	NS
Comorbidity	-0.18*	NS	NS	NS	NS	NS	NS
Health status	NS	0.20*	NS	NS	NS	NS	NS
Satisfaction with life	0.45***	0.38***	0.25**	NS	0.42***	0.43***	NS
Psychological well-being	NS	0.21*	NS	NS	NS	NS	NS
Benefit finding	0.42***	0.40***	0.44***	0.27**	0.27**	0.46***	

† Standardized beta coefficients
* p<.05
** p<.01
*** p<.001

Indications of posttraumatic growth were seen in the following domains: 'relationships with others', 'personal growth' and 'appreciation of life'. This was partially in line with a previous study in which breast cancer patients were compared to an age- and education-matched healthy comparison group [25]. Survivors showed a pattern of greater posttraumatic growth, particularly in 'relating to others', 'spiritual change' and 'appreciation of life'. Improved close relationships with others were also the most common theme reported by 52 breast cancer patients, three months after the completion of therapy. Sixty percent of those patients reported posttraumatic growth [8]. Furthermore, posttraumatic growth was also seen among breast cancer patients in other studies [27, 28] and in other cancer patients as well [1, 29].

Posttraumatic growth was negatively associated with radiotherapy and positively associated with satisfaction with life and benefit finding. This has not been investigated before. However, it has been found in the literature that posttraumatic growth was unrelated to distress or well-being but was positively associated with the perceived emotional intensity of the disease, perceived life-threat, prior talking about breast cancer, contact with another cancer survivor, a supportive husband, income, and time since diagnosis [25, 28, 30]. In addition, a substantial positive correlation with adaptive coping was found. Our findings suggest that the patients in this study who experienced the most posttraumatic growth were those who were not treated with radiotherapy and who perceived themselves as being satisfied with their life. Furthermore, they experienced benefit finding. However, given the cross-sectional nature of this study, no definitive statements can be made on the precise nature of this association.

The present study also revealed that, 10 years after diagnosis, breast cancer and/or its treatment generally results in benefit finding. Patients reportedly experienced more positive than negative influences of cancer on the different life-domains. This corroborates findings in previous studies. Sears et al (2003) demonstrated that 83% of the women with early-stage breast cancer reported at least 1 benefit of their breast cancer experience. Furthermore, similar findings were obtained in a study showing that cancer patients seemed able to derive more benefit than harm from their experiences [1]. However, benefit finding was measured with a different measurement method and patients had to be within 5 years of diagnosis; so results cannot easily be compared in detail.

Physical health was the only domain that often (42%) received a negative score in our study. We previously reported that approximately 30% of this breast cancer survivor population still experience specific complaints (e.g. a thick and painful arm and fatigue) 10 years after diagnosis [14]. Results of our study further showed that patients with a lower disease stage at diagnosis were more likely to report benefit finding 10 years after diagnosis of breast cancer. This is in contrast to previous findings, suggesting that breast cancer patients diagnosed with stage II disease perceived more benefits as a result of their experience than did those diagnosed with stage I [9]. Taken together, we feel strongly that the often reported increased quality of life and life satisfaction in cancer patients should not be considered merely as an artifact (e.g. due to response-shift), because there is sufficient reason to propose that such positive changes are real and related to posttraumatic growth and benefit finding.

The present study has a few limitations. Although only 28% of patients did not respond to our questionnaire, we do not know what their current health status is. We do know that non-respondents received radiotherapy less often and it is therefore possible that our results cannot be generalized to this patient population. Finally, due to the retrospective design of this study, it is not possible to draw conclusions on the directions of the relationships between satisfaction with life and benefit finding with posttraumatic growth. We could only demonstrate associations between these variables. In the future, prospective studies should be performed to be able to obtain a better insight into the precise nature of the relationships between these variables. Nevertheless, the results of this study are an important contribution to the limited information available on posttraumatic growth and benefit finding in this growing group of long-term breast cancer survivors.

The reactions to cancer in long-term cancer survivors differ widely among individuals. Whereas a significant number of them still suffer from the negative effects of the disease, many others believe that cancer may be one of the best things that has ever happened to them. Although health care professionals should be aware of the possibility of posttraumatic growth and benefit finding, imposing an expectation of psychological growth could potentially be harmful to patients [30]. It is important to obtain a better understanding of the determinants of growth and benefit finding (e.g. perceived emotional intensity of the disease, personality characteristics, social network features, tumour characteristics and treatment). Adaptive coping with disease is a critical component that is related to this matter [30]. An important question that needs to be answered is which patient characteristics can be altered (e.g. satisfaction with life and coping) in order to achieve posttraumatic growth and benefit finding after cancer. If these convertible characteristics are known, interventions can try to alter these characteristics and help those patients who are susceptible to negative influences of cancer on their life [31-33].

Acknowledgement

The authors want to thank all patients for their participation in the study. Furthermore, they want to thank the Comprehensive Cancer Centre South and the Foundation for the Advancement of Academic Training and Research in Healthcare (SWOOG) for financially supporting the study.

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3

A validation study of the Dutch version of the Quality of Life-Cancer Survivor (QOL-CS) questionnaire in a group of prostate cancer survivors

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(Quality of Life Research, 2006: **15** (10): 1607-1612)

Abstract

The primary objective of this study was to validate the Dutch version of the Quality of Life-Cancer Survivor (QOL-CS) questionnaire using a group of Dutch prostate cancer survivors. The QOL-CS was specifically designed to measure the quality of life (QOL) of long-term cancer survivors. We performed a population-based, cohort study of 784 prostate cancer survivors who were diagnosed with prostate cancer between 1994 and 1998. To determine the test-retest reliability, second questionnaires were sent to 109 participants, of whom 103 (94%) returned the forms. It appeared that QOL for a group of long-term prostate cancer survivors was adequately measured by the physical, psychological and social well-being QOL-CS subscales. In contrast, the subscale spiritual well-being showed a low internal consistency, although the test-retest reliability was good. These results contradict a prior validation study of a group of American ovarian cancer survivors. Cultural and/or sex differences may be responsible for this inconsistency.

Introduction

Prostate cancer is the most common male cancer in the Western world [1]. In past decades the incidence and survival of prostate cancer have increased tremendously, resulting in a rising number of cancer survivors. It is therefore important to understand how the disease affects the QOL among survivors [1]. Most QOL instruments focus on the effects of diagnosis and initial cancer treatment [2] whereas the specific concerns and needs of long-term survivors are seldom measured. The Quality of Life-Cancer Survivor (QOL-CS) is one of the few instruments that has been designed specifically for the assessment of QOL in long-term cancer survivors and has been validated or used in several American studies [3-9]. The objective of this study was to validate the Dutch translation of the QOL-CS questionnaire using a group of long-term prostate cancer survivors.

Methods

Participants

The population-based Eindhoven Cancer Registry (ECR) was used to select all men diagnosed with prostate cancer between 1/1/1994 and 31/12/1998 who were alive at time of data collection. In addition, the selected men had to be disease-free and 75 years or younger at time of diagnosis. The ECR routinely collects data on tumor characteristics like date of diagnosis, subsite, histology, stage and treatment and patient characteristics like gender, date of birth and co-morbidity at time of diagnosis.

Instruments

The QOL-CS was developed by researchers of the City of Hope National Medical Center in California USA, to measure the QOL of long-term cancer survivors [4]. It examines issues of particular concern to long-term cancer survivors such as fear of a second tumor, recurrence or metastasis, survivorship guilt and the role of spirituality and religion [3]. The QoL-CS is a 45-item visual analogue scale, based on a scale of 0 (worst outcome) to 10 (best outcome). The instrument consists of four scales: physical, psychological, social and spiritual well-being. A 'forward-backward' procedure was used to translate the English-language version of the QOL-CS into Dutch.

The SF-36 questionnaire was used to measure health-related quality of life [10]. For this validation study we only used three subscales (physical and social functioning, and emotional well-being). The Revised version of the Illness

Intrusiveness Ratings Scale (IIRS) [11] was used to assess the impact of the respondent's 'illness and/or its treatment' on life domains important to QOL [12]. The four domains included for this validation study were physical health, mental health, relationship with friends and religious expression.

Data collection procedure

The Institutional Review Board of Máxima Medical Centre in the Netherlands approved the study-protocol. After approval, questionnaires were sent to all long-term prostate cancer survivors who fulfilled the inclusion criteria, by their (former) specialists. After two months a reminder was sent to all participants who had not returned the questionnaire. A completed questionnaire was considered to imply informed consent.

Reliability and validity

The internal consistency was measured using Cronbach's alpha coefficient. To measure test-retest reliability, the first 109 participants, who returned the survey and wanted to participate in further studies, received a second set of questionnaires.

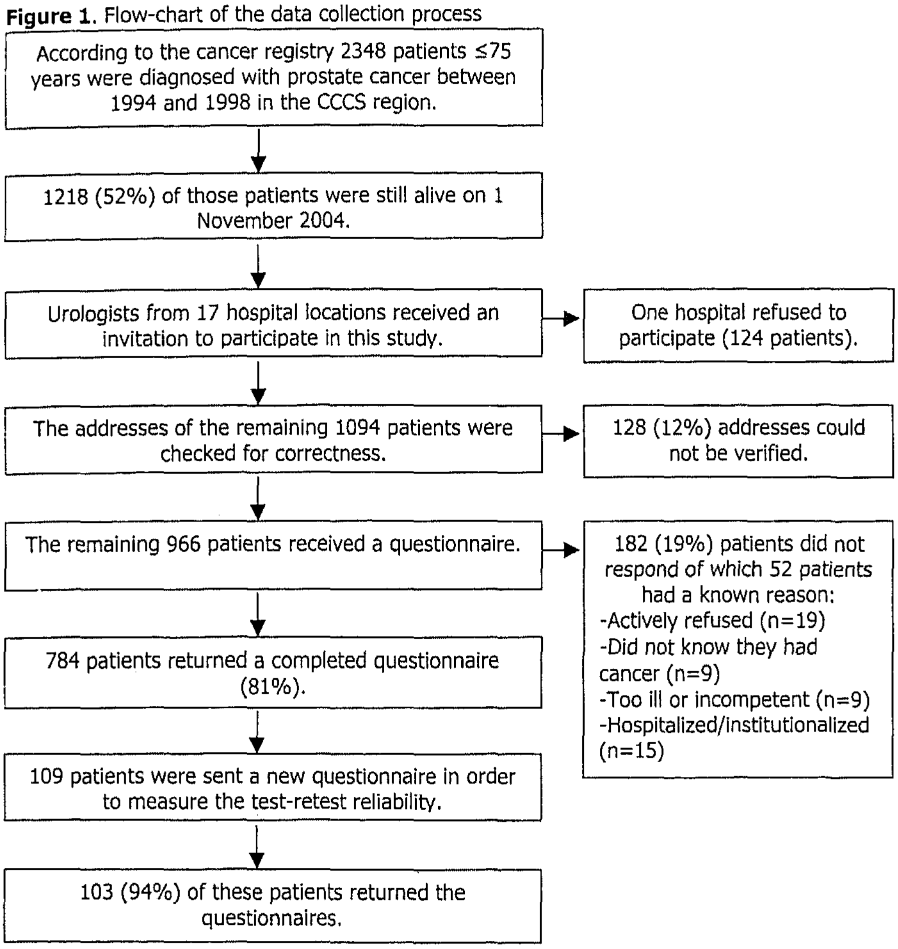
In order to measure convergent validity, correlations between comparable dimensions of the QOL-CS and the IIRS-R and between QOL-CS and the SF-36 were computed. Criteria for quantitative significance of correlations were based on the recommendations of Burnand et al. [3]. These recommendations were; < 0.30 negligible; 0.30-0.45 moderate; 0.45-0.60 substantial; and > 0.60 high.

Finally, item-discriminant validity of the QOL-CS scales was tested. The correlation between each item of the scale and its own scale was compared with the correlations between that item and every other scale. The item to own scale correlation should be higher if the categories within the QOL-CS questionnaire are valid.

Statistical analyses

Because of the non-normal distribution of the QOL-CS questionnaire, Spearman's rank was used as correlation measure for the test–retest reliability and convergent and divergent validity. Chi-square was used to evaluate the differences between people who did or did not want to participate a second time. For all analyses, SAS (Version 8.02, SAS Institute Inc., Cary, North Carolina, USA) was used.

Figure 1. Flow-chart of the data collection process



Results

In total, 966 prostate cancer survivors were sent a questionnaire, of which 784 (81%) returned a completed questionnaire (Figure 1). Of the 109 patients who received a second questionnaire, 103 (94%) completed the QOL-CS for the second time, two months after their first response.

Participant's characteristics

Table 1 presents medical and sociodemographic data for the total group of participants (n=784) and the test-retest group (n=103). Men who completed the questionnaire twice were diagnosed more often with stage II disease and more often underwent prostatectomy, compared to the total group of participants.

Table 1. Sociodemographic and medical characteristics of questionnaire respondents

	N (%)	
	First questionnaire N=784	***Second* questionnaire N=103**
Age at time of survey		
<70 years	192 (24)	25 (24)
70-74 years	212 (27)	31 (31)
75-79 years	248 (32)	34 (34)
80+ years	132 (17)	13 (13)
Stage at diagnosis		
I	164 (21)	16 (15)
II	428 (55)	65 (63)
III	96 (12)	13 (13)
IV	45 (6)	5 (5)
Unknown	51 (6)	4 (4)
Primary treatment		
Prostatectomy	257 (33)	58 (56)
Radiotherapy	323 (41)	30 (29)
Hormonal therapy	94 (12)	8 (8)
None	73 (9)	6 (6)
Unknown/other	37 (5)	1 (1)
Comorbidity		
None	279 (36)	38 (37)
1	275 (35)	39 (38)
2+	230 (29)	26 (25)
Marital status		
Married	609 (81)	84 (83)
Single	20 (3)	4 (4)
Divorced	26 (3)	4 (4)
Widowed	98 (13)	9 (9)
Living arrangement		
Living together	559 (81)	81 (85)
Living alone	123 (19)	14 (15)
Educational level		
Low	178 (24)	20 (20)
Middle	407 (55)	55 (55)
High	158 (21)	25 (25)
Occupation		
Unemployed due to disability	20 (3)	2 (2)
Retired	661 (88)	87 (87)
Employed <33 h/w	42 (5)	9 (9)
Employed 33+ h/w	13 (2)	2 (2)
Other	13 (2)	0 (0)

Table 2. Internal consistency, item to own scale correlations and item to other scale correlations

Scale	**Number of items**	**Chronbach's alpha**	**Item to own scale**	**Item to other scale**
Physical well-being	8	.86	.48 - .73	-.01 - .56
Psychological well-being	18	.89	.38 - .69	-.03 - .61
Social well-being	10	.73	.04 - .58	-.08 - .57
Spiritual well-being	8	.49	-.16 - .44	-.35 - .61
Overall quality of life	44	.91		

Reliability and validity

Internal consistency was high for all scales (Chronbach's alpha > .70) except for the spiritual well-being scale (Chronbach's alpha = .49). The overall scale had an internal consistency of .91 (Table 2). For a few items, correlation with their own subscale was low (items of social well-being and spiritual well-being), but most of the item-to-subscale correlations were moderate to high. The item-to-subscale correlations for two items ('uncertainty future' and 'survivorship guilt') in the spiritual well-being scale were negative. When the two items were deleted, Chronbach's alpha for the spiritual subscale increased to .67.

Item-discriminant validity was measured by comparison of the item-to-own scale correlation with the item-to-other scales correlation values (Table 2). For the subscales physical and social well-being, all items exhibited a higher correlation with their own scale than with the other subscales. For the subscales psychological and spiritual well-being, a few items exhibited a higher correlation with one or more of the other scales. The items 'uncertainty future' and 'survivorship guilt' exhibited a substantially higher correlation with all other subscales then with their own.

Table 3 shows the correlations between the four subscales and the overall scale. The correlations between spiritual and physical well-being, between spiritual and psychological well-being and between spiritual and social well-being were negligible (resp. $r = .09$, $r = .15$ and $r = .00$). Note that the moderate correlation between spiritual well-being and the overall scale ($r = .31$) is in contrast to the high correlations between the other subscales and the overall scale ($r \geq .79$).

The overall QOL-CS test-retest reliability assessed among 103 participants was .79. Physical, psychological, social and spiritual well-being had reliability coefficients of .69, .75, .70 and .71 respectively. All item-to-item

Table 3. Interscale correlations[*] of the QOL-CS

	Spearman rank Correlations				
	Physical Well-being	**Psychological Well-being**	**Social Well-being**	**Spiritual Well-being**	**Overall quality of life**
Physical well-being	-				
Psychological well-being	.65	-			
Social well-being	.54	.68	-		
Spiritual well-being	.09	.15	.00	-	
Overall quality of life	.79	.93	.79	.31	-

[*] Spearman rank correlations

correlations were in the range of .38 - .87, except the item 'fertility' in the social well-being scale, which had a test-retest correlation of .22. Additional subgroup analyses showed that test-retest reliability was high among participants in different stages or different therapies.

Convergent validity was measured between the QOL-CS and the SF-36. Table 4 reveals substantial to high correlations for most of the scales. The overall QOL-CS correlation with the total SF-36 scale was .67. Table 4 also shows the correlations between the QOL-CS scales and the IIRS-R of which most were moderate to substantial. There was a negligible negative association between social well-being and relationships with friends (r = -.07). The QOL-CS and the IIRS-R were weakly positively but significantly associated (r = .28).

Discussion

Results show that the physical, psychological and social subscales of the QOL-CS have good psychometric properties. The subscale spiritual well-being had low internal consistency and the subscale to scale correlation was below acceptance. Furthermore, analysis of convergent validity showed that correlations between the spiritual well-being scale and the associated IIRS-R scale were too low. In contrast, a US validation study showed that this scale was more reliable and valid in the USA [4]. This is thought to be due to differences in culture and population. Religious and spiritual elements also appeared to be less relevant in childhood cancer survivors in the USA [3]. Because the items 'uncertainty future' and 'survivorship guilt' both had extremely low and even negative item-to-own correlations, we recommend dropping these items from the Dutch version of the QOL-CS for prostate cancer survivors. This will raise the internal consistency. The performance of the QOL-CS without these two items needs to be addressed in future research.

Table 4. Convergent validity of the QOL-CS and the SF-36 and the QOL-CS and IIRS-R^

	QOL-CS			
	Physical well-being	**Psychological well-being**	**Social well-being**	**Spiritual well-being**
SF-36				
Physical functioning	.62*	.41*	.37*	.06
Emotional well-being	.55*	.62*	.41*	.15*
Social functioning	.60*	.52*	.45*	.07*
IIRS-R				
Physical health	.44*	.29*	.18	.15
Mental health	.30*	.31*	.20*	.29*
Relationship with friends	.11	-.04	-.07	.08
Religious expression	.10	-.10	-.12	.41*

^Spearman rank correlation
* P-value < 0.05

The study had several limitations. The QOL-CS results were based on a group of Dutch prostate cancer survivors. Nevertheless, we found similar reliable and valid results on the subscales physical, psychological and social well-being but not spiritual well-being as compared to the earlier US validation reports [3, 4]. Also, it is possible that response bias among those who were willing to participate twice might have confounded the results, as second time responders were diagnosed more often with stage II disease and more often underwent prostatectomy. However, additional analyses revealed that test-retest results were high for different stage and treatment subgroups of patients. In conclusion, the QOL in Dutch long-term prostate cancer survivors was adequately measured by the physical, psychological and social well-being subscale and can be used in order to measure the specific aspects of QOL important to cancer survivors. However, as the subscale spiritual well-being showed a low internal consistency, which could be related to cultural background, it seems to be appropriate to evaluate the validity and reliability of the QOL-CS in other cultural settings.

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4

Long-term quality of life among Dutch prostate cancer survivors: results of a population-based study

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(*Cancer,* 2006: **107** (9): 2186-2196)

Abstract

This study describes the health-related quality of life (HRQL) of long-term prostate cancer survivors, 5-10 years after diagnosis, and compares it to that of an age-matched normative sample of the general Dutch population. The population-based Eindhoven Cancer Registry was used to select all men diagnosed with prostate cancer from 1994 to 1998. Nine hundred and sixty-four patients received questionnaires (the SF-36 and the Quality of life-Cancer Survivors questionnaire), 780 of whom (81%) responded. Unselected long-term prostate cancer survivors reported comparable HRQL, but worse general health perceptions and better mental health than an age-matched norm population. Patients who underwent radical prostatectomy had the highest physical HRQL, followed by 'watchful waiting' patients and patients who received radiotherapy. Hormonally treated patients, in general, had the lowest physical HRQL. The results suggest that the long-term HRQL of prostate cancer survivors can vary significantly as a function of the type of primary treatment. Because baseline differences between treatment groups cannot be excluded as part of the explanation of the differences, these findings need to be verified in longitudinal studies.

Introduction

Prostate cancer is currently the most prevalent cancer among older males in western, industrialized countries [1]. Due to the introduction of PSA testing in the early 1990's, more prostate cancer is detected at an earlier disease stage at diagnosis [2]. The number of prostate cancer patients is also increasing due to the growing incidence, improved survival and the ageing of the population [3]. This has led to increasing numbers of individuals who are either cured of their cancer or are living with it as a chronic disease [4]. In the south of the Netherlands, the 5-year relative survival of prostate cancer patients is 83% and the 10-year relative survival is 69% [5]. This means that the majority of prostate cancer patients will become long-term survivors. According to the definition of the American Cancer Society, a 'long-term survivor' is a cancer patient who is alive 5 years after initial diagnosis [6].

Prostate cancer and its treatment can affect both disease-specific health-related quality of life (HRQL) (e.g. urinary, sexual and bowel functions) as well as general HRQL (e.g. energy/vitality and mental and physical health) although this latter effect is not always found [7-9]. Many studies have investigated the HRQL of patients with prostate cancer, but only a few focussed on long-term survivors [10-13]. In addition, the majority of these studies were not population-based, relatively few patients were included and studies that compare all available treatment options are scarce. Results of a population-based study that includes a large number of patients undergoing different treatments can be more easily generalized to the full population of long-term prostate cancer survivors. The aim of the present population-based study was to obtain insight into the long-term HRQL effects of prostate cancer and its various treatments, and to compare the HRQL of prostate cancer survivors with that of the general population.

Methods

Setting and Participants

A population-based, cross-sectional survey was conducted at the Eindhoven Cancer Registry (ECR). The ECR records data on all patients newly diagnosed with cancer in the southern part of the Netherlands, an area with 2.3 million inhabitants, 10 hospitals, with 17 hospital locations and two large radiotherapy institutes [5]. The ECR was used to select all patients diagnosed with prostate cancer between 1994 and 1998. Participants older than 75 years at diagnosis were excluded as it was expected that they would have difficulty in completing a self-report questionnaire without assistance. To exclude all persons who had died before November 1 2004, our database was linked with the database of the Central Bureau for Genealogy, which collects data on all deceased Dutch citizens via the civil municipal registries. After having excluded all persons who had died, data collection was started in November 2004. Approval for this study was obtained from a local certified Medical Ethics Committee.

Data collection

Urologists sent their (former) patients a letter to inform them about the study, together with the questionnaire. The letter explained that, by returning the completed questionnaire, the patient agreed to participate and consented with linkage of the questionnaire data with their disease history as registered in the ECR. Patients were reassured that non-participation did not have any consequences for their follow-up care or treatment. If the questionnaire was not returned within two months, a reminder-letter with an additional copy of the questionnaire was sent.

Measures

The ECR routinely collects data on tumour characteristics, including date of diagnosis, grade (Tumour-Node-Metastasis clinical classification [14]) and clinical stage (Tumour-Node-Metastasis clinical classification [14]), treatment, and patient background characteristics including date of birth and comorbidity at the time of diagnosis (a slightly adapted version of the Charlson comorbidity index [15]).

Primary treatment was classified as radical prostatectomy (usually retro pubic), radiotherapy, primary hormonal therapy only and watchful waiting (including transurethral resection of the prostate). The radiotherapy group only represents patients who received external beam radiotherapy; brachytherapy was not available as a treatment option in the region of the comprehensive cancer centre south between 1994 and 1998. Patients undergoing a radical prostatectomy followed by any other adjuvant therapy, such as radiotherapy or hormonal therapy, were included in the radical prostatectomy group. Patients who received radiotherapy and hormonal therapy were included in the radiotherapy group.

The Dutch version of the SF-36 questionnaire was used to assess generic HRQL [16]. According to standard scoring procedures, all scales were linearly converted to a 0-100 scale, with higher scores indicating better functioning. Differences of at least 5 points (the general health dimension) [17], 6.5 points (the physical dimensions) and 7.9 points (the mental health dimensions) were considered clinically meaningful [18]. The SF-36 scores of the patient sample were compared with those of a gender- and age-matched normative sample drawn from a large, random, nationwide normative sample of adults (n=1742) taken from the general Dutch population [19].

Generic HRQL survival issues were assessed with the Dutch version of the Quality of life-Cancer Survivors (QOL-CS) questionnaire [20] including 45 visual analogue scales, each of which ranges from 0 (worst outcome) to 10 (best outcome). These 45 visual analogue scales are grouped into four multi-item subscales on well-being: physical, psychological, social and spiritual. It examines issues of particular concern to long-term cancer survivors such as distress since diagnosis, sexuality, employment, uncertainty about the future and the role of spirituality and religion [21]. The QOL-CS has been demonstrated to be a valid and reliable instrument when administered to American prostate cancer survivors [20, 22, 23] as well as in our population of prostate cancer survivors [24], although the subscale spiritual well-being showed low reliability and validity in the latter cohort. The developers of the QOL-CS have suggested a 20% change or a 2-point difference on the 0-10 scales to indicate clinical significance.

The questionnaire also included questions on sociodemographic data, including marital status, current occupation, educational level and disease progression and current comorbidity.

Statistical analyses

All statistical analyses were performed using SAS (version 9.1 for Windows, SAS institute Inc., Cary NC). Routinely collected data from the ECR on patient and tumour characteristics enabled us to compare the group of respondents, non-respondents and patients who were lost to follow-up, using t-tests for continuous variables and chi-square analyses for categorical variables. The sociodemographic and clinical characteristics of the patients were analyzed using chi-square tests for categorical variables. Two hundred thirty-three patients were excluded from the primary analyses because they exhibited disease progression (39 new primary tumour, 83 metastasis and 111 recurrence), resulting in 572 patients to be analysed. Because a number of variables were skewed, non-parametric tests were used when appropriate.

Linear regression analyses were carried out in order to investigate the association between patient characteristics (age, comorbidity) and tumour characteristics (stage, treatment, time since diagnosis) with the composite and subscale scores of the SF-36 and with the QOL-CS. On the basis of the univariate results, multivariate models were constructed to determine which of the patient and tumour characteristics were associated independently with HRQL outcomes. We controlled for these variables in the analysis of covariance (ANCOVA), which was used to compare means of SF-36 and QOL-CS scores between different treatment subgroups.

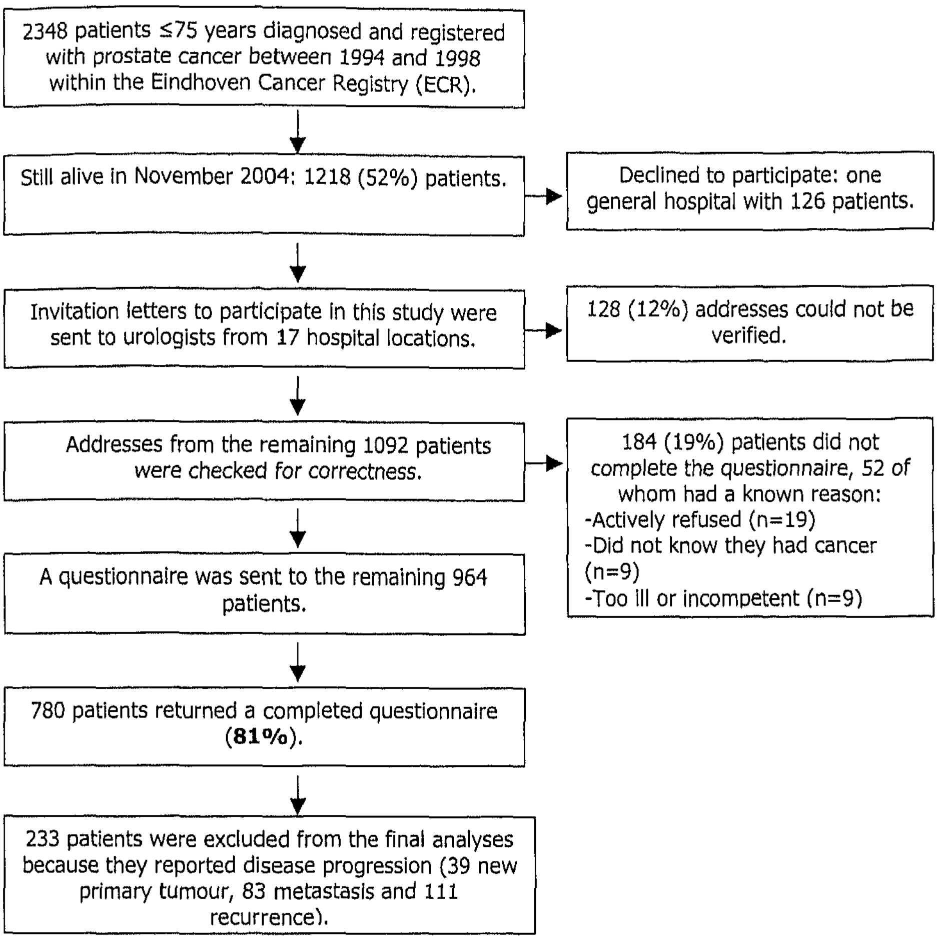
The radical prostatectomy and radiotherapy groups included patients who also received additional hormonal therapy as part of primary treatment. In the radical prostatectomy group this hormonal therapy was usually combined with additional radiotherapy. Because combining patients treated with or without adjuvant therapies could possibly influence the comparisons between the radical prostatectomy, radiotherapy and hormonal therapy groups, all analyses were performed twice, first for primary treatment groups without additional adjuvant therapies, and secondly with all treatment combinations possible.

Results

Seven hundred and eighty (81%) of the 964 prostate cancer survivors returned a completed questionnaire (Figure 1). A comparison of respondents, non-respondents and patients with unverifiable addresses indicated that non-respondents were significantly older, more often diagnosed with stage I disease and less likely to be treated with radical prostatectomy than respondents or patients with unverifiable addresses. Non-respondents were more often not treated ('watchful waiting') than respondents and patients with unverifiable addresses (Table 1).

Differences in sociodemographic and clinical characteristics of prostate cancer survivors, grouped by primary treatment, are presented in Table 2. Radical prostatectomy patients were significantly younger than those treated with radiotherapy, hormonal therapy or watchful waiting. Radical prostatectomy patients and hormonally treated patients were diagnosed mainly with stage II and grade II disease, patients treated with radiotherapy more often had stage II and grade I or II disease, and watchful waiting patients most often were diagnosed with stage I and grade I disease. Radical prostatectomy and watchful

Figure 1. Flow-chart of the data collection process



2348 patients ≤75 years diagnosed and registered with prostate cancer between 1994 and 1998 within the Eindhoven Cancer Registry (ECR).

Still alive in November 2004: 1218 (52%) patients.

Declined to participate: one general hospital with 126 patients.

Invitation letters to participate in this study were sent to urologists from 17 hospital locations.

128 (12%) addresses could not be verified.

Addresses from the remaining 1092 patients were checked for correctness.

184 (19%) patients did not complete the questionnaire, 52 of whom had a known reason:
-Actively refused (n=19)
-Did not know they had cancer (n=9)
-Too ill or incompetent (n=9)

A questionnaire was sent to the remaining 964 patients.

780 patients returned a completed questionnaire (**81%**).

233 patients were excluded from the final analyses because they reported disease progression (39 new primary tumour, 83 metastasis and 111 recurrence).

waiting patients were more often employed than patients treated with radiotherapy or hormonal therapy, probably due to their younger age. No significant differences between the different primary treatment groups were found in years since diagnosis, comorbidity, marital status, and current occupation or education level.

Patients treated with radical prostatectomy had received additional primary radiotherapy in 3% of cases and additional primary hormonal therapy in 13% of cases. Patients treated with primary radiotherapy had received additional primary hormonal therapy in 19% of cases. Additional analyses with each combination of treatments separately revealed no significant differences in

Table 1. Socio-demographic and medical characteristics of questionnaire respondents, non-respondents and patients whose addresses could not be verified.

	N (%)			
	Respondents N=780	**Non-respondents** N=184	**Patients with unverifiable addresses** N=128	**P-value**
Age at time of survey				
60-69 years	192 (25)	43 (23)	28 (22)	
70-74 years	212 (27)	33 (18)	38 (30)	
75-79 years	246 (32)	56 (30)	35 (27)	
80-85 years	130 (17)	52 (28)	27 (21)	0.01
Years since diagnosis				
5-7 years	463 (59)	107 (58)	84 (66)	
8-10 years	317 (41)	77 (42)	44 (34)	0.35
Stage at diagnosis				
I	164 (21)	66 (36)	30 (23)	
II	426 (55)	77 (42)	62 (48)	
III	96 (12)	22 (12)	21 (16)	
IV	45 (6)	9 (5)	7 (5)	
Unknown	49 (6)	10 (5)	8 (6)	0.01
Primary treatment				
Radical prostatectomy	257 (33)	35 (19)	39 (30)	
Radiotherapy	323 (41)	65 (35)	40 (31)	
Hormonal therapy	107 (14)	30 (16)	23 (18)	
Watchful waiting	93 (12)	45 (24)	20 (16)	
Unknown	0 (0)	9 (5)	6 (5)	<0.0001

HRQL (data not shown), meaning that the same significant differences between treatment groups were found using combined or separate treatment groups (Table 3). Therefore, patients undergoing a radical prostatectomy combined with any adjuvant therapy were included in the radical prostatectomy group and patients who received radiotherapy and hormonal therapy were included in the radiotherapy group.

On average, patients treated with primary hormonal therapy scored, on average 18 points lower for physical functioning ($p<0.001$) and 9 points lower for vitality ($p<0.05$) than patients in the radical prostatectomy group. The mean score for physical functioning among patients treated with radiotherapy was, on average, 11 points lower compared to patients treated with radical prostatectomy ($p<0.001$) (Table 3). Some potentially clinically meaningful differences were observed that were not statistically significant. This may be due to large within-treatment group variations.

Table 2. Socio-demographic and clinical characteristics of prostate cancer survivors without recurrent disease or new primary malignancies.

	%				
	Radical Prostatectomy N=193	**Radiotherapy N=263**	**Hormonal therapy N=60**	**Watchful waiting N=56**	**P-value**
Additional radiotherapy	3	-	-	-	
Additional hormone therapy	13	19.0			
Age at time of survey					
60-69 years	39	14	12	17	
70-74 years	31	24	21	27	
75-79 years	28	40	36	25	
80-85 years	4	22	31	31	<0.0001
Years since diagnosis					
5-7 years	60	62	57	61	
8-10 years	41	38	43	39	0.91
Stage at diagnosis					
I	4	27	16	62	
II	60	65	44	27	
III	25	5	11	0	
IV	2	0	21	1	
Unknown	10	3	7	10	<0.0001
Grade *					
I	33	40	21	70	
II	49	39	53	20	
III	16	14	24	3	
Unknown	3	7	1	7	<0.0001
Comorbidity					
None	40	34	43	32	
1	36	36	24	41	
2+	24	30	33	27	0.29
Most frequent co-morbid conditions					
1. Hypertension	30	27	33	30	0.72
2. Arthritis	22	22	20	25	0.89
3. Cardiovascular disease	11	14	7	10	0.43
Marital status					
Married	80	76	75	76	
Not married/divorced	8	6	7	1	
Widowed	10	15	13	18	
Unknown	3	4	4	4	0.12
Education level					
Low	39	45	59	37	
Medium	32	32	26	37	
High	26	18	10	23	
Unknown	3	5	4	4	0.27

Table 2 Continued. Socio-demographic and clinical characteristics of prostate cancer survivors without recurrent disease or new primary malignancies.

	%				
	Radical Prostatectomy N=193	**Radiotherapy N=263**	**Hormonal therapy N=60**	**Watchful waiting N=56**	**P-value**
Current occupation					
Employed	11	5	3	9	
Unemployed	5	2	2	1	
Retired	84	93	95	90	0.05

* Grade was based on the Tumour-Node-Metastasis clinical classification [14]. Grade I is comparable to a Gleason score of 2-4, grade II is comparable to Gleason score of 5-7 and grade III is comparable to a Gleason score of 8-10.

Because the choice of treatment is strongly associated with age, we further analysed separately the HRQL of patients <75 years and >75 years of age (Table 3). The choice of separation into two age groups was justified by ANOVA analyses, which showed differences in HRQL between these age groups for five subscales of the SF-36 (data not shown). In general, HRQL scores were higher for younger survivors than older survivors. Radical prostatectomy patients in general had higher HRQL scores compared to other treatments, especially among patients 75 years and older. Among the younger patients, the watchful waiting group (n=22) was comparable in all subscales with the radical prostatectomy group, whereas the older watchful waiting patients had constantly lower scores than those who underwent radical prostatectomy. There were also between treatment differences for patients 75 years and older for the subscales physical functioning ($p<0.05$) and social functioning ($p<0.05$).

In all age groups, prostate cancer survivors reported a statistically and clinically significant better mental health score and worse general health perceptions score compared to the normative sample (Figure 2). In addition, the youngest group of prostate cancer survivors (60-69 years) reported higher vitality scores (mean 68 vs. 62, $p<0.01$) than the age-matched normative sample from the general population. Survivors between 70 and 74 years of age showed lower scores for bodily pain (mean 81 vs. 89, $p<0.05$) compared to the normative sample.

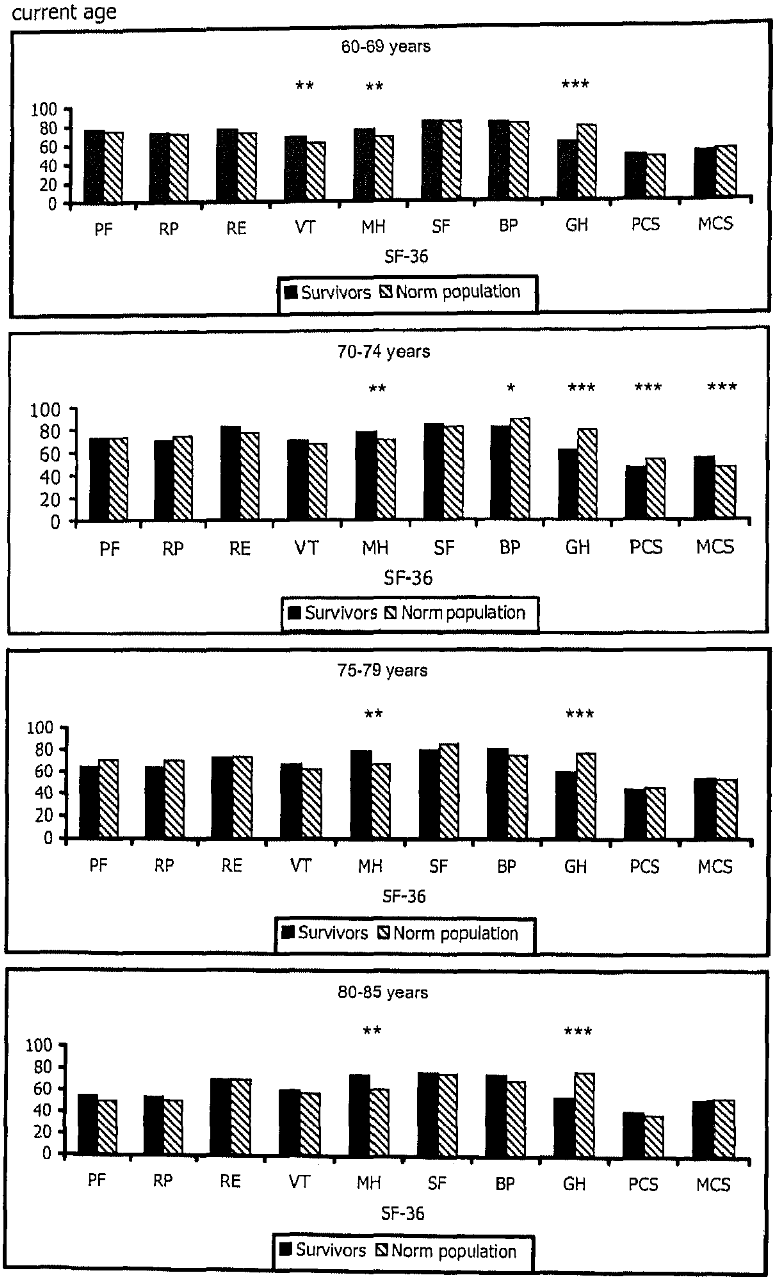
A comparison of SF-36 scores between the different treatment groups and the age-matched normative sample revealed few statistically significant differences (Figure 3). Prostate cancer patients in the radical prostatectomy, radiotherapy and watchful waiting groups reported significantly less pain than the normative sample.

Table 3. SF-36 scores among Dutch prostate cancer survivors according to treatment.

	Mean (SD)				
	Radical Prostatectomy	**Radiotherapy**	**Hormonal therapy**	**Watchful waiting**	**P-value ◇**
All ages	**N=193**	**N=263**	**N=69**	**N=69**	
Physical function	75.7 (24.4)	64.7 (28.0) a	57.4 (31.8) a	67.4 (27.0)	<0.001*
Role-Physical	72.4 (40.0)	62.4 (42.8)	62.7 (43.7)	63.0 (42.4)	0.13
Bodily pain	82.2 (22.3)	78.7 (22.9)	78.1 (27.0)	82.5 (22.3)	0.31
GHP	62.8 (19.2)	58.6 (19.6)	56.2 (22.4)	59.1 (18.7)	0.06
Vitality	70.9 (20.8)	65.2 (20.2)	62.1 (22.4) a	66.3 (21.3)	0.05*
Social functioning	85.8 (20.1)	79.7 (23.8)	78.8 (25.7)	80.7 (25.2)	0.05
Role-emotional	79.6 (35.9)	73.8 (40.6)	73.6 (40.3)	74.3 (41.8)	0.64
Mental health	78.9 (16.6)	76.6 (18.3)	73.7 (22.8)	78.4 (16.7)	0.25
PCS	46.8 (9.8)	43.8 (11.1)	42.9 (11.5)	44.6 (9.7)	0.02
MCS	53.3 (8.5)	53.1 (10.2)	52.1 (11.0)	53.5 (8.6)	0.83
<75 Year	**N=131**	**N=101**	**N=22**	**N=29**	
Physical function	78.5 (21.6)	71.6 (26.6)	66.0 (29.6)	75.0 (22.4)	0.10
Role-Physical	73.3 (39.5)	69.0 (40.3)	73.6 (38.8)	66.7 (40.2)	0.97
Bodily pain	81.7 (35.0)	80.6 (38.8)	86.4 (22.7)	80.6 (24.2)	0.96
GHP	63.0 (21.1)	61.4 (21.1)	55.0 (21.7)	62.3 (15.8)	0.38
Vitality	70.7 (16.3)	66.5 (19.2)	65.7 (21.9)	70.4 (22.6)	0.62
Social functioning	85.2 (20.2)	83.2 (24.1)	85.8 (16.9)	86.1 (16.4)	0.88
Role-emotional	80.8 (22.3)	79.0 (23.6)	78.3 (37.9)	82.7 (36.2)	0.97
Mental health	77.9 (19.2)	75.2 (20.9)	76.6 (18.7)	78.2 (16.9)	0.74
PCS	47.3 (9.6)	46.0 (10.7)	45.4 (11.0)	46.1 (10.2)	0.69
MCS	52.7 (8.8)	52.4 (11.3)	53.5 (7.6)	54.3 (9.0)	0.92
75 and older	**N=62**	**N=162**	**N=47**	**N=40**	
Physical function	69.7 (29.0)	60.1 (28.1) a	53.4 (32.4) a	61.0 (29.2) a	0.05*
Role-Physical	70.4 (41.4)	57.8 (44.0)	56.8 (45.6)	59.8 (44.8)	0.16
Bodily pain	83.5 (37.8)	77.5 (41.6)	74.0 (28.2)	83.7 (21.1)	0.17
GHP	62.4 (20.3)	56.8 (19.7)	56.8 (23.0)	56.8 (20.6)	0.25
Vitality	71.5 (17.1)	64.4 (17.7)	60.4 (22.7)	62.9 (19.9)	0.06
Social functioning	87.1 (20.1)	77.6 (23.5) a	75.3 (28.7) a	76.9 (29.5) a	0.05*
Role-emotional	77.1 (22.3)	70.4 (22.4)	71.1 (41.9)	67.7 (45.2)	0.70
Mental health	81.0 (19.4)	77.4 (18.6)	72.4 (24.6)	78.5 (16.8)	0.09
PCS	45.7 (10.1)	42.1 (11.1)	41.6 (11.7)	43.2 (9.2)	0.12
MSC	54.7 (7.5)	53.7 (9.3)	51.4 (12.4)	52.8 (8.3)	0.51

PCS: Physical component scale; MCS: Mental component scale; GHP: General health perception.
a Significantly different from radical prostatectomy (p<0.05)
* The difference between treatments is clinically meaningful
◇ P-value was adjusted for stage, age at diagnosis, grade, years since diagnosis, education, marital status and comorbidity.

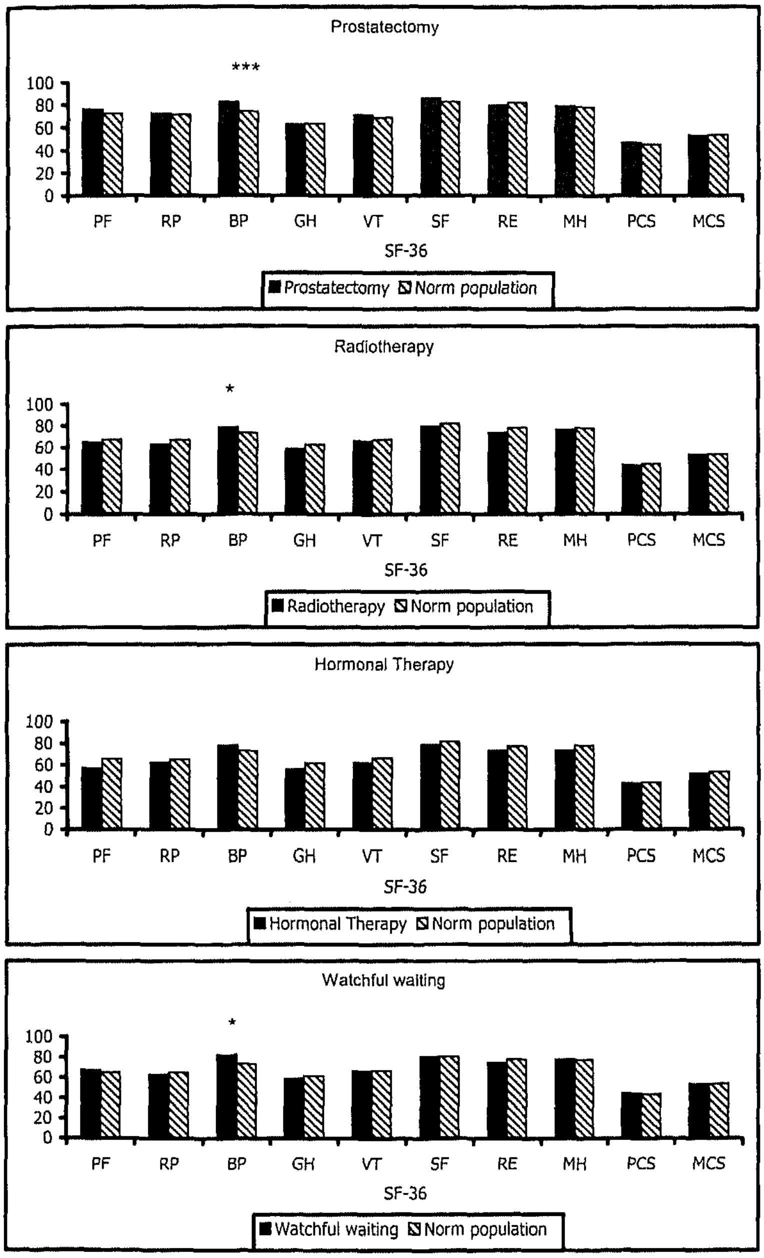
Figure 2. SF-36 subscale scores: survivors vs. norm population according to current age



*<0.05, **<0.01, ***<0.001

PF= Physical functioning, RP= Role limitations physical health, RE=Role limitations emotional problems, VT=Vitality, MH=Mental Health, SF= Social functioning, BP=Bodily pain, GH= General health, MCS=Mental component scale, PCS=Physical component scale.

Figure 3. SF-36 subscale scores: differences between survivors and an age-matched norm population according to treatment



T-test between norm population and treatments, *$p<0.05$; **$p<0.01$; *** $p<0.001$
PF= Physical functioning, RP= Role limitations physical health, RE=Role limitations emotional problems, VT=Vitality, MH=Mental Health, SF= Social functioning, BP=Bodily pain, GH= General health, MCS=Mental component scale, PCS=Physical component scale.

Table 4. QoL-CS scores for each subscale and per subscale the significant questions for Dutch prostate cancer survivors according to treatment at diagnosis.

	Mean (SD)				
	Radical Prostatectomy N=193	**Radiotherapy N=263**	**Hormonal therapy N=60**	**Watchful waiting N=56**	**P-value ◇**
Physical WB	8.3 (1.6)	7.6 (2.0)	7.7 (2.1)	7.8 (1.6)	<0.001
Psychological WB	7.0 (1.5)	6.8 (1.6)	6.6 (1.8)	7.3 (1.3)	0.05
Social WB	7.2 (1.4)	7.3 (1.7)	7.4 (1.6)	7.6 (1.6)	0.29
Spiritual WB	4.9 (1.5)	4.6 (1.5)	4.5 (1.3)	4.7 (1.2)	0.70
Total QoL-CS	6.9 (1.1)	6.7 (1.2)	6.6 (1.4)	7.0 (1.0)	0.14

◇ P-value was adjusted for stage, age at diagnosis, grade, years since diagnosis, education, marital status and comorbidity.
WB: well-being

Patients undergoing radiotherapy, hormonal therapy or watchful waiting scored statistically significantly ($p<0.001$) lower on the 'physical' subscale of the QoL-CS than the radical prostatectomy group (Table 4). Patients who were managed with watchful waiting scored significantly higher ($p<0.05$) on the 'psychological' subscale than patients who were treated. However, these statistically significant differences were not clinically meaningful.

Discussion

Five to ten years after diagnosis, radical prostatectomy patients reported the highest physical HRQL, followed by patients who were not treated (watchful waiting) and patients treated with radiotherapy. Hormonally treated patients, in general, reported the lowest physical HRQL. Long-term survivors of prostate cancer had a worse score for general health perception but a better score for mental health in comparison to an age-matched normative sample from the general Dutch population. Direct comparisons between treatment groups and age-matched norm population revealed that patients in all treatment groups had similar or even better HRQL scores.

These results confirm those of other studies in which the generic HRQL of prostate cancer survivors who underwent radical prostatectomy or radiotherapy has never been found to be worse than that of a control or normative sample [8, 10, 11]. Because research on long-term cancer survivors is relatively recent, we also compared our results with those of several studies that focused on short-term survivors. A longitudinal prospective cohort study of men with localized prostate cancer [11] found that, at a median 52-month follow-up assessment, radical prostatectomy and radiotherapy patients scored about the same or even better than the general population on all SF-36 scales. A large American study found that, 12 to 48 months after treatment for early prostate cancer, survivors reported similar overall physical and mental health compared to men without prostate cancer (SF-12) [8]. General HRQL also remained similar to that for controls in a HRQL study among 709 long-term survivors (at a median of 6.2 years after treatment) [10].

There is increasing evidence that most people not only experience negative but also certain positive effects after an encounter with a stressor [25-31]. This is also known as "benefit finding" which can be described as the identification of benefit from adversity [32]. Furthermore, patients may experience posttraumatic growth [31, 33-37] which is described as "the experience of significant *positive change arising from the struggle with a major life crisis*" [38]. Benefit finding and posttraumatic growth may explain, at least in part, the higher self-reported HRQL in survivors compared to the age-matched norm population. Another possible explanation is the fact that, although there is no prostate cancer screening program available in the Netherlands, most patients are presumably diagnosed by means of a PSA test and this could be called screening. Socio-economic status (SES) is positively associated with screening [39] and high SES is related with high HRQL [40].

Nevertheless, when we compared all prostate cancer survivors according to age groups, we found that self-reported general health perceptions were worse than that of the general population normative sample. This is a novel finding not reported in previous studies. It can possibly be attributed to either adverse late effects of treatment (e.g. incontinence, impotence or bowel problems) or a general feeling of being less healthy compared to population norms due to having had cancer in the past.

Radical prostatectomy patients have been described before as having a better HRQL after treatment than patients receiving radiotherapy [11] or androgen deprivation therapy [41]. However, several studies found no differences between treatments in terms of HRQL for short [42-44] or long-term [10, 45] survivors. Two reports from the population-based American Prostate Cancer Outcomes Study (PCOS) found no association between primary treatment (radical prostatectomy, radiotherapy, hormone ablation therapy and watchful waiting) and 2-year generic HRQL outcomes [43, 44]. The follow-up on this report, 5 years after diagnosis, did not find a difference in HRQL between radiotherapy and radical prostatectomy patients [45]. In another study among localized prostate cancer survivors and controls, measures of general HRQL remained similar for each treatment group, four to eight years after treatment [10]. A study on HRQL after a mean follow-up of 4 years did not find significant differences in either well-being or subjective HRQL between radical prostatectomy and watchful waiting patients [42]. However, subjective HRQL was measured with a single question.

Possible explanations for differences in study outcomes could be the sometimes small patient numbers primarily in the hormonal and watchful waiting treatment groups. Additionally, two studies were conducted less than five years after initial diagnosis [43, 44]. It is also possible that baseline differences between treatment groups were more pronounced in one or the other study, influencing the outcomes of short and maybe even long-term HRQL follow-up. The current study is, to our knowledge, one of the first population-based studies that included all patients with all available primary therapies given 5-10 years ago. Perhaps this specific feature caused the differences we found compared to other studies. In the literature we found only one study that included patients treated primarily with hormonal therapy, which was the therapy that generated the most HRQL differences in our study [43]. Finally, just two of the studies were population-based [43, 44].

Despite the fact that most studies did not find differences between treatments in generic HRQL, all studies did find differences in disease-specific HRQL outcomes. This may seem to be contradictory. However, a Dutch study among prostate cancer patients revealed that, while patients consider sexual, urinary and bowel functions as problems, they do not take them into account when completing HRQL questionnaires because they do not view these dysfunctions as aspects of health [46]. Another explanation may be the "response shift" phenomenon, that suggests that a person may change his internal standards or redefine his concept of HRQL over time [47, 48]. In the Dutch study mentioned above, many patients accepted the side-effects as inevitable consequences of having been treated for prostate cancer, a condition they perceived to be life-threatening [46].

Particularly noteworthy are the high HRQL scores (SF-36) observed for the small group of young watchful waiting patients, compared to the older patients in this group. A possible explanation is that the reasons for choosing watchful waiting are probably different between younger and older patients. Another possibility is that younger patients better understand or are better able to deal with such an approach.

Several limitations from the current study should be noted. First, although 12% of patients could not be sent a questionnaire because of unverifiable addresses, and 19% of patients who were sent a questionnaire did not respond, we do not know what their current health status is. Although non-respondents were more often diagnosed with stage I disease, they were also older (80-85 years) and more often received no therapy. It is therefore possible that our results cannot be generalized to the very old with prostate cancer. Furthermore, it is important to keep in mind that our results can only be generalized to a small percentage of the original group of 2348 prostate cancer patients while a large group of patients could not be included in our study (they died, there hospital declined to participate or their addresses could not be verified). Second, although the ECR routinely collects a range of clinical data, no information on either the PSA levels during the follow-up of 5-10 years or the duration of hormone treatment was available. We also do not know whether secondary hormonal therapy was started some time after primary treatment. These factors could have an impact on the HRQL of long-term survivors. Third, it is more difficult to draw conclusions from a cross-sectional study than a longitudinal study. Some baseline differences were found in characteristics of prostate cancer survivors (age, stage, grade), grouped by primary treatment. These differences are probably caused by the non-random treatment allocation. Randomized controlled trials may ensure comparable groups at baseline. However, only a selected group of prostate cancer patients will be eligible for random allocation to treatments. Fourth, patients with disease progression were excluded from our analysis. Information on HRQL of these patients is therefore lost. However, we experienced difficulties in reporting HRQL of this heterogeneous subset of patients because additional tumour characteristics for disease progression (e.g., localisation, stage, grade and time since diagnosis) were unknown. Our results can only be generalized to survivors with the best prognosis namely, those who do not show any signs of disease progression. Fifth, another limitation of our study is the possibility that some findings may be due to chance. This is due to multiple testing and using a p-value of 0.05, using a p-value of 0.01 would reduce this possibility.

Despite those limitations, the results of this study form an important contribution to the limited information available on HRQL for the growing group of long-term prostate cancer survivors, especially in hormonally treated patients or for whom a watchful waiting policy was applied. The large number of participants in this study and the high response rate allow us to extrapolate to the broad population of long-term prostate cancer survivors without disease progression.

In conclusion, the results suggest that the long-term HRQL of prostate cancer survivors can vary significantly as a function of the type of primary treatment. Because baseline differences between treatment groups cannot be excluded as part of the explanation of the differences, these findings need to be verified in longitudinal studies.

Acknowledgement

The authors want to thank all patients for their participation in the study. Furthermore, they want to thank Rotary Tilburg Triborch and the Comprehensive Cancer Centre South for financially supporting the study.

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Bowel, urinary, and sexual problems among 5-10 year prostate cancer survivors: a population-based study

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Abstract

To obtain more insight into the long-term effects of prostate cancer diagnosis and treatment on bowel, urinary, and sexual function we performed a large population-based study. Prostate-specific function was compared with an age-matched normative population of Dutch screening participants without a history of prostate cancer. Through the population-based Eindhoven Cancer Registry we selected all men diagnosed with prostate cancer between 1994 and 1998 in the southern part of the Netherlands. In total, 964 patients, alive on November first 2004, received a questionnaire (UCLA-EPIC and Sac); 780 (81%) responded. A reference group was used for comparison. Urinary problems were most common after a prostatectomy and bowel problems were most common after radiotherapy. Compared to a reference group with a similar age distribution, both urinary and bowel functioning and bother were significantly worse among survivors. Urinary incontinence was reported by 23-48% of survivors compared to 4% of the normative population. Bowel leakage occurred in 5-14% of patients compared to 2% of norms. Erection problems occurred in 40-74% of patients compared to 18% of norms. The results of this population-based study form an important contribution to the limited information available on prostate-specific problems in the growing group of long-term prostate cancer survivors. Bowel, urinary, and sexual problems occur more often among long-term survivors in comparison to a reference group and cannot merely be explained by age. Since these problems persist for many years, urologists should provide patients with adequate information on this topic before treatment. After treatment, there should be an appropriate focus on these problems.

Introduction

In the Netherlands there were approximately 53.000 prostate cancer survivors in the year 2005 and this is expected to increase to 87.000 in 2015 [1]. The number of prostate cancer patients is increasing due to the growing incidence and improved survival [1]. In addition, the introduction of PSA testing in the early 1990's has led to the detection of prostate cancer at an earlier stage at diagnosis [2]. PSA testing frequently results in over-diagnosis [3], which may explain partially the improving relative survival rates. In the south of the Netherlands, the 5- and 10-year relative survival rates of prostate cancer patients are 83% and 69%, respectively [4]. The majority of prostate cancer patients will thus become long-term survivors; long-term survivors are those alive five years after initial diagnosis [5].

Prostate cancer and its treatment can affect the lives of patients in many ways. Both disease-specific health-related quality of life (i.e. bowel, urinary, and sexual functioning and bother) as well as general health-related quality of life (i.e. physical, psychological, social, and spiritual quality of life) can be affected, although the latter effect is not always apparent [6-8]. Results of studies among short-term cancer survivors (<5 years after diagnosis) showed that bowel function is mainly affected in patients who underwent radiotherapy [7, 9-12], whereas urinary and sexual functions are mainly disrupted after radical prostatectomy [7, 9-18]. Some of these complaints will diminish over time, others are permanent [17, 19].

Knowledge of disease-specific complaints among *long-term* prostate cancer survivors is important because of the long life most patients experience after diagnosis. However, the number of relevant studies is small [17, 19-23]. But most importantly, so far no population-based study has been conducted that included both a large study population and a reference group, and also evaluated all available treatment options. The use of a reference group without prostate cancer with the same age is important to evaluate what may be attributed to age and what may be due to treatment.

The aim of the present study was to obtain more insight into the long-term effects of prostate cancer and its treatment on bowel, urinary, and sexual function in a large population-based study in comparison to prostate-specific problems in a reference group of the same age.

Methods

Setting and Participants

A population-based, cross-sectional survey was conducted at the Eindhoven Cancer Registry (ECR). The ECR contains data on all newly diagnosed cancer patients in the southern part of the Netherlands, an area with 2.3 million inhabitants, 10 hospitals, 17 hospital locations and two large radiotherapy institutes [4]. The ECR was used to select all patients diagnosed with prostate cancer between 1994 and 1998.

Participants older than 75 years at diagnosis were excluded as it was expected that they would have difficulty in completing a self-report questionnaire without assistance. To avoid addressing persons who had died before November 1 2004, our database was linked with the database of the Central Bureau for Genealogy, which collects data on all deceased Dutch citizens via the civil municipal registries. After having excluded all persons who had died, data collection was started in November 2004. Approval for this study was obtained from a certified Medical Ethics Committee.

The reference group consisted of screened participants without (a history of) prostate cancer from the European Randomized Study for Screening on Prostate Cancer (ERSPC) in the region Rotterdam, the Netherlands [24]. Between January 2003 and May 2004 the reference group of healthy men, i.e. without prostate cancer, who were due for the second or the third screening round received a short questionnaire on health by mail, attached to the invitation for screening. The questionnaire, which was the same as the questionnaire that was sent to the group of survivors, was completed by 3892 men (response 81% of mailed questionnaires, age range 58-78). Data on men who were subsequently diagnosed with prostate cancer (n=82) were excluded.

Data collection

Urologists sent their (former) patients a letter to inform them about the study, together with the questionnaire. The letter explained that, by returning the completed questionnaire, the patient agreed to participate and consented with linkage of the questionnaire data with their disease history as registered in the ECR. Patients were reassured that non-participation did not have any consequences for their follow-up care or treatment. If the questionnaire was not returned within two months, a reminder-letter with an additional copy of the questionnaire was sent. Returned questionnaires did not contain any explicit identifiers (i.e. names) but were number coded for the purpose of data collection tracking and linkage with the ECR database.

Measures

The ECR routinely collects data on tumour characteristics, including date of diagnosis, grade and clinical stage (Tumour-Node-Metastasis clinical classification [25]), treatment, and patient background characteristics including date of birth and comorbidity at the time of diagnosis (a slightly adapted version of the Charlson comorbidity index [26]).

Primary treatment was classified as radical prostatectomy (usually retro pubic), external beam radiotherapy, primary hormonal therapy only or watchful waiting (including transurethral resection of the prostate). Brachytherapy was not available as a treatment option in the region of the Comprehensive Cancer Centre South between 1994 and 1998.

Urinary and bowel function were measured with the urinary and bowel modules of the University of California, Los Angeles (UCLA) Expanded Prostate Cancer Index (EPIC) [27]. As in another Dutch study, four out of six EPIC scales were used [24]. In that particular study, the EPIC was carefully translated into Dutch with forward-backward translations. This procedure was analog to the adaptation procedure of the UCLA-PCI [28]. The four scales assess the level of urinary functioning (5 items) and bowel functioning (7 items) (e.g. frequency of urinary leakage, number of pads worn to control urinary leakage, frequency of diarrhea or abdominal cramps) and the degree of urinary and bowel bother (7 items each). All scores were transformed linearly and ranged from 0 to 100. A score of 100 indicates the best level of functioning or no bother.

Sexual function and bother were assessed by a Dutch sexual activities module (Sac) that consists of 12 single items that do not add up to a scale [28]. The Sac questionnaire contains, among others, questions on sexual activity, reasons not to be active (if applicable), the ability to have and maintain an erection, and the use of erectile dysfunction treatments. Each item has between three and five answer categories.

Besides the scale scores of UCLA-EPIC and the questions of the Sac, we evaluated three questions more in depth. One question about urinary incontinence (defined as being incontinent one or more times a day) and one question on bowel leakage (defined as leakage one or more times a week) from the UCLA-EPIC were evaluated. In addition, one question on erectile problems (defined as almost always) from the Sac was evaluated. In our opinion, these problems are clinically relevant for both urologists and patients.

The questionnaire also included items on sociodemographic data, including marital status, current occupation and educational level as well as disease progression and current comorbidity.

Statistical analyses

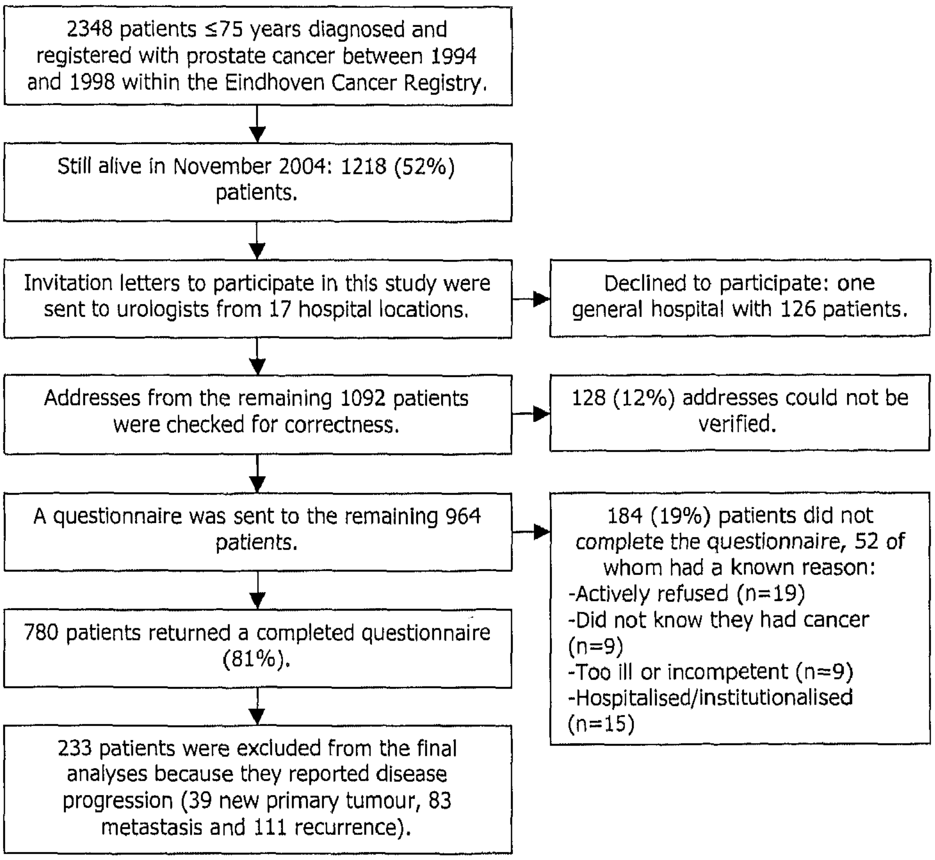
All statistical analyses were performed using SAS (version 9.1 for Windows, SAS institute Inc., Cary NC). Routinely collected data from the ECR on patient and tumour characteristics enabled us to compare the group of respondents, non-respondents and patients with unverifiable addresses using chi-square analyses. The sociodemographic and clinical characteristics of the patients were analyzed using chi-square tests for categorical variables. Two hundred and thirty-three patients were excluded from the final analyses because they exhibited disease progression (39 new primary tumour, 83 metastasis and 111 recurrence), resulting in data on 572 patients to be analysed. If variables showed a skewed distribution, non-parametric tests were used.

Linear regression analyses were carried out in order to investigate the association between patient characteristics (age, comorbidity) and tumour characteristics (stage, grade, time since diagnosis) using subscale scores of the UCLA-EPIC. Based on univariate results, multivariate models were constructed to determine which of the patient and tumour characteristics were independently associated with UCLA-EPIC outcomes. We controlled for these variables in the analysis of covariance (ANCOVA), which was used to compare means of UCLA-EPIC scores grouped according to primary treatment.

Means of UCLA-EPIC scores were also compared between survivors, grouped according to primary treatment, and a norm population. Men in the reference group were between 60 and 79 years old. Therefore, we compared them with survivors between 60 and 79 years, excluding 115 survivors for these analyses. Since we found no statistically or clinically significant differences in UCLA-EPIC scores between the norm population aged 60-69 and 70-79 years, we combined the two age groups.

The radical prostatectomy and radiotherapy groups included patients who also received additional hormonal therapy as part of their primary treatment. In the radical prostatectomy group hormonal therapy was usually combined with additional radiotherapy. Because combining patients treated

Figure 1. Flow-chart of the data collection process



with or without adjuvant therapies could possibly influence the comparisons between the radical prostatectomy, radiotherapy and hormonal therapy groups, the comparison of UCLA-EPIC scores for survivors according to treatment at diagnosis was performed twice, first for primary treatment groups without additional adjuvant therapies and secondly for all possible treatment combinations.

Results

Seven hundred and eighty (81%) of the 964 prostate cancer survivors returned a completed questionnaire (Figure 1). A comparison of respondents, non-respondents and patients with unverifiable addresses indicated that non-respondents were significantly older, more often diagnosed with stage I disease

Table 1. Socio-demographic and medical characteristics of questionnaire respondents, non-respondents and patients who were lost to follow-up.

	N (%)			
	Respondents	**Non-respondents**	**Patients with unverifiable addresses**	
	N=780	**N=184**	**N=128**	**P-value**
Age at time of survey				
60-69 years	192 (25)	43 (23)	28 (22)	
70-74 years	212 (27)	33 (18)	38 (30)	
75-79 years	246 (32)	56 (30)	35 (27)	
80-85 years	130 (17)	52 (28)	27 (21)	0.01
Years since diagnosis				
5-7 years	463 (59)	107 (58)	84 (66)	
8-10 years	317 (41)	77 (42)	44 (34)	0.35
Stage at diagnosis				
I	164 (21)	66 (36)	30 (23)	
II	426 (55)	77 (42)	62 (48)	
III	96 (12)	22 (12)	21 (16)	
IV	45 (6)	9 (5)	7 (5)	
Unknown	49 (6)	10 (5)	8 (6)	0.01
Primary treatment				
Radical prostatectomy	257 (33)	35 (19)	39 (30)	
Radiotherapy	323 (41)	65 (35)	40 (31)	
Hormonal therapy	107 (14)	30 (16)	23 (18)	
Watchful waiting	93 (12)	45 (24)	20 (16)	
Unknown	0 (0)	9 (5)	6 (5)	<0.001

and less often treated with radical prostatectomy than respondents or patients with unverifiable addresses (Table 1). Non-respondents were more often not treated ('watchful waiting') than respondents and patients with unverifiable addresses.

Differences in sociodemographic and clinical characteristics of prostate cancer survivors, grouped according to primary treatment, are presented in Table 2. Radical prostatectomy patients were significantly younger than those treated with radiotherapy, hormonal therapy or watchful waiting. Radical prostatectomy patients and hormonally treated patients were most often diagnosed with stage II and grade II disease, patients treated with radiotherapy more often had stage II and grade I or II disease, and watchful waiting patients were most often diagnosed with stage I and grade I disease. Radical prostatectomy and watchful waiting patients more often had a job than patients treated with radiotherapy or hormonal therapy, probably due to their younger age. No significant differences between the different primary treatment

Table 2. Socio-demographic and clinical characteristics of prostate cancer survivors without recurrent disease or new primary malignancies.

	%				
	Radical Prostatectomy N=193	**Radiotherapy N=263**	**Hormonal therapy N=60**	**Watchful waiting N=56**	**P-value**
Additional radiotherapy	3	-	-	-	
Additional hormone therapy	13	19			
Age at time of survey					
60-69 years	39	14	12	17	
70-74 years	31	24	21	27	
75-79 years	28	40	36	25	
80-85 years	4	22	31	31	<0.001
Age at time of survey					
Mean	72	76	77	76	<0.001
Years since diagnosis					
5-7 years	60	62	57	61	
8-10 years	41	38	43	39	0.91
Stage at diagnosis					
I	4	27	16	62	
II	60	65	44	27	
III	25	5	11	0	
IV	2	0	21	1	
Unknown	10	3	7	10	<0.001
Grade at diagnosis*					
I	33	40	21	70	
II	49	39	53	20	
III	16	14	24	3	
Unknown	3	7	1	7	<0.001
Comorbidity					
None	40	34	43	32	
1	36	36	24	41	
2+	24	30	33	27	0.29
Most frequent co-morbid conditions					
1. Hypertension	30	27	33	30	0.72
2. Arthritis	22	22	20	25	0.89
3. Cardiovascular disease	11	14	7	10	0.43
Marital status					
Married	80	76	75	76	
Not married/divorced	8	6	7	1	
Widowed	10	15	13	18	
Unknown	3	4	4	4	0.12
Education level					
Primary school	39	45	59	37	
Secondary school	32	32	26	37	
College/university	26	18	10	23	
Unknown	3	5	4	4	0.27

Table 2 Continued. Socio-demographic and clinical characteristics of prostate cancer survivors without recurrent disease or new primary malignancies.

	%				
	Radical Prostatectomy N=193	**Radiotherapy N=263**	**Hormonal therapy N=60**	**Watchful waiting N=56**	**P-value**
Current occupation					
Employed	11	5	3	9	
Unemployed	5	2	2	1	
Retired	84	93	95	90	0.05

* Grade was based on the Tumour-Node-Metastasis clinical classification [25]. Grade I is comparable to a Gleason score of 2-4, grade II is comparable to Gleason score of 5-7 and grade III is comparable to a Gleason score of 8-10.

groups were found in years since diagnosis, comorbidity, marital status, and current occupation or educational level.

Patients treated with radical prostatectomy received additional primary radiotherapy in 3% of cases and additional primary hormonal therapy in 13% of cases. Additional primary hormonal therapy was given to 19% of patients treated with primary radiotherapy. Additional analyses with each combination of treatments separately revealed no significant differences in prostate-specific problems (data not shown), meaning that the same significant differences between treatment groups were found when using combined or separate treatment groups. Therefore, we only present combined treatment groups.

Patients who underwent a radical prostatectomy reported significant deterioration of urinary functioning ($p<0.02$) in comparison to patients treated otherwise, whereas no *statistically* significant differences in urinary bother ($p=0.87$) or urinary summary score ($p=0.06$) were found between treatments (Table 3). Bowel functioning ($p<0.001$), bowel bother ($p<0.001$), and the bowel summary score ($p<0.001$) were significantly lower, and thus worse, for patients treated with radiotherapy in comparison to patients treated otherwise.

Urinary and bowel scores were compared between prostate cancer survivors, according to treatment groups, and a normative population without prostate cancer of the same age (Figure 2). Urinary functioning, urinary problems and the urinary summary score were significantly worse for survivors compared to the normative population ($p<0.001$). Bowel functioning was significantly worse for prostatectomy patients ($p<0.05$), radiotherapy patients ($p<0.001$), and hormonal therapy patients ($p<0.05$) compared to the normative

Table 3. UCLA-EPIC scores for Dutch prostate cancer survivors according to treatment at diagnosis.

	Mean (SD)				
	Radical Prostatectomy N=193	**Radio-therapy N=263**	**Hormonal therapy N=69**	**Watchful waiting N=69**	**P-value**
Urinary functioning	77.5 (18.5)	86.1 (18.0)	88.0 (15.7)	86.5 (16.6)	<0.02
Urinary bother	77.6 (16.9)	77.4 (17.7)	77.7 (17.4)	78.2 (16.9)	0.87
Urinary summary	77.3 (16.0)	81.1 (16.2)	81.7 (15.1)	81.0 (15.4)	0.06
Bowel functioning	93.5 (9.4)	87.8 (13.1)	92.7 (9.5)	92.8 (10.0)	<0.001
Bowel bother	92.5 (11.3)	84.0 (17.3)	90.7 (12.9)	92.6 (11.4)	<0.001
Bowel summary	92.8 (10.4)	85.8 (14.3)	91.8 (10.2)	92.5 (10.1)	<0.001

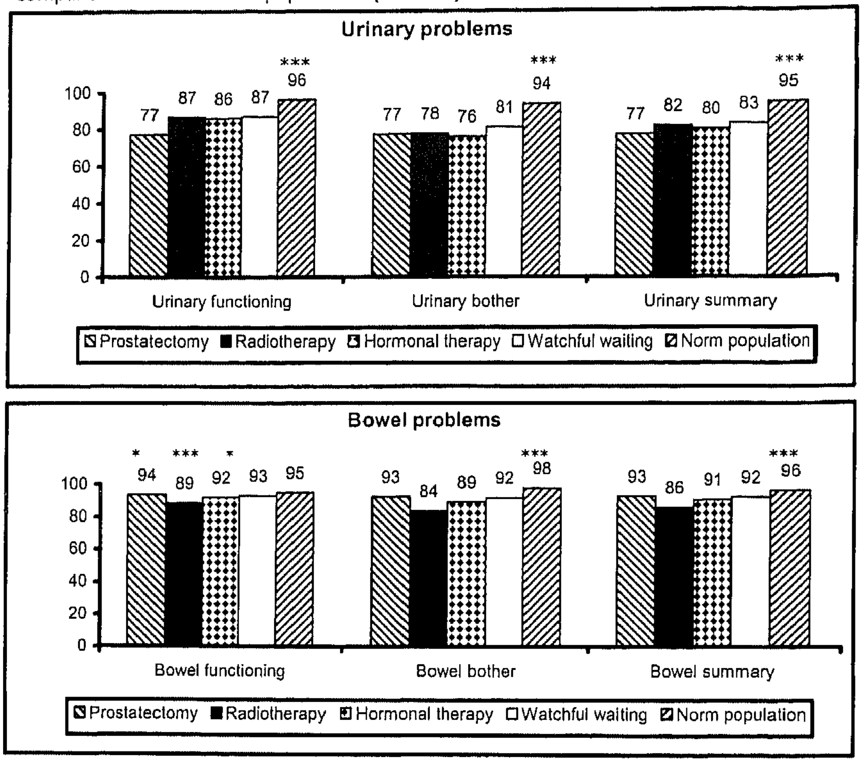
P-value was adjusted for stage, age at diagnosis, grade, years since diagnosis and comorbidity.

population. Bowel functioning of the watchful waiting group was not significantly different compared to the normative population. Bowel bother and bowel summary scores were significantly ($p<0.001$) worse for survivors compared to the norm population.

Urinary incontinence occurred at least once a day among 48% of patients after radical prostatectomy and 23 to 24% of the other patients which was significantly worse compared to 4% incontinence for the normative population of the same age (Figure 3). Bowel leakage occurred one or more times per week among 14% of radiotherapy patients, between 5 to 8% for other patients and 2% of the age-matched normative population. Bowel leakage was significantly worse for radiotherapy and hormonal therapy survivors compared to the population norm. Erection problems occurred among 74% of prostatectomy patients, 67% of radiotherapy or hormonal therapy patients and 40% of 'watchful waiting' patients. Erection function was significantly worse among survivors compared to the norm population, of which 18% of men experienced problems.

The majority of patients (n=408, 69%) stated that they were not sexually active, for 37% of these patients (n=178) this was due to erectile problems (Figure 4). Sexually active patients also indicated that they experienced problems with getting an erection (n=98, 76%) and if not (n=29, 22%) some of these men experienced problems maintaining their erection (n=7, 24%). Fifteen percent (n=20) of sexually active men reported the use of erectile dysfunction treatments, mainly medication (n=9, 45%) or injections into the penis (n=8, 40%).

Figure 2. UCLA-EPIC scores of survivors (n=432) according to treatment group in comparison with the norm population (n=3749).



We assessed whether survivors had different EPIC scores compared to the norm. When this was the case, an asterix was placed above the norm population. When only a subgroup of survivors was different compared to the norm, then an asterix was placed above that particular subgroup.

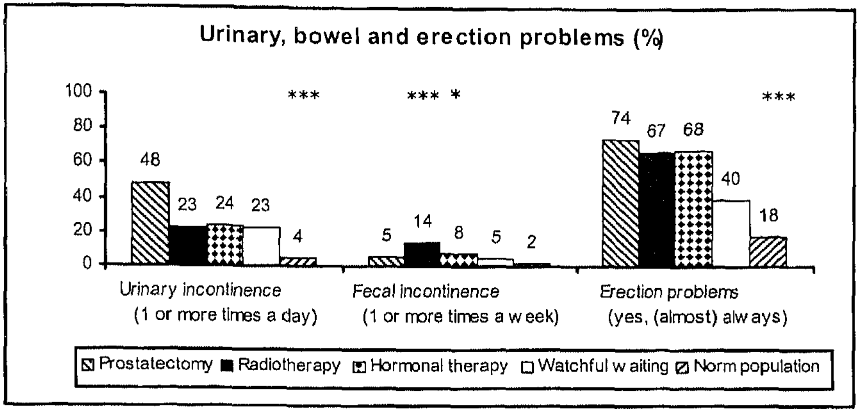
*$p<0.05$; *** $p<0.001$.

Prostate cancer survivors were age-matched with the norm population, therefore, only patients between 60-79 years old were included.

Discussion

In our studied population of 5-10 year survivors of prostate cancer, urinary problems were most common after radical prostatectomy and bowel problems were most common after radiotherapy. Both urinary and bowel functioning and bother were worse for survivors in comparison to a reference group of the same age. In addition, urinary incontinence, bowel leakage and erection problems occurred far more often among prostate cancer survivors in comparison to the normative population. Furthermore, half of the cancer

Figure 3. Prostate-specific problems among Dutch prostate cancer survivors (according to treatment groups) and an age-matched norm population in percentages.

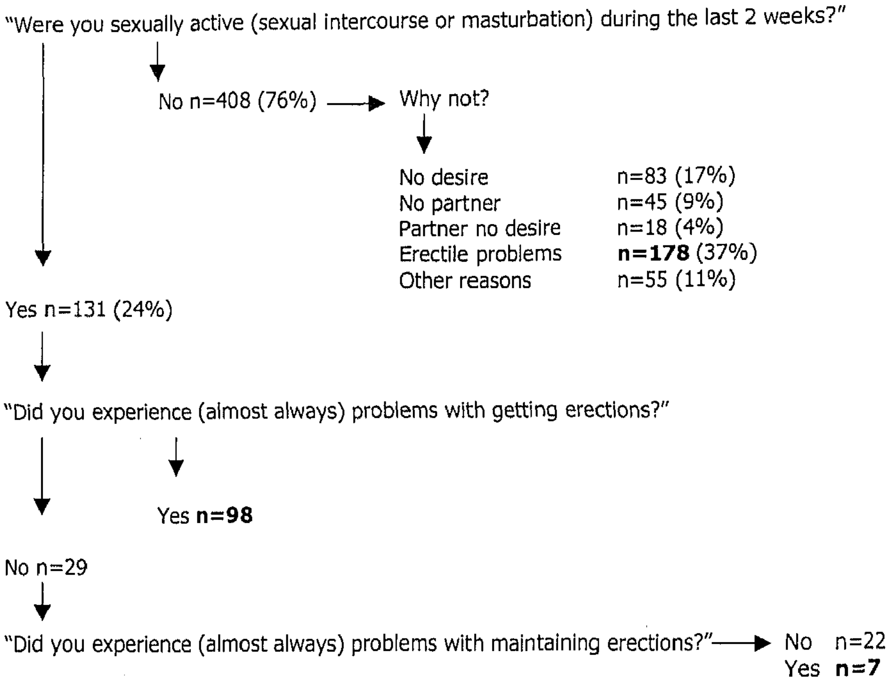


Prostate cancer survivors were compared with a male norm population between 60-79 years old; therefore only patients between 60-79 years old were included.
*$p<0.05$; *** $p<0.001$.
This figure includes combined treatment modalities. Because the majority of patients will become impotent after adjuvant hormonal therapy, the analyses were also done for each treatment separately. Patients treated with only radical prostatectomy or only radiotherapy reported erection problems in 77% and 65% of cases, respectively.

survivors reported problems with having or maintaining an erection. A minority of sexually active men made use of erectile dysfunction treatments.

Urinary problems were most common after radical prostatectomy and bowel problems were most common after radiotherapy. Our results thus confirm previous short-term [7, 9-11, 13, 14] and long-term [17, 21] studies. Furthermore, urinary and bowel problems were worse for survivors in comparison to an age-matched reference group. This was confirmed by two short-term [8, 29] and three long-term studies [17, 19, 23] of which the latter will be described below. An American study among 709 *localized* prostate cancer survivors showed radical prostatectomy, but not radiotherapy, to be associated with worse urinary incontinence relative to controls, 6.2 years after treatment. Furthermore, radiotherapy but not radical prostatectomy was associated with worse bowel functioning [17]. This same effect was also found in a study among 139 patients treated with three-dimensional conformal radiation therapy, 3-6 years after diagnosis, in which it was concluded that bladder function and bother were similar to those of the normal population (n=268) but that patients reported more bowel bother [23]. In contrast, a Swedish study of 120 patients showed that eight years after diagnosis of prostate cancer, 54% of radiotherapy patients reported urinary problems versus 31% of the age-matched controls.

Figure 4. Sexual activity and erectile dysfunction in prostate cancer survivors (n=539).



Altogether 283 **(53%)** men experienced erectile problems.

Furthermore, gastrointestinal side-effects were seen in 62% of prostate cancer survivors and 9% of the controls [19].

Besides the more general urinary and bowel functioning, we also presented more specific results on urinary incontinence and bowel leakage. The present study revealed differences in urinary incontinence and bowel leakage between treatments. This corresponds to the results of a Japanese study of 95 stage B2 and C prostate cancer patients a median of 59 months after diagnosis. They too found that urinary incontinence was more frequent among surgically treated patients compared to patients treated with radiotherapy [30]. In our study, urinary incontinence was reported by 23% of radiotherapy patients while in an American study of patients treated with three-dimensional conformal radiation therapy only 13% of radiotherapy patients reported leakage during the day, 3-6 years after diagnosis [23]. Furthermore, 5% of patients in that study reported the use of pads for bowel leakage [23], while in our population of survivors, 14% of patients reported bowel leakage. However, different questionnaires were used to measure urinary incontinence and bowel leakage. In our study bowel leakage was indicated as having bowel leakage one or more times a week and the number pads used in the American study above was not mentioned.

Half of the men in our study and 18% of the men in the reference group experienced erectile problems. Most studies on erection problems only included patients treated with radiotherapy and showed findings comparable to our results. Eight years after diagnosis of prostate cancer, 65% of radiotherapy patients (n=120) and 33% of the age-matched controls (n=125) indicated some kind of sexual problem [19]. According to a recent review, that included prospective studies using validated questionnaires and a proper definition of potency; erectile dysfunction was a problem in 60-70% of patients after radiotherapy [31]. Time elapsed since radiotherapy is important: erectile dysfunction increased between 1 and 2 years after treatment, but it did not seem to change anymore after 3 years. External radiation therapy was associated with a reduction in sexual desire, erectile capacity, and orgasm in a Swedish study of 53 patients with localized prostate cancer [15]. In a majority of these patients, this reduced the quality of life. Furthermore, of 497 patients who were potent before diagnosis, 43% became impotent after 24 months in a study on patients treated with external-beam radiotherapy in an American Prostate Cancer Outcomes Study (PCOS) [18].

Research on erectile problems after radical prostatectomy, hormonal therapy and watchful waiting is scarce. In another PCOS study, of 1187 long-term cancer survivors treated for localized prostate cancer, erectile dysfunction was more prevalent in the radical prostatectomy group (79.3%) than in the radiotherapy group (63.5%) [21]. Factors independently associated with better sexual health outcomes in 671 prostatectomy patients, 4 to 52 months after diagnosis, included younger age, a nerve-sparing technique, time since prostatectomy and smaller prostate size [32]. One year after hormonal therapy, 80% of localized prostate cancer patients reported impotence versus 30% of watchful waiting patients [33]. In our study, 5 to 10 years after diagnosis, these percentages were 69% and 40% respectively.

Although half of the men in our study reported problems with having and maintaining an erection, only 15 % of these men used erectile dysfunction treatments. This number is relatively low compared to the results of an American study reporting that erectile dysfunction was a problem in 85% of men after therapy for localized prostate carcinoma and that 59% of this group used at least one treatment for erectile dysfunction [34]. This difference can probably be explained partly by the fact that the latter study had a response rate of 49% and the sample was weighted toward men who were more interested in remaining sexually active. In addition, cultural differences can play a role. Patients treated with radical prostatectomy who used erectile aids (30%), in comparison to those who did not, reported the best outcomes for sexuality [35].

Several limitations of the current study should be noted. First, we do not know what the current health status is of the 12% of patients who could not be sent a questionnaire because of unverifiable addresses and the 19% non-respondents. Although non-respondents were more often diagnosed with stage I disease, they were also older (80-85 years) and more often received no therapy. It is therefore possible that our results cannot be generalized to the very old with prostate cancer. Secondly, it is more difficult to draw conclusions from a cross-sectional study than from a longitudinal study. Some baseline differences were found in characteristics of prostate cancer survivors (age, stage, grade) grouped according to primary treatment. These differences are attributable to the non-random treatment allocation. Randomized controlled trials may ensure comparable groups at baseline. However, only a selected group of prostate cancer patients will be eligible for random allocation of treatments. Since we only included disease-free survivors in our analyses, we cannot generalize the results of our study to those who exhibit disease progression.

Despite these limitations, the results of this study form an important contribution to the limited information available on prostate-specific problems in the growing group of long-term prostate cancer survivors. This study included an unselected group of men, treated in various general hospitals, not in centres of excellence or tertiary referral centres as in most randomized trials. Results of a population-based study are more easily generalized to the general population compared to results from randomized controlled trials. In addition, the large number of participants in this study and the high response rate of this study allow us to extrapolate to the broad population of long-term prostate cancer survivors without disease progression.

In conclusion, we have demonstrated that differences in prostate-specific problems exist between treatments, years after diagnosis and treatment. These differences cannot be explained merely by age. Nevertheless, as baseline differences between treatment groups cannot be excluded as part of the explanation of the observed differences, these findings need to be verified in longitudinal studies. In addition to the information patients provided on the questionnaires, they very often told us that they had not been aware of the fact that prostate-specific problems would persist for many years. Before treatment, urologists or oncology nurses should provide patients with adequate information on the risk of urinary, bowel and sexual problems after treatment. After treatment, health care workers should pay appropriate attention to prostate-specific problems since patients often do not feel comfortable talking about them.

Acknowledgment

The authors want to thank all patients for their participation in the study. Furthermore, they want to thank Rotary Tilburg Triborch, the Foundation for the Promotion of Academic Training and Research in Health Care (SWOOG) and the Comprehensive Cancer Centre South for financial support of the study.

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6

The impact of adjuvant radiotherapy on health related quality of life in long-term survivors of endometrial (adeno)carcinoma: a population-based study

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(Submitted for publication)

Abstract

The aim of the present study was to compare health related quality of life (HRQL) among 5-10 year survivors of stage I or II endometrial (adeno-)carcinoma (EC) treated with surgery alone or surgery with adjuvant radiotherapy and an age-matched norm population. A population-based, cross-sectional survey was conducted through the Eindhoven Cancer Registry (ECR). All patients were included who were diagnosed with EC between 1994 and 1998 (n=462). Information from the returned questionnaires were linked to routinely collected data from the ECR on patient, tumor and treatment characteristics. Responses were received from 75% of patients. Analyses were restricted to women with stage I or II disease at diagnosis, treated with either surgery alone or with adjuvant radiotherapy, and without recurrent disease or new primary malignancies (n=264). Patients who had received adjuvant radiotherapy (n=80) had a significantly higher tumor stage and grade at diagnosis ($p<0.0001$) and a higher mean time since diagnosis ($p=0.04$). Current age, number of co-morbid diseases, current marital status, nulliparity, education and current occupation were similar for both treatment groups. In multivariate analyses, adjuvant radiotherapy was independently and negatively associated with vitality, physical and social well-being scales. HRQL scores of both treatment groups were however similar to those of an age-matched norm-population. HRQL of EC survivors in general is good. EC survivors treated with surgery alone had a better HRQL than women treated with surgery and adjuvant radiotherapy, although for both groups HRQL was in the range of the norm population.

Introduction

Endometrial cancer (EC) is the most common malignancy of the female genital tract. The American Cancer Society estimated that 40,880 women have been diagnosed with and 7,310 women died of EC in 2005 [1]. EC most often occur in postmenopausal women, with a peak incidence between 55 and 70 years [2] and a median age around 66 years. About 95% are adenocarcinomas. Survival rates of EC have improved during the past decades, with an overall 5-year relative survival rate for 1995-2001 from nine SEER geographic areas of 84.4% [1]. Five year relative survival in the ECR area was 85% in the period 1996-2001 [3]. An ageing population with more diagnoses of EC, public awareness resulting in earlier diagnosis and improved treatment all have resulted in increasing numbers of EC survivors. Based on data from the Netherlands Cancer Registry, the Dutch Cancer Society estimated that in 2005, about 1700 women were diagnosed with EC in the Netherlands, with an estimated prevalence of over 17,000, expected to increase to 25,000 in the year 2015 [3]. In the US on January 1, 2002, 571,854 women were alive with a history of EC [1].

As most cancers are diagnosed at an early stage (75-80% stage I) [2], many patients are primarily treated with surgery. Three randomized trials have established that adjuvant pelvic radiotherapy provides a highly significant improvement of local control, but without a survival advantage in intermediate risk EC [4-7]. Therefore, in the Netherlands, pelvic RT is now considered indicated in 'high-intermediate risk' stage I EC: stage I EC in the presence of at least two of the following three risk factors: 1) grade 3, 2) age 60 and over, and 3) deep (>50%) myometrial invasion. However, it has been challenged whether radiotherapy is indeed indicated in these subgroups, as treatment related morbidity is noted in 25% of irradiated patients, and the impact of this morbidity on quality of life is not known [8].

Interestingly, health related quality of life (HRQL) has never been evaluated in relation to adjuvant radiotherapy in intermediate risk EC. Only a few small studies have investigated HRQL among EC survivors [9-13], but they had low (<40%) response rates [10, 14], or did not associate different EC treatments with outcome [9, 11-13]. The aim of the present study was to obtain insight into the long-term effects of EC and its treatment on HRQL. Therefore, we assessed HRQL in a population-based study among 5-10 year survivors of stage I or II EC treated with surgery alone or adjuvant radiotherapy. Furthermore, a comparison of HRQL was made between EC survivors and an age-matched norm population [14]. The results of this study are expected to provide the growing group of (long-term) EC survivors and specialists with additional information to help make an informed decision about adjuvant radiotherapy or anticipate on possible late consequences of EC and its treatment.

Methods

Setting and Participants

A population-based, cross-sectional survey was conducted through the ECR. The ECR records data on all patients newly diagnosed with cancer in the southern part of the Netherlands, an area with 2.3 million inhabitants, 17 hospital locations and two large radiotherapy institutes. In November 2004 we selected all patients diagnosed with EC between 1994 and 1998. To exclude all persons who had died before November 1 2004, our database was linked with the database of the Central Bureau for Genealogy, which collects data on all deceased Dutch citizens through the civil municipal registries. After exclusion of all deceased patients, data collection was started in November 2004. Participants older than 75 years at diagnosis were excluded from the survey 5-10 years afterwards, as it was expected that they would have difficulty in completing a self-report questionnaire without assistance because of very old age. Approval for this study was obtained from the Medical Ethics Committee of Máxima Medical Centre in Veldhoven.

Data collection

Gynecologists sent their (former) patients a letter to inform them about the study together with the questionnaire. By replying the patients explicitly agreed to participate and consented with linkage of the outcome of the questionnaire with their disease history as registered in the ECR. If the questionnaire was not returned within two months, a reminder-letter was sent. Returned questionnaires only contained a study number which guaranteed anonymity.

Measures

The ECR routinely collects data on tumor characteristics like date of diagnosis, subsite, histology, stage (Tumor-Node-Metastasis clinical classification) primary treatment and patient characteristics including gender, date of birth and since 1993 comorbidity at time of diagnosis (a slightly adapted version from the Charlson comorbidity index) [15].

The Dutch version of the SF-36 questionnaire was used to measure generic QOL [16]. As prescribed, scores were standardized on a scale from 0 to 100, with higher scores indicating better functioning. In order to compare generic QOL in long-term EC survivors to a norm population, we used age matched SF-36 scores available from the general Dutch female population [14].

Generic QOL survivorship issues were assessed with the Dutch version of the Quality of life-Cancer Survivors (QOL-CS) instrument [17]. The QOL-CS is a 45-item visual analogue scale, based on a scale of 0 (worst outcome) to 10 (best outcome). The questionnaire contains four multi-item sub-scales: physical, psychological, social and spiritual well-being. It examines issues of particular concern to long-term cancer survivors such as fear of a second tumor, recurrence or metastasis, survivorship guilt and the role of spirituality and religion [18]. The QOL-CS proved to be psychometrically valid and reliable in American populations [17, 19, 20] as well as in a Dutch population of prostate cancer survivors in the ECR region, except for the subscale spiritual well-being, which showed low reliability and validity in the latter cohort [21]. Chronbach's alphas in the current group of endometrial cancer survivors were respectively .84 for the physical, .85 for the psychological, .69 for the social and .38 for the spiritual subscale. For the total score it was .89.

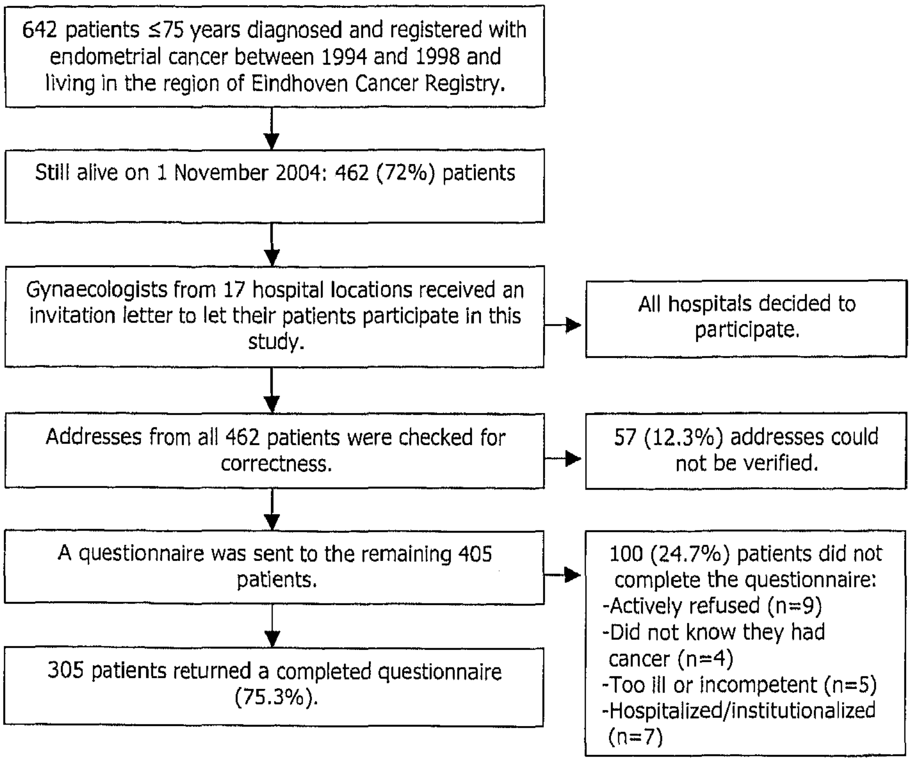
Four additional items were added concerning sexual activity in the past 4 weeks, based on a scale of 1 to 4.

The questionnaire also included items on sociodemographic data, including marital status, current occupation and educational level as well as disease progression and current comorbidity.

Statistical analyses

All statistical analyses were performed using SAS (version 9.1 for Windows, SAS institute Inc., Cary NC). Routinely collected data from the ECR on patient and tumor characteristics enabled us to compare non-respondents with respondents, using chi-square statistics or Fisher's exact test for categorical variables and t-test for continuous variables. These tests were also used to compare women treated with surgery alone with those who also received adjuvant RT. For comparison of outcomes between the treatment groups and the norm population, analysis of covariance (ANCOVA) was used in order to adjust for the effects of age, tumor stage and grade. Multivariate linear regression analyses were carried out in order to investigate the independent association between patient characteristics (age, comorbidity, marital status,

Figure 1. Study population



education and occupation) and tumor characteristics (stage, grade, treatment, time since diagnosis) with the composite and subscale scores of the SF-36 and QOL-CS.

Results

On November 1 2004, 462 out of 642 endometrial (adeno)carcinoma patients diagnosed between 1994 and 1998 were alive (Figure 1). Fifty-seven women were excluded because their addresses could not be verified, resulting in 405 women who were sent a questionnaire. The patient and tumor characteristics of the 57 women whose addresses could not be verified appeared to be not dissimilar to the 405 who were sent a questionnaire (data not shown). Responses were received from 305 patients (75%). The non-

Table 1. Demographic and clinical characteristics of respondents and non-respondents

	N (%)		
	Respondents N=305	**Non-respondents N=100**	**P-value**
Age at time of survey, mean (SD)	67.9 (8)	71.2 (8)	<0.001
Age range	43-85	52-85	
Age			
<64	113 (37)	22 (22)	0.001
65-69	76 (25)	17 (17)	
70-74	48 (16)	26 (26)	
75+	68 (22)	35 (35)	
Years since diagnosis, mean (SD)	8.0 (1)	7.9 (1)	0.43
5-6 years	91 (30)	32 (32)	0.82
7-8 years	142 (47)	43 (43)	
9-10 years	72 (24)	25 (25)	
Stage at diagnosis			
I	268 (88)	89 (89)	0.47
II	23 (7)	4 (4)	
III	8 (3)	5 (5)	
IV	1 (0)	1 (1)	
Unknown	5 (2)	1 (1)	
Primary treatment			
Surgery alone	205 (67)	68 (68)	0.93
Surgery and adjuvant Radiotherapy	91 (30)	28 (28)	
Systemic with/without surgery	6 (2)	3 (3)	
Other/none	3 (1)	1 (1)	

respondents were somewhat older, but there were no differences with the respondents when comparing years since diagnosis, stage at diagnosis or primary treatment (Table 1). Further analyses were then restricted to women with stage I or II disease at diagnosis, treated with either surgery alone or surgery and RT, and without recurrent disease or new primary malignancies (n=264). Twenty-two irradiated patients received a combination of brachytherapy (BRT) and external beam RT (EBRT), the other 58 women only received EBRT. Women who received both BRT and EBRT were more often diagnosed with stage II EC. But, as both RT subgroups were not different from each other when comparing all other characteristics or HRQL outcomes (data not shown), results are presented for both RT groups combined. Women with surgery and adjuvant RT appeared to be somewhat older compared to those receiving surgery alone, although this was not statistically significant (Table 2). Irradiated patients had a significantly higher tumor stage and grade at diagnosis ($p<0.0001$), despite that they showed a higher mean time since diagnosis ($p=0.04$). Current age, number of co-morbid diseases, current marital

Table 2. Socio-demographic and clinical characteristics of EC survivors with stage I or II disease, without recurrent disease or new primary malignancies, treated with surgery alone or adjuvant RT.

	N (%)		
	Surgery alone N=184	**Surgery and RT N=80**	**P-value**
Age at time of survey, mean (SD)	67.8 (7)	69.4 (8)	0.10
Range	54-85	44-82	
Age			
<64	71 (38)	19 (24)	0.07
65-69	49 (27)	21 (26)	
70-74	27 (15)	19 (24)	
75+	37 (20)	21 (26)	
Years since diagnosis, mean (SD)	7.7 (1)	8.1 (1)	0.04
5-6 years	61 (33)	17 (21)	0.14
7-8 years	84 (46)	41 (51)	
9-10 years	39 (21)	22 (28)	
Stage at diagnosis			
Ia	49 (27)	4 (6)	<0.0001
Ib	96 (52)	25 (31)	
Ic	30 (16)	40 (50)	
IIa	7 (4)	8 (10)	
IIb	2 (1)	3 (4)	
Grade			
1	91 (49)	18 (23)	<0.0001
2	67 (36)	46 (58)	
3	16 (9)	16 (20)	
Unknown	10 (5)	-	
Lymphadenectomy	12 (7)	1 (1)	0.05
Co-morbidity at time of survey			
None	49 (27)	20 (25)	0.95
1	66 (36)	30 (38)	
2+	69 (38)	30 (38)	
Most frequent co-morbid conditions			
Arthritis	70 (38)	31 (39)	0.91
Hypertension	69 (38)	32 (40)	0.70
Diabetes	29 (16)	12 (15)	0.88
Marital status			
Married	108 (59)	53 (66)	0.72
Not married/divorced	18 (10)	8 (10)	
Widowed	50 (27)	16 (20)	
Unknown	8 (4)	3 (4)	
Nulliparous	32 (17)	15 (19)	0.90
Education level			
Low	103 (56)	50 (63)	0.60
Medium	53 (29)	21 (26)	
High	20 (11)	5 (6)	
Unknown	8 (4)	4 (5)	

RT= Radiotherapy

Table 2 Continued. Socio-demographic and clinical characteristics of EC survivors with stage I or II disease, without recurrent disease or new primary malignancies, treated with surgery alone or adjuvant RT.

	N (%)		
	Surgery alone N=184	**Surgery and RT N=80**	**P-value**
Current occupation			
Employed	22 (12)	6 (8)	0.33
Unemployed	91 (49)	35 (44)	
Retired	63 (34)	36 (45)	
Unknown	8 (4)	3 (4)	

status, nulliparity, education and current occupation were similar for both treatment groups.

Compared to women who received surgery alone, women who were also irradiated reported lower scores on all subscales of the SF-36 and QOL-CS. The ANCOVA revealed a significant effect for treatment on the subscales vitality, social functioning and mental health, after adjustment for differences in age at the time of survey, years since diagnosis, stage of tumor and grade of tumor, see Table 3. Physical and social well-being, measured by the QOL-CS were also statistically significantly less in those who received radiotherapy, as was the total QOL-CS score. No differences in sexual activity were found, but vaginal dryness was more often reported by the 25 sexually active irradiated women (NS).

In a direct comparison between treatment groups and age-matched SF-36 norm-data, both groups of cancer survivors scored significantly better on the subscale bodily pain, i.e. less pain (Figure 2). Women treated with surgery alone had similar or even better scores on all subscales, whereas irradiated women almost always had non-significant lower scores when compared to the norm-data.

Multivariate linear regression analyses with SF-36 (Table 4a) and QOL-CS (Table 4b) subscales as outcome variables showed the independent association with measured tumor and patients characteristics. Older women demonstrated worse scores for physical functioning, role limitations due to physical health and the physical component scale as measured by the SF-36, but their psychological and social well-being and total QOL scores as measured by the QOL-CS were better. Tumor stage was positively associated with physical functioning (SF-36), whereas tumor grade was positively associated with social well-being and the

Table 3. Analysis of covariance (ANCOVA) of outcome variables for patients treated with surgery alone, or adjuvant RT.

	Mean (SD)		
	Surgery alone N=184	**Surgery and RT N=80**	**P-value**
SF-36*			
PF	68.3 (27.6)	65.2 (27.3)	0.22
RP	65.7 (40.8)	58.7 (44.0)	0.22
BP	74.5 (24.0)	72.7 (25.2)	0.26
GH	63.2 (19.8)	58.2 (20.6)	0.12
VT	65.7 (18.6)	59.1 (19.0)	0.01
SF	82.2 (20.0)	76.1 (23.2)	0.04
RE	74.3 (40.1)	66.2 (44.4)	0.21
MH	75.7 (17.3)	70.1 (18.0)	0.02
PCS	45.1 (11.2)	45.5 (10.6)	0.40
MCS	51.9 (10.3)	49.9 (9.5)	0.08
QoL-CS*			
Physical well-being	7.8 (1.7)	7.5 (2.1)	0.04
Psychological well-being	6.6 (1.5)	6.4 (1.5)	0.08
Social well-being	7.6 (1.8)	7.2 (1.5)	0.03
Spiritual well-being	4.8 (1.4)	4.7 (1.3)	0.62
Total score	6.8 (1.2)	6.5 (1.2)	0.02
Sexual Functioning (in past 4 weeks):	N=133	N=51	
Interested in sex	1.6 (0.7)	1.6 (0.7)	0.90
Sexually active	1.6 (0.6)	1.5 (0.6)	0.78
If sexually active:	N=70	N=25	
Enjoyable sex	2.0 (0.8)	2.1 (0.9)	0.45
Dry vagina during sexual activity	2.2 (1.2)	2.6 (1.1)	0.17

RT= Radiotherapy

SF-36= Short Form-36, PF= Physical Functioning, RP= Role limitations Physical health, BP= Bodily Pain, GH= General Health, VT= Vitality, SF= Social Functioning, RE= Role limitations Emotional problems, MH= Mental Health, PCS= Physical Component Scale, MCS= Mental Component Scale

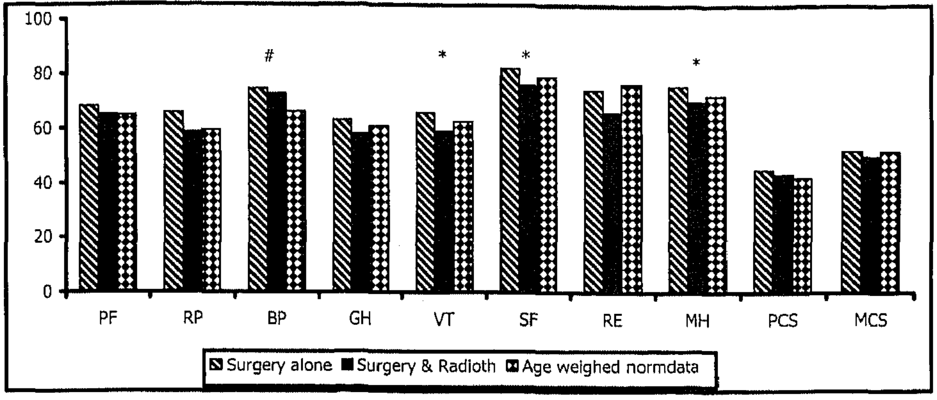
QoL-CS=Quality of Life in Cancer Survivors

* Higher score correlates with better quality of life

† Adjusted for age at time of survey, stage and grade of tumor at diagnosis

total QOL, both measured by the QOL-CS. Women who were irradiated scored significantly lower on the SF-36 vitality associated with all subscales of the SF-36 and QOL-CS. Higher educated women reported better physical functioning (SF-36), and better social well-being (QOL-CS).

Figure 2. SF-36 subscale scores: Endometrial cancer survivors, stage I or II, treated with surgery alone or adjuvant RT versus an age-weighed norm population of Dutch women.



SF-36= Short Form-36, PF= Physical Functioning, RP= Role limitations Physical health, BP= Bodily Pain, GH= General Health, VT= Vitality, SF= Social Functioning, RE= Role limitations Emotional problems, MH= Mental Health, PCS= Physical Component Scale, MCS= Mental Component Scale.

*<0.05: Statistically significant difference between both treatment groups

#<0.05: Statistically significant difference between age weighed norm-data and both treatment groups

Discussion

The results of this study show that 5-10 years after diagnosis EC survivors treated with surgery alone had a better HRQL than women treated with surgery and adjuvant radiotherapy. Radiotherapy appeared to be independently and negatively associated with vitality (SF-36) and physical and social well-being (QOL-CS) among long term EC survivors. HRQL scores of both treatment groups were in the range of those of an age-matched norm-population.

Although adjuvant radiotherapy in EC is associated with tissue damage that may result in treatment related morbidity [22, 23] and assumed to lead to a diminished HRQL [24], only few studies have investigated long-term HRQL in EC survivors and the association with treatment. A Swedish study comparing HRQL of 61 EC survivors with healthy controls showed a poorer HRQL in the EC survivors, but did not have information about tumor or treatment characteristics to be associated with this [9], whereas a retrospective analysis of 70 EC stage I survivors who were at least 5 years after diagnosis demonstrated that adjuvant radiotherapy significantly worsened the HRQL of patients undergoing surgery [10].

Table 4a. Multivariate Linear Regression Model Evaluating Independent Variables for SF-36 subscale scores, for all patients combined (n=264).

	SF-36 subscales†									
Independent variable	**PF**	**RP**	**BP**	**GH**	**VT**	**SF**	**RE**	**MH**	**PCS**	**MCS**
Age	-.38**	-.21*	NS	NS	NS	NS	NS	NS	-.29**	NS
Time §	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Tumor stage	.12*	NS	NS	NS	NS	NS	NS	NS	NS	NS
Tumor grade	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Radiotherapy	NS	NS	NS	NS	-.15*	NS	NS	NS	NS	NS
Comorbidity	-.28**	-.29**	-.36**	-.27**	-.25**	-.15*	-.16*	-.14*	-.38**	NS
Marital status	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Education	.17*	NS	NS	NS	NS	NS	NS	NS	NS	NS
Occupation	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

SF-36= Short Form-36, PF= Physical Functioning, RP= Role limitations Physical health, BP= Bodily Pain, GH= General Health, VT= Vitality, SF= Social Functioning, RE= Role limitations Emotional problems, MH= Mental Health, PCS= Physical Component Scale, MCS= Mental Component Scale

† Standardized beta coefficients

* p<.05, ** p<.001

§ Time since diagnosis

Table 4b. Multivariate Linear Regression Model Evaluating Independent Variables for QOL-CS subscale scores, for all patients combined (n=264).

	QOL-CS subscales†				
Independent variable	**Physical Well-being**	**Psychological Well-being**	**Social Well-being**	**Spiritual Well-being**	**Total score**
Age	NS	.19*	.25*	NS	.20*
Time since diagnosis	NS	NS	NS	NS	NS
Tumor stage	NS	NS	NS	NS	NS
Tumor grade	NS	NS	.19*	NS	.18*
Radiotherapy	-.18*	NS	-.17*	NS	-.18*
Comorbidity	-.29**	-.30**	-.17*	-.22*	-.34**
Marital status	NS	NS	NS	NS	NS
Education	NS	NS	.15*	NS	NS
Occupation	NS	NS	NS	NS	NS

QOL-CS=Quality of Life in Cancer Survivors

† Standardized beta coefficients

* p<.05, ** p<.001

A study among 20 irradiated EC survivors, 3-4 years after diagnosis revealed that survivors scored lower than the general population on role functioning and higher on diarrhea [12]. HRQL was also significantly lower evaluated by 49 irradiated EC survivors, 2 years after diagnosis, compared to healthy controls [25].

In contrast, a study among 73 EC survivors 5-20 years after diagnosis, found HRQL scores that approximated that of healthy controls, and found no association with treatment modality [26]. All studies were conducted in small samples of EC populations. The response rate was (sometimes) very low [10, 27]. Outcomes were often not associated with different treatment modalities [9, 12, 28, 29], or analyzed in combination with other gynecologic cancers [30]. Therefore it is difficult to compare these results with ours or to draw firm conclusions. The diminished HRQL across many subscales of both SF-36 and QOL-CS measures in irradiated women is however consistent with results from a study among irradiated long-term cervical cancer survivors [25]. Fatigue, as measured by the vitality subscale of the SF-36 and the physical well-being subscale of the QOL-CS, was consistently more often reported by irradiated EC survivors. Radiotherapy-induced fatigue is a common early and chronic side-effect of radiotherapy, reported in up to 30% of patients at follow-up visits [24]. In contrast to studies among cervical cancer survivors [25, 26], sexual dysfunction was not associated with radiotherapy in our population of EC survivors, although only 70% completed the questions on these issues and only 36% completed further questions about sexual pleasure and dry vagina. As the mean age of EC survivors is higher than cervical cancer survivors, and the women who did not respond to these questions were significantly older than those who did, it is possible that sexuality does not play an important role in the lives of these older women.

Patients in this study were treated 5-10 years ago, when there were no national treatment guidelines with respect to the indication for adjuvant radiotherapy. After the PORTEC trial [6], the indication for radiotherapy has been restricted to 'high-intermediate' risk patients (EC stage I in the presence of at least two of the following three risk factors: 1) grade 3, 2) age 60 and over, and 3) deep (>50%) myometrial invasion), resulting in a reduction in referral for radiotherapy in EC patients in the South-Eastern Netherlands [27].

Three randomized clinical trials have shown that adjuvant radiotherapy improves loco-regional control, but does not translate into an overall survival benefit [5-7, 31], meaning that most patients with locoregional relapse after surgery alone can be salvaged in second instance. Furthermore, 5-year actuarial rates of treatment related morbidity were 26% in patients who received adjuvant radiotherapy, and 4% in those who received surgery alone [22]. In the high-risk group of patients with stage IC and grade 3 tumors, adjuvant radiotherapy improved local control, but did not decrease the frequency of metastatic disease [28]. A recent retrospective analysis in the US however revealed a significant association between improved overall and relative survival and adjuvant radiotherapy in stage IC disease [29].

Although optimizing survival and local control of cancer is the first priority, HRQL after treatment is increasingly recognized as an important aspect of patient care. When different treatment options result in similar survival, or survival benefit is unclear then HRQL becomes even more important. The results of our large population-based analyses will therefore add information to the ongoing discussion about whether or not, or rather which patients to treat with adjuvant radiotherapy. Currently, the randomized PORTEC-2 trial compares the efficacy, morbidity and quality of life among patients treated with either EBRT or BRT alone, in order to evaluate if vaginal brachytherapy provides equal local control, less morbidity and better quality of life for patients with high-intermediate risk endometrial carcinoma.

The present study has a few limitations. Although the response rate was high, we do not know what the current health status was of the non-respondents or the women whose addressed could not be verified. The characteristics of the women whose addresses could not be verified were similar to the others. Also, the non-respondents appeared to be fairly similar to the respondents with regard to tumor or treatment characteristics, but they were somewhat older. Although all analyses were adjusted for the effect of age, it is possible that our results are not generalizable to very old women with EC. Furthermore, we did not have information about physical activity or the prevalence of obesitas in both treatment groups, whereas it has been shown that exercise and body-weight are important correlates of quality of life in EC survivors [30]. However, as comorbidity (in particular diabetes) was equally prevalent in both treatment groups we do not expect to find large differences with respect to body-weight or exercise. In addition, differences between patient groups (disease characteristics, but also HRQL) at diagnosis might have influenced the outcomes. However, as all analyses were restricted to disease-free survivors and adjusted for differences in tumor stage and grade, it seems unlikely that the outcomes can be fully explained by characteristics at diagnosis.

Future studies comparing HRQL between both treatment groups should also include disease or treatment specific questionnaires. We received several comments from irradiated women about the specific radiation-induced morbidity they experienced. Response shift, when a person changes his internal standards, or when he redefines his concept of HRQL[31], is another explanation for not finding an association between treatment and generic HRQL. For example, EC survivors experiencing less bodily pain than the general Dutch population of the same age, could possibly be explained by the response shift phenomenon. However, we have not investigated this phenomenon in our study population.

The results of the present study contribute to the limited information available about HRQL associated with different treatment modalities in the growing group of long-term survivors of EC. It has been suggested that a trade-off has to be made between the risk of locoregional recurrence and the survival rate after salvage treatment on one hand, and morbidity and cost of adjuvant RT on the other hand [6]. We believe that HRQL should also be included in this trade-off analysis. The challenge therefore remains to select high-risk patients who would benefit most from adjuvant therapy, taking into account disease-free and overall survival, but also HRQL. Results from the randomized PORTEC-2 trial will show whether EBRT can be replaced by BRT to optimize local control with less morbidity and better quality of life for patients with high-intermediate risk EC.

Acknowledgement

This study was supported by a grant from Rotary Triborch, Tilburg, The Netherlands. We would like to thank Carien Creutzberg for critically reviewing and commenting previous versions of this paper.

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Quality of life among long-term non-Hodgkin lymphoma survivors: a population-based study

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(Accepted pending revisions, Cancer)

Abstract

The aim of this population-based study was to document the long-term effects (5-15 years post-diagnosis) of non-Hodgkin's lymphoma and its treatment on health-related quality of life (HRQL) and social problems. The population-based Eindhoven Cancer Registry was used to select all patients diagnosed with non-Hodgkin's lymphoma from 1989 to 1998. Three hundred sixty patients were invited to complete the SF-36 and the Quality of Life-Cancer Survivors questionnaire, of whom 294 (82%) responded. Patients who received chemotherapy reported significantly worse psychological and social well-being and HRQL than patients not treated with chemotherapy. Radiotherapy and watchful waiting were not associated significantly with HRQL outcomes. Patients diagnosed 10-15 years earlier reported better social well-being than patients diagnosed 5-9 years earlier. In comparison to an age-matched general population normative sample, patients reported significantly worse general health and less vitality, but also less bodily pain. Practical problems were reported with work (41%), obtaining health care insurance (6%), life insurance (15%), and a home mortgage (22%). Five to fifteen years after diagnosis, the general health perceptions and vitality levels of non-Hodgkin's lymphoma survivors remain significantly lower than those of general population peers. Additionally, survivors face practical problems with work and finances that deserve additional attention during the period of rehabilitation.

Introduction

In the Netherlands, the annual incidence of non-Hodgkin's lymphoma is 1 in 8000. There are approximately 2000 new cases annually [1]. The disease occurs predominantly in individuals older than 45 years. The number of survivors from non-Hodgkin's lymphoma continues to increase. Whereas there were about 11.000 non-Hodgkin's lymphoma survivors in the Netherlands in the year 2000, this number is expected to increase to 19.000 in 2010 [1]. The increasing incidence of cancer in general, the aging of the population, the use of appropriate staging techniques, and effective treatments all contribute to this rapid increase [2]. For individuals under the age of 60 at diagnosis, the 5-year and 10-year relative survival rates are 75% and 63%, respectively. For those above the age of 60 years, these figures are 50% and 34%, respectively [3].

Cancer and its treatment can have a significant effect on the health-related quality of life (HRQL) of patients during diagnosis and treatment, but also years after the treatment has been completed [4]. Both so-called "generic" and "condition-specific" HRQL can be affected. Whereas a fairly large number of studies have been conducted on the HRQL of patients with Hodgkin's lymphoma, investigations of the HRQL of patients with non-Hodgkin's lymphoma are rather scarce [5-8], even though the latter disease is much more common. In some studies, mixed samples of lymphoma patients or leukaemia and lymphoma patients are pooled together [9-11].

We believe that it is important to describe HRQL in patients with non-Hodgkin's lymphoma, and to report this separately from HRQL in Hodgkin's lymphoma patients because of differences in age at diagnosis and treatment. To the best of our knowledge, to date, only one study has investigated the HRQL of long-term survivors of non-Hodgkin's lymphoma [5]. We employ here the definition of long-term survivorship recommended by the American Cancer Society: surviving the initial diagnosis for 5 years or more [12]. In that study of 44 survivors, lower levels of physical HRQL were reported than in a healthy control group.

The aim of the present, population-based study was to document the long-term HRQL effects of non-Hodgkin's lymphoma and its treatment. Specifically, we investigated the association between a range of sociodemographic (e.g., age, marital status, employment status, education) and clinical (e.g., disease stage, grade, therapy, comorbidity, time since diagnosis) factors and self-reported HRQL. In addition, a comparison was made between the HRQL of non-Hodgkin lymphoma survivors with that of an age-matched normative sample drawn from the general population. Finally, the study documented the prevalence of a range of practical problems experienced by this survivor group, including changes in work status, and problems with obtaining health care and life insurances, and home mortgages.

Methods

Setting and Participants

A population-based, cross-sectional survey was conducted at the Eindhoven Cancer Registry (ECR). The ECR records data on all patients newly diagnosed with cancer in the southern part of The Netherlands, an area with 2.3 million inhabitants, 18 hospital locations and two large radiotherapy institutes [3]. The ECR was used to select all patients diagnosed with non-Hodgkin's lymphoma between 1989 and 1998. We defined non-Hodgkin with the following ICD-0 codes [13]; 9590.3 - 9596.3 (Malignant lymphomas, NOS or diffuse), 9670.3 - 9719.3 (Malignant lymphoma diffuse, specified type), 9760.3 - 9764.3 (Immunoproliferative diseases), 9850.3 (lymphosarcoma cell leukaemia). Participants older than 75 years at diagnosis were excluded as it was expected that they would have difficulty in completing a self-administered questionnaire without assistance. To exclude all persons who had died before November 1 2004, our database was linked with the database of the Central Bureau for Genealogy, which collects data on all deceased Dutch citizens via the civil municipal registries. Data collection was started in November 2004. Approval for the study was obtained from a local, certified Medical Ethics Committee.

Data collection

The responsible clinicians sent their (former) patients a letter inviting them to participate in the study and a copy of the survey instrument. In the letter it was explained that, by returning a completed questionnaire, the patient agreed to participate and consented to linkage of the questionnaire data with information about their disease and treatment history as registered at the ECR. Patients were reassured that non-participation did not have any consequence for their follow-up care or treatment. If the questionnaire was not returned within two months, a reminder letter was sent together with an additional copy of the questionnaire. Returned questionnaires did not contain any explicit identifiers (i.e. names), but rather were number coded for purposes of data collection tracking and linkage with the ECR database.

Study Measures

The ECR routinely collects data on tumour characteristics including date of diagnosis, subsite, histology, stage (Tumour-Node-Metastasis clinical classification [14]), treatment and patient background characteristics including gender, date of birth and comorbidity at the time of diagnosis (a slightly adapted version of the Charlson comorbidity index [15]).

The Dutch language version of the SF-36 Healthy Survey was used to assess generic HRQL [16]. Following standard scoring procedures, all 8 scales were linearly converted to a 0-100 scale, with higher scores being indicative of better functioning. The internal consistency reliability of all scales was above the 0.70 criteria recommended for group comparisons. Two higher-order component scores for physical and mental health were also calculated. The SF-36 scores of the patient sample were compared with those of an age-matched normative sample drawn from a large, random, nationwide sample of adults (n=1742) drawn from the general Dutch population [17].

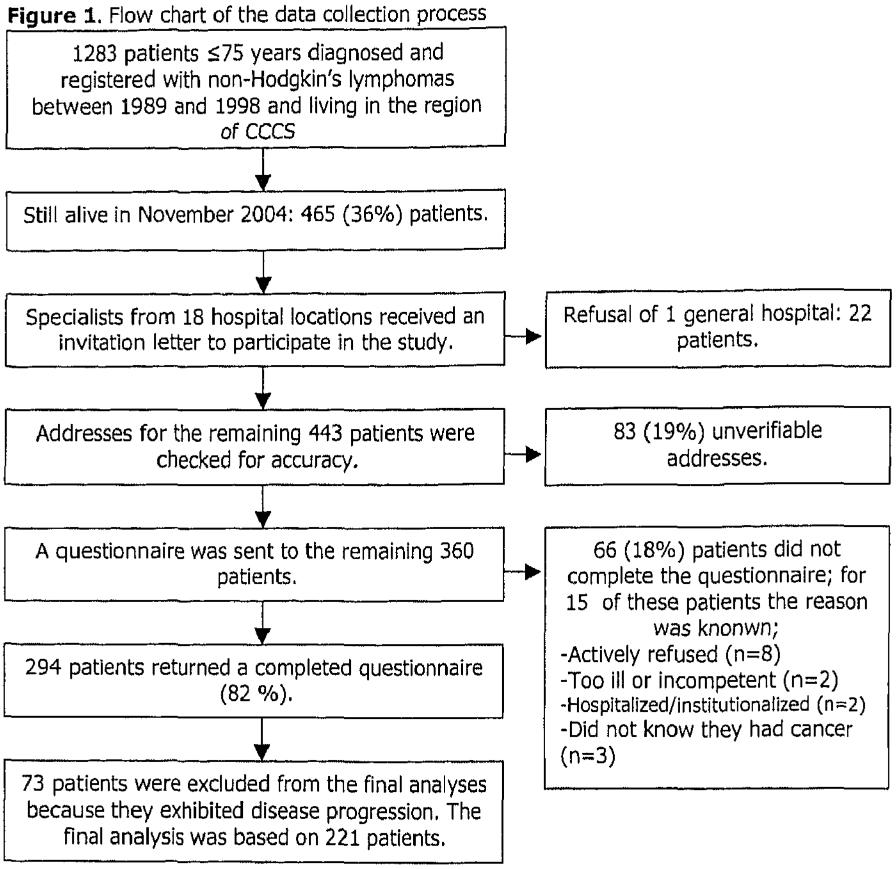
HRQL survivorship issues were assessed with the Dutch language version of the Quality of life-Cancer Survivors (QOL-CS) questionnaire [18, 19], composed of 45 visual analogue scales, each of which ranges from 0 (worst outcome) to 10 (best outcome). The questionnaire contains four multi-item subscales assessing physical, psychological, social and spiritual well-being. It examines issues of particular concern to long-term cancer survivors, such as distress since diagnosis, sexuality, employment, uncertainty about the future and the role of spirituality and religion [20]. The QOL-CS has been demonstrated to be a valid and reliable instrument when used among American [18, 21, 22] and Dutch [19] cancer survivors, although the subscale spiritual well-being showed low reliability and validity in the latter cohort.

The questionnaire also included questions on marital status, educational level, disease progression, and current comorbidity. Furthermore, patients were asked questions on changes in occupation and problems with insurance and financial loans (i.e., home mortgage) due to cancer.

Statistical analysis

Routinely collected data from the ECR on patient and tumour characteristics enabled us to compare the group of respondents, non-respondents and patients with unverifiable addresses, using Student's t-tests for continuous variables and the chi-square statistic for categorical variables. Survivors with recurrent disease or a new primary malignancy were excluded from further analysis.

Figure 1. Flow chart of the data collection process



Multivariate linear regression analyses were carried out to investigate the independent association between sociodemographic (age, comorbidity, marital status, education and occupation) and clinical variables (time since diagnosis, stage, grade, treatment) and the SF-36 and QOL-CS scale scores, using a p-value of <0.01 as statistically significant. The independent variables were categorized as follows. Age and time since diagnosis were entered as continuous variables. Tumour stage was entered as stage I (reference), II, III, IV, unknown. Tumour grade was entered as uncommon, indolent, (reference), aggressive and other. Therapies were entered as therapies (reference) versus no therapies. Comorbidity was entered as comorbidity (reference) versus married, divorced. Education was entered as high (reference) versus low. Occupation was entered as work (reference), no work, retired.

Table 1. Sociodemographic and clinical characteristics of questionnaire respondents, non-respondents and patients with unverifiable addresses.

	N (%)			
	Respondents **N=294**	**Non-Respondents** **N=66**	**Patients with unverifiable addresses** **N=83**	**P-value**
Sex				
Male	149 (51)	35 (53)	54 (65)	
Female	145 (49)	31 (47)	29 (35)	0.07
Age at time of survey				
<55 years	92 (31)	21 (32)	41 (49)	
55-69 years	109 (37)	24 (36)	20 (24)	
70+ years	93 (32)	21 (32)	22 (27)	0.04
Years since diagnosis				
5-9 years	198 (67)	47 (71)	51 (61)	
10-15 years	96 (33)	19 (29)	32 (39)	0.43
Stage at diagnosis				
I	114 (39)	31 (47)	26 (31)	
II	62 (21)	9 (14)	18 (22)	
III	27 (9)	4 (6)	10 (12)	
IV	76 (26)	10 (15)	17 (20)	
Unknown	15 (5)	12 (18)	12 (14)	<0.01
Grade				
Uncommon	4 (1)	2 (3)	2 (2)	
Indolent	86 (29)	19 (29)	26 (31)	
Aggressive	170 (58)	27 (41)	39 (47)	
Unknown	34 (12)	18 (27)	16 (19)	0.03
Primary treatment				
Chemotherapy	112 (38)	16 (24)	23 (28)	
Radiotherapy	38 (13)	11 (17)	13 (16)	
RT+CH*	69 (24)	17 (26)	22 (27)	
S+/-RT+/-CH**	38 (13)	9 (14)	7 (8)	
Watchful waiting	33 (11)	12 (18)	15 (18)	
Unknown	4 (1)	1 (2)	3 (4)	0.30

*RT+CH: Radiotherapy combined with chemotherapy

** S+/-RT+/-CH: Surgery with or without radiotherapy/with or without chemotherapy

Analysis of variance was used to compare the mean scores of the non-Hodgkin lymphoma sample on the individual SF-36 scales and higher order component scales with those of the Dutch general population normative sample.

Percentages of patients experiencing changes in their work situations, and problems with insurance and home mortgage were calculated. Work-related outcomes were assessed only for those individuals younger than 60 years at diagnosis, because that is the age at which a substantial percentage of Dutch workers retire.

Table 2. Sociodemographic and clinical characteristics of survivors without recurrent disease, metastasis or new primary malignancies.

	N (%)
	N=221
Sex	
Male	112 (51)
Female	109 (49)
Age at diagnosis	Mean=45.4
<55 years	122 (55)
55-69 years	80 (36)
70+ years	19 (9)
Age at time of survey	Mean=55.3
<55 years	79 (36)
55-69 years	73 (33)
70+ years	69 (31)
Time since diagnosis	
5-9 years	145 (66)
10-15 years	76 (34)
Stage at diagnosis	
I	90 (41)
II	49 (22)
III	19 (8.6)
IV	51 (23)
Unknown	12 (5)
Primary treatment	
Chemotherapy	82 (37)
Radiotherapy	33 (15)
Radiotherapy + Chemotherapy	58 (26)
S+/-RT+/-CH*	28 (13)
Watchful waiting	20 (9)
Comorbidity	
No	101 (46)
Yes	120 (55)
Most frequent co-morbid conditions	
1. Arthrosis	48 (22)
2. Hypertension	43 (19)
3. Asthma	21 (10)
Marital status	
Married	147 (67)
Not married/divorced	39 (18)
Widowed	24 (11)
Unknown	11 (5)

Table 2 Continued. Sociodemographic and clinical characteristics of survivors without recurrent disease, metastasis or new primary malignancies.

	N (%)
	N=221
Education level	
Low	93 (42)
Medium	66 (30)
High	48 (22)
Unknown	14 (6)

* S+/-RT+/-CH: Surgery with or without radiotherapy/with or without chemotherapy

Results

Questionnaires were sent to 360 non-Hodgkin's lymphoma survivors, and 294 completed questionnaires were returned (82% response rate) (Figure 1). Comparison between respondents, non-respondents and patients with unverifiable addresses showed that the latter were generally younger. Non-respondents were more often diagnosed with stage I disease, while respondents were more often diagnosed with aggressive non-Hodgkin's lymphoma (Table 1). Seventy-three respondents were excluded from the final analysis because they had progressive disease or therapy was unknown. The final analysis was based on 221 patients.

The mean age at diagnosis was 45.4 years; patients were approximately 10 years older at the time of the survey (Table 2). The majority of the respondents was married (67%), had a medium (30%) or high (22%) educational level and was not employed (70%) at the time of the survey. A large percentage of patients had been diagnosed with stage I disease (41%) and the treatment most often received was chemotherapy only (37%) or chemotherapy in combination with radiotherapy (26%). Half of the patients reported one or more comorbid conditions, the most common of which were arthritis (22%) hypertension (19%) and asthma (10%).

The results of the multivariate linear regression analyses, with the SF-36 scales as outcome variables, are reported as beta coefficients in Table 3a. Older patients scored significantly lower on the SF-36 physical functioning than younger patients. Patients with comorbid health conditions reported significantly poorer physical functioning, and more pain than those without such

Table 3a. Multivariate Linear Regression Model Evaluating Independent Variables for SF-36 subscale scores.

	SF-36 subscales†									
Independent variable	**PF**	**RP**	**BP**	**GH**	**VT**	**SF**	**RE**	**MH**	**PCS**	**MCS**
Age (time of questionnaire)	-0.37***	NS	NS	NS	NS	-0.26*	NS	NS	-0.24*	NS
Time since diagnosis	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Tumor stage	NS	NS	NS	-0.19*	NS	NS	NS	0.23*	NS	0.21*
Tumor grade	NS	NS	NS	NS	NS	NS	NS	NS	NS	-0.29*
Radiotherapy	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Chemotherapy	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Watchful waiting	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Comorbidity	-0.18*	-0.19*	-0.22**	NS	NS	NS	NS	NS	-0.24**	NS
Marital status	NS	NS	-0.17*	NS	NS	-0.20*	NS	NS	-0.18*	NS
Education	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Occupation	NS	NS	NS	NS	0.33**	NS	NS	0.30**	NS	NS

SF-36= Short Form-36, PF= Physical Functioning, RP= Role limitations Physical health, BP= Bodily Pain, GH= General Health, VT= Vitality, SF= Social Functioning, RE= Role limitations Emotional problems, MH= Mental Health, PCS= Physical Component Scale, MCS= Mental Component Scale

† Standardized beta coefficients

*$p<0.05$; **$p<0.01$; *** $p<0.001$

Table 3b. Multivariate Linear Regression Model Evaluating Independent Variables for QOL-CS subscale scores.

	QoL-CS subscales†				
Independent variable	**Physical well-being**	**Psychological well-being**	**Social well-being**	**Spiritual well-being**	**Total score**
Age (at time of questionnaire)	NS	NS	NS	NS	NS
Time §	NS	0.17*	0.21**	NS	NS
Tumor stage	NS	0.19*	NS	NS	0.16*
Tumor grade	NS	NS	NS	NS	NS
Radiotherapy	NS	NS	NS	NS	NS
Chemotherapy	NS	-0.22**	-0.30**	NS	-0.25**
Watchful waiting	NS	NS	NS	NS	NS
Comorbidity	-0.18*	NS	NS	NS	NS
Marital status	NS	NS	NS	NS	NS
Education	NS	NS	NS	NS	NS
Occupation	NS	NS	NS	NS	NS

† Standardized beta coefficients
*p<0.05; **p<0.01; *** p<0.001
§ Time since diagnosis

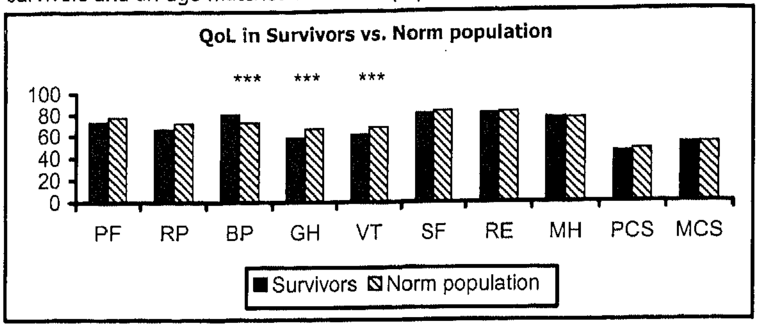
conditions. Patients with a job reported being more vital and had better mental well-being scores than those who were not working.

The results of the multivariate linear regression analyses, with the QOL-CS scales as outcome variables, are reported as beta coefficients in Table 3b. Time since diagnosis was associated positively with social well-being as measured by QOL-CS. Having had chemotherapy was associated with lower scores on psychological well-being, social well-being and the QOL-CS total score.

The HRQL of survivors as measured by the SF-36 was compared with that of an age-matched normative sample from the general Dutch population (Graph 1). The survivor group exhibited significantly lower scores than the normative sample for general health perception ($p<0.001$) and vitality ($p<0.001$) but higher scores for bodily pain (indicating less pain) ($p<0.001$). No statistically significant differences were observed for any of the other SF-36 scales.

Table 4 reports the results pertaining to the work situation, and problems in obtaining health care and life insurance, and a home mortgage. The majority of the survivors (59%) stated that their work situation had not changed as a result of having had cancer. Nevertheless, 41% of the survivors indicated that they had changed jobs, reduced the number of hours worked or stopped

Graph 1. SF-36 subscale scores: differences between Non-Hodgkin lymphoma survivors and an age-matched normative population



*** $p<0.001$
PF= Physical functioning, RP= Role limitations physical health, RE=Role limitations emotional problems, VT=Vitality, MH=Mental Health, SF= Social functioning, BP=Bodily pain, GH= General health, MCS=mental component scale, PCS=Physical component scale.
Higher scores are indicative of better functioning.

working entirely (including work disability) as a result of having had cancer. Only 6% of the survivors reported having experienced cancer-related problems in obtaining health insurance. Fifteen percent reported problems obtaining life insurance and 22% with obtaining a mortgage. If we limit these latter figures to those individuals who actually attempted to obtain insurance or a mortgage during the period following their cancer diagnosis, the percentages with problems was substantially higher (12%, 60% and 73% for health insurance, life insurance and mortgage, respectively).

Discussion

The results of this study indicate that patients who received chemotherapy experienced a worse psychological and social well-being and HRQL than patients not treated with chemotherapy. Patients diagnosed 10-15 years ago reported better psychological and social well-being than patients diagnosed 5-9 years earlier. In comparison to healthy adults from the general population, patients reported worse general health and less vitality but also less bodily pain. Practical problems, including changes in work situation and problems obtaining new health insurance, life insurance and mortgages were relatively common.

Table 4. Changes in work situation and problems with insurances and mortgages.

	N (%)
	N=150 §
Changes in work situation	
Nothing changed	89 (59)
Occupational re-settlement	5 (3)
Stopped with working	10 (7)
Working less hours	19 (13)
Incapable of working	22 (15)
Fired	3 (2)
	N=221
Problems with;	
Health care insurance	
Yes	12 (6)
No	85 (39)
Did not try	111 (51)
Life insurance	
Yes	33 (15)
No	22 (10)
Did not try	147 (68)
Mortgage	
Yes	47 (22)
No	17 (8)
Did not try	131 (61)

§ number of patients ≤60 years at time of diagnosis

To our knowledge, there is only one study among 141 non-Hodgkin lymphoma patients that also investigated HRQL *in relation to treatment*. In that study, patients receiving chemotherapy reported lower overall HRQL scores compared to patients who did not receive chemotherapy [7]. The present study thus confirmed those results.

Improvement in HRQL over a long period of time has not been documented previously in patients with non-Hodgkin's lymphoma, although it is known they experience a significant improvement in HRQL soon after completion of therapy in comparison to their baseline levels [6]. HRQL differences observed were significant only when measured with the QOL-CS and not with the SF-36. This may reflect, in large part, the fact that the QoOL-CS was developed specifically for use among cancer survivors, whereas the SF-36 is a generic HRQL instrument. The QOL-CS was also used in a combined group of leukaemia and lymphoma survivors (n=53) who were alive 10 or more years after diagnosis. Comparing their scores with those of the subsample of our study who were >10 years post-diagnosis yielded fairly similar results: physical (mean = 7.6 vs. 7.9), psychological (mean = 6.6 vs. 7.1), social (mean = 7.6 vs. 7.4), spiritual (mean = 6.5 vs. 4.6) and overall HRQL (mean = 7.0 vs. 6.9) [9]. The substantially lower scores observed in our study on the subscale spiritual well-being is probably related to cultural differences between American and Dutch survivors, as has been described previously [19, 23].

Differences in general health perceptions between survivors and an age-matched normative sample from the general population were in line with a previous study that included Hodgkin and non-Hodgkin lymphoma survivors, 2-16 years after diagnosis [5] and by studies that only included Hodgkin's lymphoma survivors [24-28]. Differences in vitality scores were also confirmed; vitality was higher in controls (n=2214) than in Hodgkin's lymphoma survivors (n=459) [26]. Results from a Swedish study among lymphoma patients (n=95) are somewhat at variance with our results since they did not find an effect for vitality, general health perceptions or bodily pain. In that study it was concluded that patients had a similar HRQL compared to a reference population, except for role functioning scores [11]. However, comparison of these results with those of our study is hampered by the fact that they were based on a short follow-up period (on average, 8 months following diagnosis) and included both Hodgkin lymphoma and non-Hodgkin lymphoma patients.

The lower pain levels reported by the non-Hodgkin lymphoma survivors as compared with the healthy controls have not been reported previously in the literature. We suspect that this is either a chance finding or, if real, may reflect a 'response shift' phenomenon whereby individuals redefine their internal standards for rating their level of functioning or symptoms (in this case pain) as a result of their illness experience [29, 30]. Patients may accept pain as an inevitable consequence of having been treated for cancer, a condition they perceive as life threatening. Common benign aches and pains, such as headache, may then be considered as less burdensome by non-Hodgkin lymphoma survivors than by their general population counterparts.

Changes in the work situation of non-Hodgkin lymphoma survivors have not been reported previously in the literature but were comparable to those reported for Hodgkin's disease survivors [27, 30, 31]. The percentage of survivors experiencing problems with obtaining health care and life insurance is also in line with the existing literature on Hodgkin lymphoma survivors [25, 27, 31, 32]. Twenty-two percent of survivors in our study experienced problems obtaining a mortgage due to their disease. These problems were reported by 14% of Hodgkin lymphoma survivors [25] in one study and by 28%-33% of survivors in another study [27]. The degree to which problems with obtaining insurance and mortgages occur in the general Dutch population is not known and therefore these results need to be interpreted with some caution. In any case, these results suggests that patients should be informed about the possible financial consequences of being a cancer survivor, and perhaps counselled in how they can best deal with such issues.

The present study has some limitations that should be noted. First, although we had information about the initial cancer and treatment characteristics of the non-respondents and patients whose addresses could not be verified, we do not know whether non-respondents declined to participate in the study because of poor health. Second, the cross-sectional nature of the study does not allow one to determine causal associations or to document changes in HRQL over time. However, we attempted to gain insight into the role of such factors as disease stage, age at diagnosis, grade, years since diagnosis, education, marital status and comorbidity at diagnosis by including them in the multivariate analyses examining factors associated significantly with a range of HRQL outcomes. The strengths of our study, as compared to many earlier survivorship studies, include the population-based versus clinic-based sampling frame, and the high response rate that facilitates generalizing the results to the larger population of long-term, disease-free non-Hodgkin lymphoma survivors.

In conclusion, 5-15 years after diagnosis, the general health perceptions and vitality levels of non-Hodgkin's lymphoma survivors remain significantly lower than those of general population peers. Additionally, survivors face practical problems with work and finances that deserve additional attention during the period of rehabilitation.

Acknowledgement

The regional Interzol clinical study group for Heamato-oncology and the Foundation for the Promotion of Academic Training and Research in Health Care (SWOOG) financially supported this study. Floortje Mols also received a grant from the Beunke Fund for Lymphoma Research.

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8

Better quality of life among 10-15 year survivors of Hodgkin's lymphoma compared to 5-9 year survivors: a population-based study

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(*European Journal of Cancer*, 2006: **42**: 2794–2801)

Abstract

This study describes quality of life (QOL) of long-term Hodgkin's lymphoma survivors and compares it to an age-matched normative sample. The population-based Eindhoven Cancer Registry was used to select all patients diagnosed with Hodgkin's lymphoma from 1989 to 1998. Eighty percent of survivors completed the SF-36 and the Quality of Life-Cancer Survivors questionnaire (QOL-CS). QOL was better among patients diagnosed 10-15 years ago compared to patients diagnosed 5-9 years ago. Patients diagnosed 5-9 years ago experienced lower general health, social functioning, mental health and vitality compared to an age-matched normative sample while patients diagnosed 10-15 years earlier reported lower general health but better physical functioning. Most patients reported that their work situation did not change. Problems obtaining health insurance, life insurance and mortgages were high. QOL among Hodgkin's lymphoma survivors is lower compared to an age-matched normative sample. Survivors furthermore experience some (financial) problems in the years after diagnosis.

Introduction

Hodgkin's lymphoma is a relatively uncommon malignancy. In the Netherlands, the incidence is 1 in 50.000 [1], with approximately 350 new cases annually. The disease affects men more often than women. Onset occurs most frequently between the ages of 20 and 35 years. Between 35 and 50 years it occurs less often, especially in females, but from the age of 50 onward there is again a rise in incidence with age. Hodgkin's lymphoma is considered a curable disease although conditional 5-year survival is <90% [2]. The use of appropriate staging techniques and treatment methods has resulted in high long-term survival rates. In the south of the Netherlands, 5-year relative survival is 82% and 10-year relative survival is 77% depending on stage [3]. If a person is alive 5 years after initial diagnosis, he is considered a 'long-term survivor' according to the guidelines of the American Cancer Society [4]. In 2000 there were about 4.450 Hodgkin's lymphoma survivors in the Netherlands and this group is expected to increase to nearly 7000 survivors in 2010 [1]. This illustrates the rapid increase in the numbers of individuals who are either cured of their cancer or living with it as a chronic disease [5].

Hodgkin's lymphoma survivors face very specific problems that have become more apparent as greater numbers of successfully treated patients have been followed for longer periods of time. They concern mainly chronic medical as well as psychosocial complications that can affect their QOL. Patients can be treated with systemic therapy, radiotherapy or a combination of both. These interventions may result in severe infections and may cause thyroid, cardiovascular, pulmonary, digestive or gonadal dysfunction, hypothyroidism and secondary malignancy [6, 7]. To date, a number of studies has evaluated the long-term effects of Hodgkin's lymphoma and its treatment on QOL [8-17]. These studies indicate that survivors more often have a decreased self-reported health status, increased levels of generalized distress, fear of recurrence and other worries about their disease, and problems in the realms of intimacy and sexuality. Furthermore, survivors may experience fatigue and loss of energy and late effects on skin and mucous membrane. Practical problems may also occur, including employment and insurance discrimination and difficulties with financial loans [9-11, 17-19]. However, most of these studies were either based on a small number of survivors [9, 11], were primarily investigating fatigue [17, 19] or included patients who were treated up to two decades ago [9, 11, 17].

The aim of the present, cross-sectional study was to obtain insight into the QOL of long-term Hodgkin's lymphoma survivors in a large population-based study. We compared the QOL of individuals who had survived the disease for 5-9 years with that of patients who had survived 10-15 years. We also studied the differences in QOL between Hodgkin's lymphoma survivors and an age-matched normative sample from the general Dutch population. Finally, we assessed changes in work situations, and problems with insurance and loans.

Methods

Setting and Participants

A population-based, cross-sectional survey was conducted at the Eindhoven Cancer Registry (ECR). The ECR records data on all patients newly diagnosed with cancer in the southern part of the Netherlands, an area with 2.3 million inhabitants, 18 hospital locations and two large radiotherapy institutes [3]. The ECR was used to select all patients diagnosed with Hodgkin's lymphoma between 1989 and 1998. Participants older than 75 years at diagnosis were excluded, as it was expected that they would have difficulty in completing a self-report questionnaire without assistance. To exclude persons who had died before November 1, 2004, our database was linked with the database of the Central Bureau for Genealogy, which collects data on all deceased Dutch citizens via the civil municipal registries. Data collection started in November 2004. Approval for the study was obtained from a local, certified Medical Ethics Committee.

Data collection

Medical specialists sent their (former) patients a letter to inform them about the study and a copy of the questionnaire. The letter explained that by returning the completed questionnaire, the patient agreed to participate and consented with linkage of the outcome of the questionnaire with their disease history as registered in the ECR. Patients were reassured that non-participation would not have any consequence for their follow-up care or treatment. If the questionnaire was not returned within two months, a reminder letter with an additional copy of the questionnaire was sent.

Study measures

The ECR routinely collects sociodemographic and clinical data, including date of birth, gender, date of diagnosis, subsite, histology, stage (Tumour-Node-Metastasis clinical classification [20]), treatment, and comorbidity at the time of diagnosis (a slightly adapted version of the Charlson comorbidity index [21]).

The Dutch version of the SF-36 questionnaire was used to assess generic QOL [22]. According to standard scoring procedures, all scales were linearly converted to a 0-100 scale, with higher scores indicating better functioning. Differences of at least 5 points (the general health dimension) [23], 6.5 points (the physical dimensions) and 7.9 points (the mental health dimensions) were considered clinically meaningful [24]. The SF-36 has been demonstrated to be valid and reliable [25, 26]. The SF-36 scores of the patient sample were compared with those of an age-matched normative sample drawn from a large, random, nationwide normative sample of adults (n=1742) taken from the general Dutch population [26].

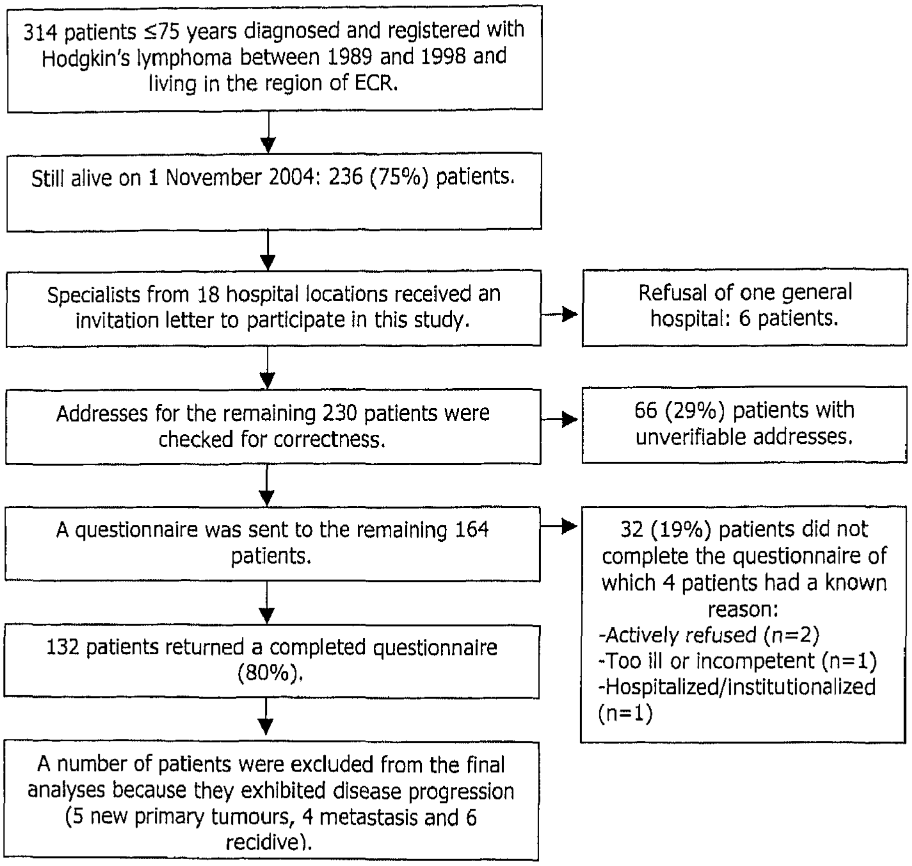
Generic HRQL survival issues were assessed with the Dutch version of the Quality of life-Cancer Survivors (QOL-CS) instrument [27, 28], a 45-item visual analogue scale, each of which ranges from 0 (worst outcome) to 10 (best outcome). The questionnaire contains four multi-item subscales on well-being: physical, psychological, social and spiritual. It examines issues of particular concern to long-term cancer survivors such as fertility, employment, uncertainty about the future and the role of spirituality and religion [29]. The QOL-CS has been demonstrated to be a valid and reliable instrument [27, 28, 30, 31].

The questionnaire also included questions on sociodemographic data, disease progression, current comorbidity and questions on insurance and loans.

Statistical analysis

All statistical analyses were performed using SAS (version 9.1 for Windows, SAS institute Inc., Cary NC). Routinely collected data from the ECR on patient and tumour characteristics enabled us to compare the group of respondents, non-respondents and patients with unverifiable addresses, using t-tests for continuous variables and chi-square analyses for categorical variables. Survivors with recurrent disease or a new primary malignancy were excluded from further analysis. Because a number of subscales were skewed, non-parametric tests were used when appropriate. Linear regression analyses were carried out in order to investigate the association between patient characteristics (e.g. age, comorbidity) and tumour characteristics (e.g., stage, treatment, time since diagnosis) with the composite and subscale scores of the SF-36 and QOL-CS. On the basis of the univariate results, multivariate models were constructed to determine which patient and tumour characteristics were

Figure 1. Flow-chart of the data collection process



independently associated with QOL outcomes. We controlled for these variables in the analysis of covariance (ANCOVA), which was used to compare means of SF-36 and QOL-CS scores among different subgroups. Mean scores on the SF-36 domain and summary scales were compared between our study sample and a Dutch general population normative sample, matched for age.

Percentages of patients experiencing changes in work situations and having problems with insurance and mortgages were calculated. We only analysed the changes in the work situation of patients who were younger than 60 years at diagnosis, because that is the age when most people in the Netherlands retire.

Table 1. Socio-demographic and medical characteristics of questionnaire respondents, non-respondents and patients with unverifiable addresses

	N (%)			
	Respondents **N=132**	**Non-Respondents** **N=32**	**Patients with unverifiable addresses** **N=66**	**P-value**
Age at time of survey				
20-34 years	36 (28)	10 (32)	29 (45)	
35-49 years	47 (36)	11 (35)	21 (32)	
50+ years	46 (36)	10 (32)	15 (23)	0.20
Years since diagnosis				
5-9 years	54 (41)	12 (38)	32 (48)	
10-15 years	78 (59)	20 (63)	34 (52)	0.49
Stage at diagnosis				
I	32 (24)	10 (31)	19 (29)	
II	62 (47)	12 (38)	30 (45)	
III	28 (21)	6 (19)	9 (14)	
IV	6 (5)	3 (9)	6 (9)	
Unknown	4 (3)	1 (3)	2 (3)	0.82
Primary treatment				
Systemic only	38 (29)	8 (25)	16 (24)	
Radiotherapy only	25 (19)	6 (19)	18 (27)	
RT+ST*	66 (50)	16 (50)	29 (44)	
None/Other/unknown	3 (2)	2 (6)	3 (5)	0.15

*RT+ST: Radiotherapy combined with systemic therapy

Results

Questionnaires were sent to 164 patients, 132 (80%) of whom returned completed forms (Figure 1). No statistically significant differences in age at time of survey, years since diagnosis, stage at diagnosis or initial treatment were found between respondents, non-respondents and patients with unverifiable addresses (Table 1). A number of patients was excluded from the final analyses because they exhibited disease progression (5 new primary tumours, 4 metastasis and 6 recurrence), leaving 117 patients for the analysis.

Most patients were treated with a combination of radiotherapy and chemotherapy (Table 2). More than half of the patients reported one or more co-morbid conditions: arthrosis, thyroid disease and hypertension were the most common. Marital status, education level and current occupation were similar for the two groups.

Table 2. Socio-demographic and clinical characteristics of long-term Hodgkin's lymphoma survivors without recurrent disease or new primary malignancies.

	N (%)		
	5-9 year survivors N=48	**10-15 year survivors N=68**	**P-value**
Age at time of survey			
20-34 years	13 (27)	19 (28)	
35-49 years	17 (35)	24 (35)	
50+ years	16 (33)	24 (35)	0.85
Age at diagnosis			
20-34 years	16 (33)	33 (49)	
35-49 years	18 (38)	15 (22)	
50+ years	9 (19)	12 (18)	0.27
Stage at diagnosis			
I	13 (27)	17 (25)	
II	25 (52)	27 (40)	
III	7 (15)	19 (28)	
IV	3 (6)	3 (4)	
Unknown	0 (0)	2 (3)	0.30
Primary treatment			
Systemic only	14 (29)	21 (31)	
Radiotherapy only	5 (10)	14 (21)	
RT+ST*	29 (60)	33 (49)	0.28
Comorbidity			
None	23 (48)	30 (44)	
1	19 (40)	25 (37)	
2+	6 (13)	13 (19)	0.80
Most frequent co-morbid conditions			
1. Arthrosis	7 (15)	15 (22)	0.31
2. Thyroid disease	5 (10)	13 (19)	0.20
3. Hypertension	6 (13)	7 (10)	0.71
Marital status			
Married	27 (56)	47 (69)	
Not married/divorced	18 (38)	18 (26)	
Widowed	1 (2)	1 (1)	
Unknown	1 (4)	1 (3)	0.72
Education level			
Low	12 (25)	13 (19)	
Medium	17 (35)	37 (54)	
High	17 (35)	16 (24)	
Unknown	2 (4)	2 (3)	0.25
Current occupation			
Employed	35 (73)	43 (63)	
Unemployed	10 (21)	17 (25)	
Retired	1 (2)	6 (9)	
Unknown	2 (4)	2 (3)	0.42

*RT+ST: Radiotherapy combined with systemic therapy

Table 3. SF-36 and QOL-CS scores for long-term Hodgkin's lymphoma survivors according to years since diagnosis.

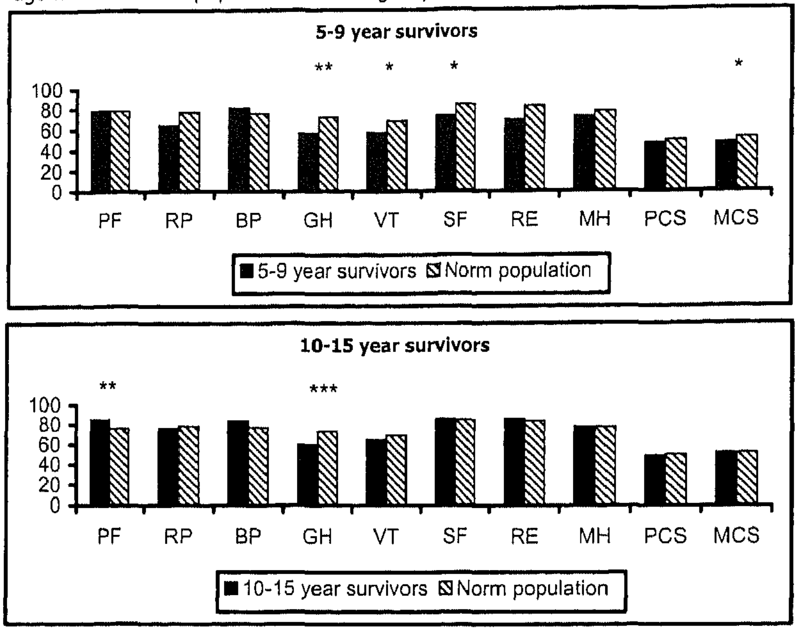
	Mean (SD)		
	5-9 year survivors N=48	**10-15 year survivors N=68**	**P-value ◇**
SF-36 scales			
Physical functioning	78.7 (23.8)	85.1 (18.7)	0.11
Role-Physical	64.4 (42.6)	76.2 (36.6)	0.12
Bodily pain	81.4 (24.1)	84.0 (22.3)	0.54
General health perception	56.6 (25.7)	59.8 (21.9)	0.45
Vitality	57.1 (23.5)	64.8 (17.4)	<0.05
Social functioning	73.1 (27.3)	85.4 (19.9)	<0.01
Role-emotional	69.5 (41.0)	85.7 (29.8)	<0.05
Mental health	72.3 (20.0)	77.8 (14.3)	0.09
Physical component scale	47.0 (11.4)	48.7 (10.7)	0.73
Mental Component scale	47.1 (12.5)	52.1 (8.3)	<0.05
QoL-CS Subscales			
Physical	7.7 (1.8)	8.0 (1.6)	0.28
Psychological	6.3 (1.6)	6.3 (1.4)	0.97
Social	6.5 (1.7)	6.8 (1.7)	0.36
Spiritual	4.5 (1.3)	4.5 (1.1)	0.82
Total	6.3 (1.3)	6.4 (1.1)	0.56

◇ P-value was adjusted for stage, age at diagnosis, treatment, years since diagnosis, education, marital status and comorbidity.

Patients who had survived 10-15 years after diagnosis reported higher QOL scores for all subscales of the SF-36 and QOL-CS than patients who had survived 5-9 years (Table 3). This effect was statistically and clinically significant for the subscales vitality (64.8 vs. 57.1, P<0.05), social functioning (85.4 vs. 73.1, P<0.01), and role-emotional (85.7 vs. 69.5, P<0.05). It was also statistically significant for the mental component scale of SF-36 (52.1 vs. 47.7, P<0.05). Additional analyses, comparing QOL (SF-36 and QOL-CS) for different treatment methods, did not yield any significant differences (data not shown).

The SF-36 scores of the 5-9 year and 10-15 year survivors were compared with those of an age-matched norm population (Figure 2). Patients diagnosed 5-9 years ago had lower mean scores for the subscales general health (p<0.01), vitality (p<0.05) and social functioning (p<0.05) and for the mental component scale (p<0.05) compared to the age-matched normative population, these differences were statistically and clinically relevant. Patients diagnosed 10-15 years ago scored lower for the general health scale

Figure 2. SF-36 subscale scores for Hodgkin's lymphoma survivors vs. an age-matched norm population according to years since diagnosis.



*p<0.05; **p<0.01; *** p<0.001
PF= Physical functioning, RP= Role limitations physical health,
RE=Role limitations emotional problems, VT=Vitality, MH=Mental Health,
SF= Social functioning, BP=Bodily pain, GH= General health,
MCS=mental component scale, PCS=Physical component scale.
For a description of the norm population, see the 'study measures' section of this article.

(p<0.001) compared to an age-matched norm population, but they had higher scores on the physical functioning subscale (p<0.01), these differences were also statistically and clinically relevant.

The QOL-CS contained the question: "To what degree are you concerned about your fertility?". The mean score was low and there were no significant differences observed as a function of treatment methods or time since diagnosis (data not shown). Among patients under the age of 40, 51% indicated that they did not worry at all, and only 13% indicated that they were very worried. Of the patients above 40 years of age, 77% indicated that they were not at all worried about fertility.

The impact of cancer on the work situation, health insurance, life insurance and home loans is shown in Table 4. No significant differences were

Table 4. Changes in work situation and problems with insurance and mortgages.

	N (%)		
	5-9 year survivors N=43 §	**10-15 year survivors N=64 §**	**P-value**
Changes in work situation			
Nothing changed	27 (63)	48 (75)	0.20
Occupational re-settlement	5 (12)	2 (3)	0.11
Stopped working	0 (0)	1 (2)	1.00
Working more hours	0 (0)	2 (3)	0.51
Working less hours	8 (19)	5 (8)	0.13
Incapable of working	4 (9)	5 (8)	1.00
Fired	2 (5)	1 (2)	0.56
Problems with;	**N=48**	**N=68**	
Health insurance			
Yes	3 (6)	10 (15)	
No	13 (27)	30 (44)	
Did not try	31 (65)	26 (38)	0.06
Life insurance			
Yes	3 (6)	12 (18)	
No	10 (21)	17 (25)	
Did not try	34 (71)	36 (53)	0.14
Mortgage			
Yes	15 (31)	24 (35)	
No	3 (6)	11 (16)	
Did not try	29 (60)	29 (43)	0.11

§ Percentage of patients ≤60 years at time of diagnosis.

found between 5-9 year survivors and 10-15 year survivors. The majority of patients (63% and 75%) stated that their work situation had not changed due to cancer. However, 7 patients followed occupational retraining due to cancer, 13 patients switched to part-time work, and 1 patient chose to stop working entirely following diagnosis and treatment. In addition, 9 patients indicated that they were unable to work, and 3 patients said that they had been fired due to cancer. Six percent of the 5-9 year survivors and 15% of the 10-15 year survivors who wanted new health insurance experienced problems obtaining it in the years after their diagnosis. Six percent of the 5-9 year survivors and 18% of the 10-15 year survivors reported problems obtaining life insurance, and 31% of the 5-9 year survivors and 35% of the 10-15 year survivors experienced problems obtaining a mortgage due to cancer. These numbers represent problems in the total group of Hodgkin lymphoma patients. However, if we only look at patients who *actually tried* to get a new health insurance, life insurance or mortgage, the percentage of problems are much higher (25%; 38%; and 63% respectively).

Discussion

The aim of the present study was to describe the QOL for long-term Hodgkin's lymphoma survivors 5-15 years after diagnosis, and to compare it to the general Dutch population. QOL was better among patients diagnosed 10-15 years ago compared to patients diagnosed 5-9 years ago. Patients diagnosed 5-9 years ago experienced lower general health, social functioning, mental health and vitality compared to an age-matched normative sample while patients diagnosed 10-15 years earlier reported lower general health but better physical functioning. Most patients reported that their work situation did not change. Problems obtaining health insurance, life insurance and mortgages were high.

The statistically significant differences observed between 5-9 and 10-15 year survivors appeared to be clinically meaningful [23, 24]. It is important to note that these results were not confounded by differences in sociodemographic or clinical characteristics between the groups. The observed differences in QOL between 5-9 and 10-15 year survivors have not been reported previously in the literature. In a Norwegian study of 459 Hodgkin lymphoma survivors, time since diagnosis was not found to have a significant effect on QOL [8]. Similarly, a Dutch study of 81 Hodgkin's lymphoma survivors found no significant association between time since treatment and SF-36 scores [11]. An Austrian study comparing patients treated 2-5 years earlier versus more than 5 years earlier also failed to detect time effects [15].

Self-reported QOL was not found to be associated significantly with type of treatment received. This is largely in line with existing literature on this topic [8, 12]. However, in an Austrian study, Hodgkin's lymphoma patients who received combined modality treatments were found to have a lower QOL in comparison to those treated with either radiotherapy or chemotherapy alone [15]. The difference in findings between studies may be due to the fact that treatment methods have changed over time. Our study consisted of patients treated between 1989 and 1998, whereas the Austrian study included patients treated between 1969 and 1994 who were therefore more often treated with MOPP (nitrogen mustard, vincristine, procarbazine and prednisone). However, a study of patients treated between 1971 and 1991 did not find differences in QOL between treatment methods [8].

Differences in QOL observed between the survivors and the normative sample have been noted earlier. In a Spanish study, patients (n=46) reported lower physical functioning and worse social functioning compared with healthy controls (n=46) [12]. A Dutch study among long-term Hodgkin's lymphoma survivors found that, in comparison to healthy controls (n=114), patients (n=81) reported significantly worse physical functioning and role functioning and lower perceived overall health [11]. These effects were confirmed by a Norwegian study, that also found significant differences in social functioning and vitality [8]. A French study concluded that physical, role, cognitive and social functioning were significantly lower among survivors (n=93) compared to controls (n=186) [9]. Finally, a Swedish study reported that patients (n=121) rated their physical health as worse than that of controls (n=236) [10]. In all studies mentioned above, survivors reported worse physical functioning compared to controls, also when they included patients who had survived more than 10 years after diagnosis. However, in our study, physical functioning of 5-9 year survivors was similar to that of controls, whereas surprisingly 10-15 year survivors reported an even better physical functioning than controls.

We expected to find somewhat more problems with fertility [6], especially for patients treated with combination drug regimens such as MOPP [32]. In other studies fertility was affected in 19%-34% of cases [9, 14, 32, 33]. However, we assessed whether survivors were *concerned* about their fertility, but we did not have any direct measure of actual problems with fertility. It is possible that fertility was affected in a number of our respondents but that it did not worry them.

The prevalence of thyroid disease was quite low in our study (10-19%) compared to other studies (57-65%) [34-37]. However, information on the presence of thyroid disease was not available from patients' medical records but was based on a self-reported questionnaire.

Fatigue is one of the most frequently reported symptoms among long-term Hodgkin's lymphoma survivors [38]. The prevalence of chronic fatigue ranges from 25-30%, compared to 12% of the general population [39]. It is common even many years after diagnosis [14, 17, 34]. In our study, 5-9 year survivors reported significantly more fatigue in comparison with the norm population. This was not the case for those patients who had survived 10-15 years. Interventions may help to reduce fatigue, but this has only been investigated in a small group of Hodgkin's lymphoma patients with chronic fatigue who followed a home-based exercise intervention [40]. Further studies are therefore necessary.

Work situation changed in approximately one-third of the sample, which corroborates previous findings [7, 9, 14]. The number of patients experiencing problems obtaining health insurance or life insurance was also in line with the literature [11, 14, 32]. Problems obtaining a mortgage were slightly higher than in the existing literature, where problems were reported by 14% of survivors [11] in one study and by 28%-33% of survivors in another [9]. However, we should note that the majority of patients in our study had not attempted to obtain a mortgage after their diagnosis. We recommend that more attention should be paid and more information should be given to patients on the financial aspects of being a cancer survivor.

The present study had certain limitations that should be noted. Although only 20% of patients did not respond and 29% of patients were lost to follow-up, we do not know what their current health status is.

However, non-respondents did not differ significantly from the respondents or from patients whose addresses could be verified in terms of age, disease stage, treatment, or years since diagnosis. In addition, it is important to keep in mind that our results can only be generalized to a small percentage of the original group of 314 Hodgkin lymphoma patients while a large group of patients could not be included in our study (they died, there hospital declined to participate or their addresses could not be verified. Furthermore, it is more difficult to draw conclusions on QOL based on a cross-sectional study in comparison to a longitudinal study. Although baseline differences have not been found between patients treated 5-9 and 10-15 years ago, only randomized controlled trials can ensure comparable groups at baseline. However, only a selected group of patients will be eligible for randomized controlled trials. By controlling for stage, age at diagnosis, grade, years since diagnosis, education, marital status and comorbidity at diagnosis in our analysis, we attempted to minimize errors. Our results about problems obtaining mortgages and life and health insurance have to be interpreted with caution because we have no reference data available from a healthy control group; furthermore, we do not know whether other factors (such as other diseases or age) might have played a role in this.

We can conclude that QOL in Hodgkin's lymphoma survivors is lower compared to an age-matched normative sample from the general population.

Survivors furthermore experience some specific (financial) problems in the years after diagnosis.

Acknowledgement

The regional Interzol clinical study group for Heamato-oncology and "The Foundation for the promotion of Academic Training and Research in Health Care" (SWOOG) financially supported this study. Floortje Mols also received a grant from the Beunke fund for lymphoma research.

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9

Increased health care utilisation among 10-year breast cancer survivors

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(*Supportive care in cancer*, 2006: **14** (5): 436-443)

Abstract

We investigated self-reported health care utilisation of women who survived breast cancer for 10 years and identified predictors of health care utilisation. The population-based Eindhoven Cancer Registry was used to select all women who were diagnosed with breast cancer in 1993, in six hospitals in the Netherlands and were disease-free at the time of data collection. Health status, psychological well-being, satisfaction with life and health care use were compared with same age controls. Logistic regression was used to identify predictors of health care utilisation. Of the 254 women who were sent a questionnaire, 183 (72%) responded. Breast cancer survivors had a similar health status and psychological well-being, and a better satisfaction with life compared to same age controls. The proportion of breast cancer survivors (79%) who visited a specialist in the past 12 months was significantly higher compared to controls (53%). Young breast cancer survivors (45-54 at time of completing questionnaire) more often visited a physical therapist (56%) or complementary caregiver (26%) than controls (29% respectively 13%). Spontaneously reported problems (fatigue, arm problems) as a consequence of cancer and comorbidity showed the strongest associations with health care utilisation. Although self-reported health, satisfaction with life and psychological well-being were similar or even better in long-term breast cancer survivors compared to population controls, survivors more often attended a specialist, physical therapist and complementary caregiver in the past 12 months. Survivors of young age appear to have the highest use of health care services compared to age-matched controls, especially related to fatigue and arm problems.

Introduction

Advances in the early diagnosis and treatment of breast cancer have led to increasing numbers of individuals who are either cured for their cancer or experience it as a chronic disease [1]. The number of survivors is also increasing as a result of the ageing of the population. As the number of breast cancer survivors has been rapidly growing (with >4% per year in the Netherlands) [2], more information on the physical and psychological long-term effects of cancer and its treatment is becoming available. Studying the long-term (side) effects of different treatments is important to obtain insight into medical and psychosocial needs of patients and possibly to adjust current therapies in order to minimise late complications.

So far, most studies of the effects of breast cancer and its treatment have focused on long-term well-being (e.g. cancer or treatment related complaints, quality of life, health status etc.). These studies have demonstrated that fatigue, physical complaints and menopausal problems, more often occur in breast cancer survivors compared to healthy women, even years after diagnosis [3, 4]. Young age at diagnosis [5], having undergone lymph node dissection [6-8] and chemotherapy [9, 10] seemed to affect well-being after many years. It is likely that these long-term side effects also result in an increased health care utilisation, compared to the general female population, although little is known about this. Insight into the health care utilisation may reveal the need for specific care programmes for cancer survivors.

The present study compares self-reported health care utilisation of women who survived breast cancer for 10 years with the general Dutch female population and identifies predictors of health care utilisation.

Methods

Study Participants

We used the population-based Eindhoven Cancer Registry to select all women (n=254) who were diagnosed with invasive breast cancer in 1993, in six community hospitals in the south of the Netherlands and were still alive at the time of data collection (October 2003). The participants had to be disease-free and currently not in need of cancer treatment. We only included women who were younger than 75 at diagnosis, and therefore younger than 85 at the time of data collection. Eligible women were sent a questionnaire by their (sometimes former) specialist. Completion of the self-administered questionnaires was considered to imply informed consent.

Measures

The CentERdata Health monitor was used to measure health status (8 items), satisfaction with life (5 items) and psychological well-being (5 items) [11], all with a 5-point Likert-scale. Higher scores indicate better health status (range: 0-40), better satisfaction with life (range: 0-25) and better psychological well-being (range: 0-25). The CentERdata Health monitor has been validated with a high internal consistency of the three different subscales of 0.88, 0.75, and 0.82 [11]. Norm scores of this questionnaire are available for a Dutch population sample consisting of 1893 men and women. For this study we used norm-scores and standard deviations (SD) of 149 women in the age group 45-54 years, 83 women in the age group 55-64 years, 66 women in the age group 65-74 years and 10 women who were 75 years of age or older. Health status, satisfaction with life and psychological well-being among survivors were defined to be clinically meaningful different from the norm-scores when they were one or more SD(s) above or below the mean of the Dutch female population sample.

In addition to the validated CentERdata Health monitor, women were asked – in an open question- whether they had complaints that *according to them* were related to having had breast cancer in the past, and whether they had comorbid disease(s). In addition, women were asked if they had visited their general practitioner (GP), a medical specialist, a physical therapist, or complementary caregiver in the past twelve months. The health care utilisation questions were asked in a similar way as is done via the annual monitoring of the health care situation of the Dutch population by Statistics Netherlands (http://statline.cbs.nl). Norm-data of the year 2003 were used from 400 women in the age group 45-54 years, 313 women in the age group 55-64 years, 396 women in the age group 65-74 years and 325 women who were 75 years or older.

Statistical Analyses

All data were analysed using SAS (version 8.02, SAS Institute Inc., Cary, North Carolina, USA). Differences in characteristics of respondents and non-respondents were analysed by means of the chi-square statistic. Since age has repeatedly been reported to be an important factor for long-term well-being and is also related tot health care utilisation, we analysed the results by four different age-groups. Differences between the age groups with respect to mean scores on the (domains of the) CentERdata Health monitor were analysed by

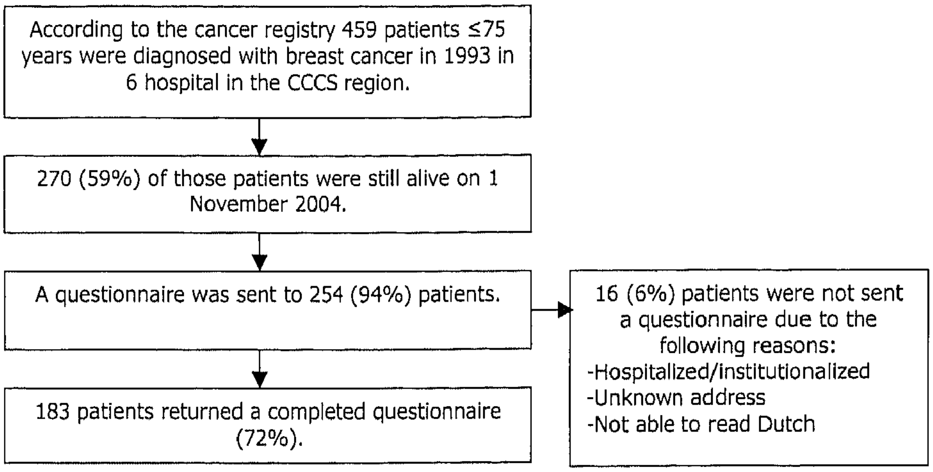

Figure 1. Flow-chart of the data collection process

means of anova, differences between the survivors and controls were analysed using a t-test. Differences between age groups with respect to physical problems or comorbidity were also analysed by means of the chi-square statistic, as were differences in health care use between survivors and controls. Finally, logistic regression was used to identify statistically significant predictors of health care utilisation.

Results

Of the 254 women who were sent a questionnaire, 183 (72%) responded. Most participants (87%) were diagnosed with breast cancer stage I or II (Table 1). In almost all women the axillary lymph nodes had been dissected (97%). The 71 non-respondents were not different from the participants with respect to stage at diagnosis, surgical treatment or systemic therapy. The non-respondents exhibited a slightly different age distribution: more women in the youngest and oldest age group (p=0.06), and they received radiotherapy less often (p=0.03). The latter was also shown when comparing treatment combinations between respondents and non-respondents.

Within the group of 10-year survivors there was no difference when comparing the mean scores or distributions of the three domains of the CentERdata Health monitor among the four age groups (Table 2). Comparison with norm scores from a general female population of the same age, revealed

Table 1. Characteristics of 10 year, disease free survivors of breast cancer (n=254)

	N (%)		
	Respondents N=183	**Non-Respondents** N=71	**P-value**
Age at diagnosis[1]			
35-44 yrs	25 (14)	17 (24)	
45-54	63 (34)	18 (25)	
55-64	60 (33)	17 (24)	
65+	35 (19)	19 (27)	0.06
Stage at diagnosis			
I	80 (44)	25 (35)	
II	79 (43)	40 (56)	
III	13 (7)	3 (4)	
IV	1 (1)	- (-)	
Unknown	10 (5)	3 (4)	0.28
Surgical treatment			
Breast Conserving Therapy	105 (57)	32 (45)	
Mastectomy	74 (40)	36 (51)	
Unknown	4 (3)	3 (4)	0.18
Lymph node dissection	178 (97)	67 (94)	0.26
Systemic therapy			
Hormonal therapy	29 (16)	10 (14)	0.72
Chemotherapy	19 (10)	12 (17)	0.15
Radiotherapy	131 (72)	41 (58)	0.03
Treatment combinations			
Surgery alone	48 (26)	22 (31)	
Surgery + Rth	87 (48)	26 (37)	
Surgery + Rth + Chemo	17 (8)	7 (10)	
Surgery + Rth + Hormonal	26 (14)	7 (10)	
Surgery + Chemo	1 (1)	5 (7)	
Surgery + Hormonal	3 (2)	3 (4)	
Other	1 (1)	1 (1)	0.02

[1] all survivors were approached 10 years after diagnosis, thus current age is ten years older
Rth=radiotherapy

that health status and psychological well-being were similar to the general population. In contrast, satisfaction with life was significantly higher among breast cancer survivors in all four age groups. In those aged 45-54, 55-64 and 75+ this higher satisfaction with life was also clinically meaningful.

A strong age gradient was found when comparing spontaneously reported problems as a consequence of cancer and comorbidity (Table 2). A painful, numb or tingling arm (n=64) and fatigue (n=18) were the most often reported problems. Other spontaneously reported problems were: problems

Table 2. Physical and psychological well-being in disease free 10-year breast cancer survivors and a control sample of the Dutch population

	Mean scores (SD)				
	Age at time of completing questionnaire				**P-value**
	45-54	**55-64**	**65-74**	**75+**	
CentERdata Health monitor					
Health Status (range: 0-40)					
10-year survivors	33 (6)	31 (8)	33 (7)	29 (6)	0.11
Controls [1]	30 (6)	32 (6)	33 (5)	29 (7)	0.02
Satisfaction with life (range: 0-25)					
10-year survivors	22 (4)***	22 (3)***	21 (4)***	23 (3)***	0.42
Controls [1]	18 (3)	19 (3)	19 (3)	17 (3)	0.03
Psychological well-being (range: 0-25)					
10-year survivors	18 (3)	19 (4)	20 (4)	20 (4)	0.51
Controls [1]	19 (3)	20 (3)	20 (3)	19 (4)	0.22
Current problems as a consequence of cancer [2]	N (%)				
Painful, numb or tingling arm	13 (52)	24 (38)	17 (28)	10 (29)	0.037
Fatigue	5 (20)	10 (16)	2 (3)	1 (3)	0.003
Comorbidity [3]	12 (48)	35 (56)	33 (55)	24 (69)	0.14

[1] controls from CentERdata Health monitor[11]: 45-54 years, n=149; 55-64 years, n=83; 65-74 years, n=66, 75+ years, n=10.

[2] spontaneously reported answers to the question 'Do you have specific complaints/restraints that are a consequence of cancer or its treatment?' Problems with own appearance, fear, and sexual problems were the other self-reported complaints.

[3] 'Do you have any other diseases at this moment?' 'If yes, which?'

*** p<0.001: significantly higher than control group

with own appearance, fear, and sexual problems. With increasing age, the frequency of self-reported cancer related problems decreased (p-trend <0.05), whereas the frequency of self-reported comorbidity increased (p-trend=0.14). A painful arm was reported by 52% of the youngest age group versus 29% of the oldest age group. Spontaneously reported fatigue as a consequence of cancer was almost non-existent (3%) in women who were 65 years or older when they completed the questionnaire, whereas it was a frequently (17%) reported problem in those younger than 65. Additional multivariate analyses revealed that, after adjustment for age and comorbidity, having received chemotherapy increased the risk of reporting fatigue by more than 5 times (OR=5.2 95%; CI=1.4-19) (data not shown).

The percentage of breast cancer survivors who had visited their GP in the past 12 months was not different from the general female Dutch population (Table 3). As expected, the proportion of breast cancer survivors (79%) who visited a specialist in the past 12 months was much higher (53%; p<0.001).

Table 3. Health care utilisation during past 12 months in disease free 10-year breast cancer survivors and a control sample of the Dutch population

	% visits or contact			
	45-54	**55-64**	**65-74**	**75+**
General practitioner				
10-year survivors	88	85	85	90
Controls[1]	80	81	88	89
Medical specialist				
10-year survivors	83***	78***	80**	79*
Controls[1]	44	49	59	58
Physical therapist				
10-year survivors	56**	47**	31	32
Controls[1]	29	27	27	32
Complementary caregiver				
10-year survivors	26*	10	11	10*
Controls[1]	13	10	8	3
Patient support group				
10-year survivors	9	10	2	11
Controls[1]	-	-	-	-

[1] Data collected by Statistics Netherlands in 2003.

* $p<0.05$: significantly higher than control group

** $p<0.01$: significantly higher than control group

*** $p<0.001$: significantly higher than control group

Young breast cancer survivors (45-54 and 55-64 years) more often visited a physical therapist (56% and 47%) than the general female Dutch population (29% and 27%; $p<0.01$). The youngest group (45-54 years) also visited a complementary caregiver twice as often compared to the general female Dutch population (26% versus 13%; $p<0.05$).

Factors predicting health care utilisation are summarized in Table 4. Contact with a GP or physical therapist in the past 12 months was clearly related to a worse subjective health status, psychological well-being, comorbidity and spontaneously reported problems presumably as a consequence of cancer (more specifically; a painful arm). In addition, a physical therapist was significantly more often visited by younger survivors than by older survivors. With each point increase of the health status or psychological well-being score (e.g., better score), the chance of contacting a specialist decrease with 10% and 20% respectively. Contact with a complementary caregiver was also predicted by worse psychological well-being and spontaneously reported fatigue. Women who had undergone a breast amputation more often had contact with a patient support group than women who received radiotherapy

Table 4. Univariate association between patient- and tumour characteristics at diagnosis, questionnaire outcome and health care utilisation during the past 12 months (before the study)

	OR (95% CI) Visited during past 12 months				
	General Practitioner	**Specialist**	**Physical therapist**	**Complementary caregiver**	**Patient support group**
Current age					
45-54	1.0	1.0	1.0	1.0	1.0
55-64	0.8 (0.2-3.1)	0.7 (0.2-2.4)	0.7 (0.3-1.8)	0.3 (0.1-1.2)	1.1 (0.2-6.1)
65-74	0.8 (0.2-3.2)	0.8 (0.2-2.9)	0.4 (0.1-1.0)*	0.3 (0.1-1.2)	0.2 (0.1-2.3)
75+	1.2 (0.2-6.5)	0.8 (0.2-3.1)	0.4 (0.1-1.1)	0.3 (0.1-1.5)	1.3 (0.2-8.3)
Stage at diagnosis					
I	1.0	1.0	1.0	1.0	1.0
II	0.9 (0.3-2.3)	0.7 (0.3-1.7)	0.7 (0.4-1.3)	1.3 (0.5-3.4)	2.7 (0.7-10.6)
III & IV	0.3 (0.1-1.5)	0.6 (0.1-2.6)	1.0 (0.3-3.5)	[1]	[1]
Treatment (yes vs no)					
Breast amputation	1.0 (0.4-2.4)	1.0 (0.5-2.3)	1.4 (0.7-2.6)	0.7 (0.3-1.9)	5.0 (1.3-19.3)*
Hormonal therapy	0.8 (0.3-2.6)	1.4 (0.4-4.4)	0.7 (0.3-1.7)	0.6 (0.1-2.6)	[1]
Chemotherapy	0.8 (0.2-3.1)	2.3 (0.5-10.6)	1.4 (0.5-3.5)	2.1 (0.6-7.0)	1.6 (0.3-8.0)
Radiotherapy	0.9 (0.3-2.4)	1.6 (0.7-3.5)	1.0 (0.5-2.0)	1.0 (0.4-2.8)	0.2 (0.1-0.6)*
CentERdata Health monitor					
Health status	0.8 (0.7-0.9)*	0.9 (0.8-1.0)*	0.9 (0.9-1.0)*	1.0 (0.9-1.1)	1.0 (0.9-1.1)
Satisfaction with life	0.9 (0.7-1.0)	0.9 (0.8-1.0)	0.9 (0.8-1.0)	0.9 (0.8-1.0)	1.1 (0.9-1.4)
Psychological well-being	0.8 (0.7-0.9)*	0.9 (0.8-1.0)*	0.9 (0.8-1.0)*	0.9 (0.8-1.0)*	0.9 (0.8-1.1)
Comorbidity					
0	1.0	1.0	1.0	1.0	1.0
1	3.7 (1.2-11.8)*	1.5 (0.6-3.9)	1.6 (0.7-3.5)	1.6 (0.4-5.3)	2.0 (0.5-8.1)
≥ 2	19.1 (2.5-148)*	2.1 (0.8-5.4)	2.5 (1.2-5.3)*	1.8 (0.6-5.5)	0.8 (0.2-3.9)
Problems [2] (yes vs no)					
Current problems	2.8 (1.1-7.0)*	1.1 (0.5-2.4)	3.0 (1.6-5.9)*	2.8 (1.0-8.1)	4.3 (0.9-20.4)
Painful arm (yes vs no)	3.3 (1.1-10.2)*	1.2 (0.5-2.7)	2.1 (1.1-4.1)*	1.1 (0.4-2.7)	1.3 (0.4-4.2)
Fatigue (yes vs no)	1.5 (0.3-6.8)	4.5 (0.6-35.2)	2.3 (0.8-6.3)	6.2 (2.1-18.5)*	1.7 (0.3-8.6)

* p<0.05

[1] Numbers were too small to calculate the OR; [2] Current problems as a consequence of cancer

(e.g., breast conserving therapy) ten years ago. Additional analyses with treatment combinations as presented in Table 1 gave no different results.

In multivariate analyses, including only variables that were significantly related in univariate analyses, none of the variables reached statistical significance anymore, most likely due to the small numbers.

Discussion

Long-term breast cancer survivors had a similar self-reported health status and psychological well-being as the general female population of the same age, whereas satisfaction with life was higher among survivors. Yet, more than half of the survivors reported current health problems that they thought were related to having had cancer in the past. In particular, a painful, numb or tingling arm and fatigue were frequently reported. Breast cancer survivors also had a higher medical consumption as shown by more visits to a medical specialist, physical therapist and complementary caregiver compared to the general female Dutch population. Factors associated with health care utilisation were self-reported health status, psychological well-being, comorbidity and spontaneously reported problems as a consequence of cancer (a painful arm and fatigue). Women who had undergone breast amputation were 5 times more likely to contact a support group than women who had had breast-conserving therapy.

Long-term breast cancer survivors generally experience a good overall quality of life, but do report specific health problems [12]. Arm problems [8, 13-17] and fatigue [3] are frequently reported. Both complaints have mainly, or most severely been reported by women who were relatively young at diagnosis [8, 15, 16] whereas fatigue more often has been reported by women who had undergone chemotherapy [3, 18], in accordance with our results. It could be that younger women possibly live under greater physical strain compared to older women when diagnosed, as they often combine work, taking care of –younger-children and running a household [19]. But, older women might also be more inclined to attribute their health problems to old age rather than to their breast cancer treatment.

The percentage of long-term breast cancer survivors who visited their GP in the past 12 months was comparable to the general Dutch female population. Although self-reported health status, psychological well-being and cancer related problems were associated with GP contact, comorbidity appeared to be the strongest predictor in the past 12 months. A previous study among persons with at least one chronic disease, based on the Netherlands Health Interview Survey, also showed that comorbidity was strongly associated with the volume and variety of used health care services [20]. In a Medicare-based study among older cancer survivors, remote history of cancer (>6 years earlier) did not influence emergency room visitation, hospital admission or nursing home admission, whereas comorbid conditions did [21]. The failure to find an increased use of GP service among breast cancer survivors can possibly be explained by the already high proportion of women in the general population who visited their GP in the past twelve months (>80%). In accordance with our results, a recent study among 258 Norwegian breast cancer survivors showed that the use of GP care was similar to that of age-matched controls [22]. However, as in our results, the use of specialist health care services was significantly higher among Norwegian breast cancer survivors (49%) than among controls (27%).

The high proportion of breast cancer survivors who visited a medical specialist in the past 12 months in our study is probably due to the routine, annual follow-up examination that many women and doctors still prefer, even at 10 years after diagnosis. Breast cancer survivors in the Netherlands are usually seen once a year from the third year since diagnosis. An analysis based on Medicare data of 5,965 elderly women diagnosed with non-metastatic breast cancer showed that survivors, compared to controls, received high-quality preventive services. The authors suggest that follow-up may provide regular contact with the health system, maximizing the likelihood of receiving appropriate general medical care [23].

The higher utilisation of physical therapy among young breast cancer survivors (<65 years) was related to the arm problems in this group. Comorbidity also was an important predictor for the use of physical therapy. Fortunately, introduction of the sentinel node technique in the late nineties has resulted in fewer women with axillary lymph node dissection and its related arm problems and increased health care use [24-26].

Among the youngest (45-54 years) and oldest (75+) breast cancer survivors the proportion of women that visited a complementary caregiver was increased compared to the general female Dutch population. Self-reported fatigue appeared to be the strongest predictor for visiting a complementary caregiver in the past year. The rationale of that can only be speculated. Canadian breast cancer survivors using complementary/alternative medicine (CAM) rated CAM practitioners more highly on 'providing emotional support' compared to conventional practitioners [27]. CAM users were younger, more educated, had greater household incomes, were more likely to have attended a support group and were more likely to have had chemotherapy than non CAM-users [27].

Additional analyses in our study showed that, after adjustment for age and comorbidity, having received chemotherapy at diagnosis increased the risk of reporting fatigue by more than 5 times. This phenomenon, which is supported by other studies, should be weighed against the tendency to broaden the indication for (adjuvant) chemotherapy. High income, high education and young age were important predictors for the use of complementary alternative medicine [28, 29]. In agreement with our study, patients who initiated the use of complementary alternative medicine after breast cancer surgery reported more depression, worse general mental health and greater fear of recurrence compared to those who did not [30].

Breast cancer survivors who had a breast amputation 10 years ago were more likely to have contacted a patient support group during the past 12 months than survivors who received breast conserving therapy and additional radiotherapy. This may be explained by the preservation of the woman's female identity and acceptance of body configuration among the latter [3, 31].

There are a few limitations associated with this population-based study on health care use in cancer survivors. First, this study is based on self-reported health status, complaints, comorbidity and health care use. Estimates of health care use may be unreliable because of the difficulty of dating and recalling the contacts with health care providers, although we do not expect that this possible information bias is different for survivors and controls.

The cross-sectional design makes it difficult to draw conclusions about the causal relationship between self-reported health status, complaints, comorbidity and health care use. We do not know whether the rather small proportion of non-respondents are those who have refused because of poor health, or in contrast, were in better health. Based on information about the age, stage and treatment, the non-respondents did not differ very much from the respondents when comparing demographic or medical information at initial diagnosis. Lastly, some of the subgroups were so small that it is possible that we introduced type II errors, i.e. not finding an association which is actually present.

Nevertheless, this population-based study has certain strengths, especially compared to survivorship studies in a clinical (trial) setting with selected patients. The high response rate makes it possible to extrapolate our findings to other long-term breast cancer survivors. Furthermore, having information about cancer stage and treatment modality at diagnosis assists the clinician in predicting further health care utilisation, although one should keep in mind that treatment since 1993 has changed.

In conclusion, although self-reported health, satisfaction with life and psychological well-being was similar or even better in long-term breast cancer survivors compared to population controls, survivors more often attended a specialist, physical therapist and complementary caregiver in the past 12 months. Survivors of young age appear to have the highest use of health care services compared to age-matched controls, especially related to fatigue and arm problems.

Acknowledgment

This study was financially supported by the Dutch Cancer Society.

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10

Increased health care utilisation among long-term cancer survivors compared to the average Dutch population: a population-based study

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(*Submitted for publication*)

Abstract

In the present study self-reported health care utilization of cancer survivors is compared with those of an age- and sex-matched normative population and predictors of health care utilization are identified. A population-based, cross-sectional survey among 1893 long-term survivors of endometrial and prostate cancer and malignant lymphomas (Hodgkin's and non-Hodgkin's) diagnosed between 1989-1998 was conducted using the cancer registry of the Comprehensive Cancer Centre South. Cancer survivors visited their general practitioner somewhat more often compared to the age and sex-matched general Dutch population but this effect was not always statistically significant. In addition, they visited their medical specialist significantly more often. Survivors only sporadically (0-3%) visited or required a dietician, sexologist, oncology nurse, pastor, creative therapy, or recovery program. Contact with a psychologist, physiotherapist and other cancer survivors took place somewhat more often. Patients visited a medical specialist less often if they were diagnosed with endometrial cancer (OR=0.2; 95% CI=0.1-0.5), if they were diagnosed between 10-15 years ago (OR=0.6; 95% CI=0.1-0.5) and if they were not married or divorced (OR=0.5; 95% CI=0.3-0.9). Contact with a psychologist was related to having a university or college degree (OR=3.6; 95% CI=1.3-9.4). Cancer survivors visited their specialist more often compared to the normative population. Changes in health care, such as less administrative work for the specialist and more efficiency, are probably necessary in order to cope adequately with the increasing demand on the system. Nurse practitioners and specialized oncology nurses will become even more crucial in the near future in order to be able to deal with this increasing workload.

Introduction

The prevalence of cancer is rising. The increasing incidence of cancer in general, the aging of the population, and more effective treatment all contribute to this rapid increase [1]. In addition, cancer is changing from a life-threatening disease into a chronic condition [2]. A large number of cancer patients will therefore become long-term survivors: i.e. those alive 5 years after initial diagnosis [3].

Cancer and its treatment can have a significant effect on health care utilisation of patients during diagnosis and treatment but also years after treatment has been completed. To date, consequences of cancer for health care utilisation of long-term cancer survivors have rarely been studied. It is known that long-term breast cancer survivors used more health care services compared to an age-matched female norm population [4]. Furthermore, a large minority of breast cancer patients (23-26 months after diagnosis) required supportive care (e.g. psychologist, physiotherapist) but about one-third of patients were unable to access at least one of these services [5]. Moreover, cancer survivors reported a greater need for mental health services than individuals without a history of cancer, especially those who were under the age of 65 and diagnosed at a younger age, were formerly married, or had other comorbid chronic conditions [6]. The difference in health care utilisation between long-term cancer survivors and the general population could not be attributed to the higher prevalence of common somatic complaints. Cancer-related health issues might explain the increase in use of health care [7]. Furthermore, 2 years after diagnosis, one-third of prostate cancer patients used complementary and alternative medicine; this could be predicted by the presence of comorbid diseases [8].

Insight into the health care utilisation of cancer patients is essential for health care planning and may also reveal the need for specific care programs for cancer survivors. However, only a few studies on health care utilisation of *long-term* cancer survivors exist. In the present study therefore self-reported health care utilization of cancer survivors are compared with those of the general population and predictors of health care utilization are identified.

Setting and Participants

A population-based, cross-sectional survey was conducted at the Eindhoven Cancer Registry (ECR). The ECR records data on all patients newly diagnosed with cancer in the southern part of the Netherlands, an area with 2.3

million inhabitants, 10 hospitals, with 18 hospital locations and two large radiotherapy institutes [9]. The ECR was used to select all patients diagnosed with prostate cancer or endometrial cancer between 1994 and 1998 and all patients diagnosed with Hodgkin's lymphoma or non-Hodgkin's lymphoma between 1989 and 1998. Participants older than 75 years *at diagnosis* were excluded as it was expected that they would have difficulty in completing a self-report questionnaire without assistance. To exclude all persons who had died before November 1 2004, our database was linked to the database of the Central Bureau for Genealogy, which collects data on all deceased Dutch citizens via the civil municipal registries. After having excluded all persons who had died, data collection was started in November 2004. Approval for this study was obtained from a local certified Medical Ethics Committee.

Data collection

Medical specialists sent their (former) patients a letter to inform them about the study, together with the questionnaire. The letter explained that, by returning the completed questionnaire, the patient agreed to participate and consented to linkage of the questionnaire data with their disease history as registered in the ECR. Patients were reassured that non-participation would not have any consequences for their follow-up care or treatment. If the questionnaire was not returned within two months, a reminder-letter with an additional copy of the questionnaire was sent.

Measures

The ECR routinely collects data on tumour characteristics, including date of diagnosis, grade (Tumour-Node-Metastasis clinical classification [10]), clinical stage [10], treatment, and patient background characteristics including date of birth and comorbidity at the time of diagnosis (a slightly adapted version of the Charlson comorbidity index [11]). The questionnaire also included questions on sociodemographic data, including marital status, current occupation, educational level as well as disease progression and current comorbidity.

The Dutch version of the SF-36 questionnaire was used to assess generic health related quality of life (HRQL) [12]. According to standard scoring procedures, all scales were linearly converted to a 0-100 scale, with higher scores indicating better functioning. The internal consistency and reliability of all scales was above the 0.70 criteria recommended for group comparisons.

Only the two higher-order component scores for physical and mental health were used.

Generic HRQL survival issues were assessed with the validated Dutch version of the Quality of Life-Cancer Survivors (QOL-CS) questionnaire [13, 14], which included 45 visual analogue scales, each of which ranged from 0 (worst outcome) to 10 (best outcome). These 45 visual analogue scales were grouped into four multi-item subscales on well-being: physical, psychological, social and spiritual. They assess issues of particular concern to long-term cancer survivors such as distress, sexuality, employment, uncertainty about the future and the role of spirituality and religion [15]. The QOL-CS has been demonstrated to be a valid and reliable instrument when administered to cancer survivors [13, 14, 16, 17].

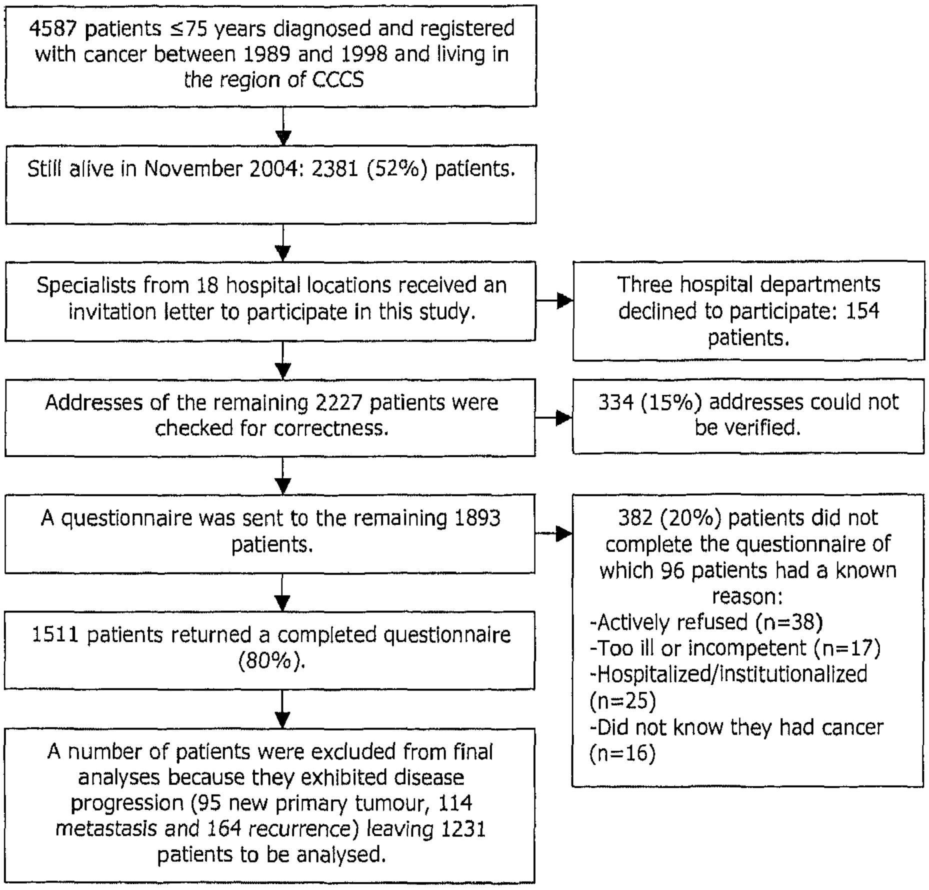
This study was done in the Netherlands, a country in which every person has equal access to care. The items concerning health care utilisation included questions on the number of visits to a general practitioner, medical specialists, and other health care professionals. These questions were similar to the questions on health care utilisation used annually by Statistics Netherlands for a panel of Dutch citizens.

Statistical analyses

All statistical analyses were performed using SAS (version 9.1 for Windows, SAS institute Inc., Cary NC). Routinely collected data from the ECR on patient and tumour characteristics enabled us to compare the group of respondents, non-respondents and patients with unverifiable addresses, using the chi-square test for categorical variables. Sociodemographic characteristics, clinical characteristics and HRQL scores of patients with different types of cancer are given in percentages. A number of these respondents were excluded from the primary analyses because they exhibited disease progression (95 new primary tumour, 114 metastasis and 164 recurrence), resulting in 1231 patients to be analysed.

The percentages of patients visiting a general practitioner or medical specialist in the past 12 months were compared to the percentage of people from the general population visiting these health care professionals. This comparison was made according to tumour type; for each tumour type, an age-matched reference group from the general population was formed. Percentages were compared using binominal distributions.

Figure 1. Flow-chart of the data collection process



4587 patients ≤75 years diagnosed and registered with cancer between 1989 and 1998 and living in the region of CCCS

Still alive in November 2004: 2381 (52%) patients.

Specialists from 18 hospital locations received an invitation letter to participate in this study.

Three hospital departments declined to participate: 154 patients.

Addresses of the remaining 2227 patients were checked for correctness.

334 (15%) addresses could not be verified.

A questionnaire was sent to the remaining 1893 patients.

382 (20%) patients did not complete the questionnaire of which 96 patients had a known reason:
-Actively refused (n=38)
-Too ill or incompetent (n=17)
-Hospitalized/institutionalized (n=25)
-Did not know they had cancer (n=16)

1511 patients returned a completed questionnaire (80%).

A number of patients were excluded from final analyses because they exhibited disease progression (95 new primary tumour, 114 metastasis and 164 recurrence) leaving 1231 patients to be analysed.

Based on the following question; "*After cancer treatment*, did you receive any additional care for cancer-related problems? If yes, please indicate the kind of additional care from the list below", the health care utilisation of groups of patients with different types of cancer were expressed in percentages.

Multivariate Logistic Regression analyses were carried out in order to analyze the association between patient (age, gender, comorbidity, marital status, educational level, HRQL) and tumour characteristics (type of tumour, stage at diagnosis, time since diagnosis, primary treatment) with health care utilisation (the percentage of patients visiting a general practitioner or medical specialist in the past year and the percentage of patients visiting a psychologist or physiotherapist after cancer treatment). If the patient or tumour

Table 1. Sociodemographic and medical characteristics of questionnaire respondents, non-respondents and patients with unverifiable addresses

	N (%)			
	Respondents	**Non-Respondents**	**Patients with unverifiable addresses**	
	N= 1511	**N= 382**	**N= 334**	**P-value**
Mean age				
at time of survey	68 year	69 year	62 year	<0.001
Age at time of survey				
< 40 years	81 (5)	23 (6)	61 (18)	
40-60 years	219 (15)	47 (12)	59 (18)	
60-80 years	1043 (69)	232 (61)	180 (54)	
80+ years	168 (11)	80 (21)	34 (10)	<0.001
Years since diagnosis				
5-9 years	1314 (87)	324 (85)	271 (81)	
10-15 years	197 (13)	58 (15)	63 (19)	0.02
Stage at diagnosis				
I	626 (41)	199 (52)	133 (40)	
II	590 (39)	109 (29)	118 (35)	
III	89 (6)	26 (7)	27 (8)	
IV	133 (9)	23 (6)	31 (9)	
Unknown	73 (5)	25 (7)	25 (8)	<0.001
Treatment				
Surgery	720 (48)	200 (52)	129 (39)	<0.001
Radiotherapy	643 (43)	150 (39)	143 (43)	0.48
Hormonal therapy	211 (14)	51 (13)	30 (9)	0.05
Chemotherapy	318 (21)	61 (16)	92 (28)	<0.001
Wait and see	85 (6)	24 (6)	24 (7)	0.53

characteristics appeared to be statistically significant ($p<0.1$) in univariate analysis, they were included in the multivariate analysis. The percentages of patients visiting, for example, a dietician, sexologist or oncology nurse were excluded from our analyses due to the small numbers of patients involved.

Results

One thousand five hundred and eleven (80%) of 1893 patients returned a completed questionnaire (Figure 1). A comparison of respondents, non-respondents and patients with unverifiable addresses indicated that the non-respondents were significantly older, more often diagnosed with stage I disease, more likely to have been treated with surgery and were less likely to have received chemotherapy than respondents (Table 1).

Sociodemographic characteristics, clinical characteristics and HRQL of cancer survivors, according to type of tumour, are presented in Table 2.

Table 2. Sociodemographic and clinical characteristics of long-term cancer survivors without recurrent disease or new primary malignancies.

	N (%)			
	Endometrial Cancer	**Prostate Cancer**	**Hodgkin's Lymphoma**	**Non-Hodgkin's Lymphoma**
	N=283	**N=604**	**N=119**	**N=225**
Mean age				
at time of survey	68 years	75 years	45 years	60 years
Age at time of survey				
< 40 years	0 (0)	0 (0)	51 (43)	22 (10)
40-60 years	41 (15)	10 (2)	49 (41)	81 (36)
60-80 years	224 (79)	486 (81)	18 (15)	110 (49)
80+ years	18 (6)	108 (18)	1 (1)	12 (5)
Gender				
Male	0 (0)	604 (100)	61 (51)	116 (52)
Female	283 (100)	0 (0)	58 (49)	109 (48)
Stage at diagnosis				
I	249 (88)	172 (29)	31 (26)	91 (40)
II	22 (8)	355 (59)	52 (44)	49 (22)
III	7 (3)	18 (3)	26 (22)	19 (8)
IV	1 (0)	25 (4)	6 (5)	52 (23)
Unknown	4 (1)	34 (6)	4 (3)	14 (6)
Primary treatment				
Surgery	280 (98)	296 (48)	2 (2)	28 (12)
Chemotherapy	4 (1)	0 (0)	99 (83)	160 (71)
Radiotherapy	91 (32)	276 (46)	81 (68)	102 (45)
Hormonal therapy	1 (0)	153 (25)	0 (0)	0 (0)
Comorbidity				
None	78 (28)	223 (37)	55 (46)	103 (46)
1 or more	72 (283)	381 (63)	64 (54)	122 (54)
Most frequent comorbid conditions				
1. Hypertension	104 (37)	174 (29)	13 (11)	44 (20)
2. Arthrosis	107 (38)	135 (22)	22 (19)	48 (21)
3. Asthma	32 (11)	84 (14)	13 (11)	21 (9)
Marital status				
Married	174 (64)	462 (80)	76 (66)	151 (71)
Not married/divorced	27 (10)	36 (6)	37 (32)	39 (18)
Widowed	70 (26)	79 (14)	2 (2)	24 (11)
Educational level				
Primary school	162 (60)	260 (45)	26 (23)	94 (45)
Secondary school	80 (30)	190 (33)	56 (49)	67 (32)
College/university	28 (10)	123 (22)	33 (29)	50 (24)
Current occupation				
Employed	33 (12)	41 (7)	79 (69)	67 (32)
Unemployed	136 (50)	16 (2)	29 (25)	59 (28)
Retired	102 (38)	517 (90)	7 (6)	87 (41)

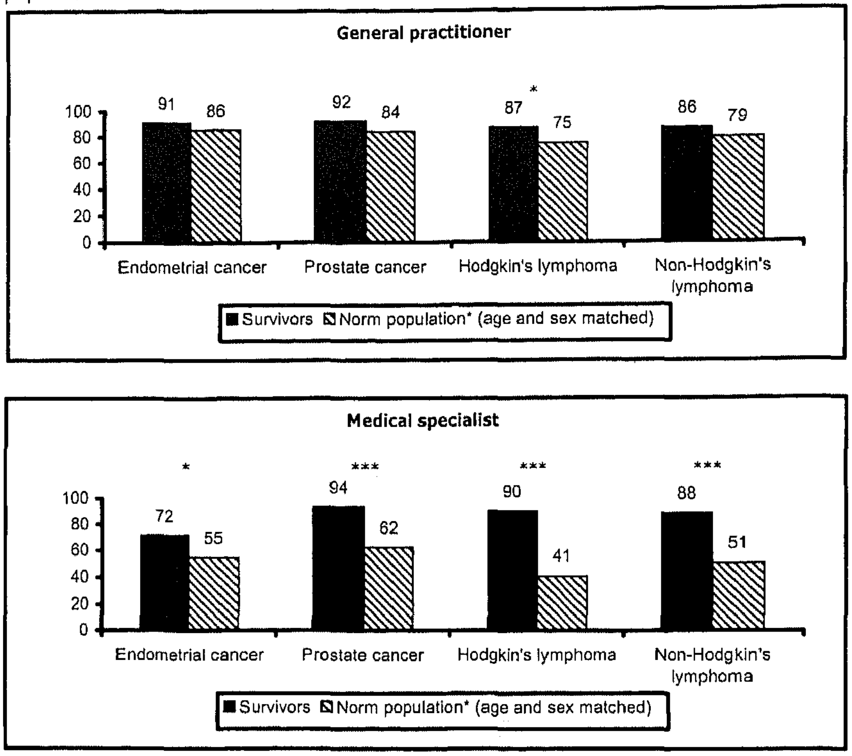
Table 2 Continued. Sociodemographic and clinical characteristics of long-term cancer survivors without recurrent disease or new primary malignancies.

	Mean (S.D.)			
	Endometrial Cancer N=283	**Prostate Cancer** N=604	**Hodgkin's Lymphoma** N=119	**Non-Hodgkin's Lymphoma** N=225
Quality of life				
Total QOL-CS score	6.7 (1)	6.8 (1)	6.4 (1)	6.6 (1)
SF-36 Physical	45.1 (11)	45.0 (11)	47.8 (11)	44.8 (11)
SF-36 Mental	51.1 (10)	53.1 (10)	50.0 (11)	52.1 (9)

Hodgkin and non-Hodgkin's lymphoma survivors were more often diagnosed at a later stage compared to endometrial and prostate cancer survivors. Endometrial and prostate cancer survivors usually underwent surgery while lymphoma survivors predominantly received radiotherapy and chemotherapy. Endometrial and prostate cancer survivors reported comorbidity more often, in particular hypertension and arthritis. The majority of patients was married, but endometrial cancer survivors were more often widows, they also had a lower educational level and were more often unemployed. Hodgkin's lymphoma survivors were most often employed; prostate cancer survivors were most often retired. The latter also reported the highest HRQL (QOL-CS) and mental well-being (SF-36), whereas the Hodgkin's lymphoma survivors had the lowest scores on both scales. They did however report the highest physical HRQL (SF-36).

Compared to the age-matched sample from the female norm population, endometrial cancer survivors visited their general practitioner somewhat more often (91 vs. 86%) and their medical specialist significantly more often (72 vs. 55%; P<0.05) (Graph 1). The percentage of prostate cancer patients who visited their general practitioner was higher (92 vs. 84%) but not significantly different from that of the general age-matched male population whereas the percentage of prostate cancer patients who visited their medical specialist was significantly higher (94 vs. 62%; P<0.001). The percentages of Hodgkin's lymphoma survivors who visited their general practitioner (87 vs. 75%; P<0.05) and medical specialist (90 vs. 40%; p<0.001) in the past year were significantly higher compared to the age-matched sample from the norm population. Finally, the percentage of non-Hodgkin's lymphoma survivors visiting the general

Graph 1. Differences in the percentage of contacts per year with a general practitioner and medical specialist between cancer survivors and an age- and sex-matched norm population.



Data collected by Statistics Netherlands in 2005
*$p<0.05$; **$p<0.01$; *** $p<0.001$

practitioner was higher (86 vs. 79%) but not significantly different compared to the age-matched norm population. Non-Hodgkin's lymphoma survivors however visited their medical specialist more often in the past 12 months (88 vs. 51; $p<0.001$).

Cancer survivors, with little variation per tumour, only sporadically (0-3%) used the following additional care services after cancer treatment: dietician, sexologist, pastor, creative therapy, recovery program, and oncology nurse (Table 3). Additional support of a psychologist, physiotherapist and contact with other cancer survivors occurred somewhat more often. Lymphoma survivors consulted a psychologist most often (6-10% vs. 1-3%) and they also had more contact with other survivors (5-6% vs. 0-1%). Hodgkin's lymphoma survivors visited a physical therapist the most (13% vs. 3-4%).

Table 3. Long-term cancer survivors and their percentage of health care use related to cancer type.

	N (%)			
	Endometrial Cancer N=283	**Prostate cancer N=604**	**Hodgkin's Lymphoma N=119**	**Non-Hodgkin's lymphoma N=225**
Dietician	6 (2)	4 (1)	2 (2)	7 (3)
Psychologist	8 (3)	7 (1)	12 (10)	13 (6)
Sexologist	2 (1)	5 (1)	1 (1)	2 (1)
Pastoral care	2 (1)	2 (0)	0 (0)	3 (2)
Creative therapy	0 (0)	2 (0)	0 (0)	4 (2)
Recovery program	5 (2)	5 (1)	1 (1)	2 (1)
Oncology nurse	3 (1)	3 (0)	2 (2)	5 (2)
Physiotherapist	8 (3)	25 (4)	15 (13)	8 (4)
Contact with cancer survivors	1 (0)	6 (1)	7 (6)	10 (5)

Due to rounding errors, the numbers will not always add up to 100.

Factors predicting health care utilisation are summarized in Table 4. If patients had one or more comorbid diseases, contact with a general practitioner (OR= 2.1; 95% CI=1.3-3.2) and contact with a medical specialist (OR=1.9; 95% CI=1.2-3.0) was also almost doubled. Patients had contact with a medical specialist less often if they were diagnosed with endometrial cancer (OR=0.2; 95% CI=0.1-0.5), if they were diagnosed between 10-15 years ago (OR=0.6; 95% CI=0.1-0.5) and if they were not married or divorced (OR=0.5; 95% CI=0.3-0.9). Contact with a psychologist was clearly related to a high educational level (OR=3.6; 95% CI=1.3-9.4). None of the factors in our model predicted the frequency of visiting a physiotherapist.

Discussion

Cancer survivors visited their general practitioner somewhat more often compared to the age- and sex-matched general Dutch population but this effect was not always statistically significant. In addition, they visited their medical specialist significantly more often. Survivors only sporadically visited a dietician, sexologist, pastor, or required creative therapy, a recovery program, or an oncology nurse. Additional support of a psychologist, physiotherapist and contact with other cancer survivors occurred somewhat more often. Patients had contact with a medical specialist less often if they were diagnosed with endometrial cancer, if they were diagnosed between 10-15 years ago and if they were not married. Contact with a psychologist was clearly related to a high educational level.

Table 4. Multivariate Logistic Regression Model Evaluating Independent Variables for percentage of patients visiting a general practitioner or specialist in the past 12 months and the percentage of patients visiting a psychologist or physiotherapist after cancer treatment.

	OR (95% CI)			
	General practitioner	**Medical specialist**	**Psychologist**	**Physiotherapist**
Tumour type				
Prostate cancer	1.0	1.0	1.0	1.0
Endometrial cancer	1.4 (0.7-2.9)	0.2 (0.1-0.5)*	1.9 (0.4-9.0)	0.7 (0.3-1.8)
Hodgkin's lymphoma	1.2 (0.4-3.1)	1.3 (0.5-3.4)	2.5 (0.4-14.6)	1.2 (0.2-5.9)
Non-Hodgkin's lymphoma	0.8 (0.4-1.6)	0.8 (0.4-1.8)	2.8 (0.6-13.2)	0.4 (0.1-1.8)
Time since diagnosis				
5-9	-	1.0	-	-
10-15	-	0.6 (0.1-0.5)*	-	-
Age at time of survey				
< 40 years	1.0	-	1.0	1.0
40-60 years	1.0 (0.4-2.6)	-	0.4 (0.1-1.2)	1.3 (0.4-4.2)
60-80 years	1.1 (0.4-3.2)	-	0.3 (0.1-1.1)	0.6 (0.2-2.4)
80+ years	1.5 (0.4-6.3)	-	0.2 (0.0-1.7)	0.4 (0.1-3.0)
Gender				
Male	-	1.0	1.0	-
Female	-	1.1 (0.5-2.5)	1.2 (0.5-2.8)	-
Stage at diagnosis				
I	1.0	1.0		-
II	0.6 (0.4-1.1)	1.2 (0.7-2.0)		-
III	0.4 (0.2-0.9)	0.8 (0.3-2.0)		-
IV	0.7 (0.3-1.7)	1.7 (0.6-4.7)		-
Unknown	0.6 (0.2-1.8)	1.1 (0.4-3.5)		-
Primary treatment (yes vs. no)				
Surgery	1.5 (0.8-2.6)	-	1.1 (0.3-3.5)	-
Chemotherapy	-	-	0.9 (0.3-2.7)	0.5 (0.1-1.9)
Radiotherapy	-	-	-	-
Hormonal therapy	-	-	2.0 (0.2-16.7)	-
Watchful waiting	-	-	-	-
Comorbidity				
0	1.0	1.0	-	-
>1	2.1 (1.3-3.2)*	1.9 (1.2-3.0)*	-	-
Marital status				
Married	1.0	1.0	1.0	1.0
Not married/divorced	0.6 (0.3-1.1)	0.5 (0.3-0.9)*	1.0 (0.4-2.6)	0.8 (0.3-2.1)
Widowed	1.0 (0.5-2.0)	1.2 (0.6-2.1)	2.2 (0.7-7.2)	0.4 (0.1-1.9)
Educational level				
Primary school	-	-	1.0	-
Secondary school	-	-	1.8 (0.7-4.7)	-
College/university	-	-	3.6 (1.3-9.4)*	-

Table 4 Continued. Multivariate Logistic Regression Model Evaluating Independent Variables for percentage of patients visiting a general practitioner or specialist in the past 12 months and the percentage of patients visiting a psychologist or physiotherapist after cancer treatment.

	OR (95% CI)			
	General practitioner	**Medical specialist**	**Psychologist**	**Physiotherapist**
Quality of life				
Total QOL-CS score	1.0 (0.8-1.3)	1.0 (0.8-1.2)	0.8 (0.5-1.1)	0.9 (0.6-1.3)
SF-36 Physical	1.0 (0.9-1.0)	1.0 (1.0-1.0)	-	1.0 (0.9-1.0)
SF-36 Mental	1.0 (0.9-1.0)	1.0 (1.0-1.0)	1.0 (0.9-1.0)	1.0 (0.9-1.0)

OR = Odds Ratio, CI= Confidence Interval
*p<0.05
- These variables were not significant in univariate analysis, therefore, they were not included in the multivariate model.

Our results partly confirm the results of a Norwegian study among cancer survivors who were alive five or more years after diagnosis [7]. In that study, the use of specialist health care services was significantly higher among breast cancer survivors (49%) than among controls (27%). The difference in visiting a medical specialist remained, even 10 years after diagnosis, but the frequency of visiting a general practitioner normalized over time. In addition, previous findings of a Dutch study among 10-year breast cancer survivors partly confirmed our findings [4]. The proportion of breast cancer survivors (79%) who visited a specialist in the past 12 months was significantly higher compared to controls (53%). However, no differences were found in the number of visits to a general practitioner.

In our study, the percentage of patients visiting a general practitioner was only significantly higher among Hodgkin's lymphoma survivors, not patients with non-Hodgkin's lymphoma, prostate cancer or endometrial cancer. In the general population, older persons visit their general practitioner more often compared to younger persons. This is mainly due to comorbidity. This could explain why we did not find a difference between the percentage of survivors and the normative population who visited their general practitioner in the past 12 months. The normative population did not have cancer but they probably had a number of other diseases for which they visited their general practitioner. We compared Hodgkin's lymphoma survivors with a normative population of the same age. The individuals in the normative population were young and did not have comorbid diseases very often; they therefore did not visit their general practitioner often.

The high proportion of survivors who visited a medical specialist in the past 12 months in our study can partly be explained by routine annual follow-up examinations. This can also explain why patients had less contact with a medical specialist if they were diagnosed between 10-15 years ago compared to patients diagnosed 5-9 years ago. Among long-term American colorectal cancer survivors, medical costs proved to be much higher compared to the medical costs of the general population and these costs exceeded the expected costs for surveillance 6-10 years after initial diagnosis [18].

Comorbidity was associated with more visits to a general practitioner or medical specialist. A previous study of our breast cancer research group also showed that comorbidity predicted visits to a general practitioner [4]. However, in that particular study, visits to a medical specialist were not significantly related to the presence of comorbid diseases. Another Dutch study of individuals with at least one chronic disease also showed that comorbidity was closely associated with the volume and variety of health care services used [19]. An American study among prostate cancer patients concluded that comorbidity predicted the use of complementary and alternative medicine [8].

In our questionnaire, we asked patients whether they received any additional care for cancer-related problems after cancer treatment. Survivors only sporadically wanted additional support. However, the survivors in our study were diagnosed and treated between 1989 and 1998. Additional care after cancer treatment was not common in those days. It would be interesting to ask the same question of patients diagnosed and treated in 2006 in order to estimate the increase in the percentage of survivors receiving additional care after cancer.

Additional care of a psychologist occurred somewhat more often. Hodgkin's lymphoma survivors consulted a psychologist in 10% of cases while endometrial cancer, prostate cancer and non-Hodgkin's lymphoma survivors visited a psychologist in 1-6% of cases. This effect could partly be explained by education. In our study, Hodgkin's lymphoma survivors had the highest educational level and survivors with a high educational level visited a psychologist 3.6 times more often compared to patients with a low educational level. A Canadian study on the use of supportive care services by women with breast cancer (n=1659) reported that 5% of women visited a psychologist [5]. In addition, an American study reported that cancer survivors contacted a mental health provider in 7% of cases [6]. In our study, the percentage of patients who visited a psychologist was positively related to a higher educational level. To our knowledge, this effect has not been described before for cancer patients. However, a higher educational level predicted the use of complementary and alternative medicine among cancer patients [8, 20] and it also predicted the use of cancer support services in an American study [21].

Several limitations of the current study should be noted. First, only 15% of patients could not be sent a questionnaire because of unverifiable addresses and 20% of patients who were sent a questionnaire did not respond, so we do not know what their current health status is. Non-respondents were significantly older, more often diagnosed with stage I disease, and more likely to have undergone surgery and less likely to have received chemotherapy than respondents or patients with unverifiable addresses. It is therefore possible that our results cannot be generalized to very old patients, patients diagnosed with stage I disease, and patients treated with surgery or chemotherapy. Second, it is more difficult to draw conclusions from a cross-sectional study than a longitudinal study. No conclusions can be drawn on the nature and direction of the relationships. Since we only included disease-free survivors in our analyses, we cannot generalize the results of our study to those who have disease progression.

Despite these limitations, the results of this study form an important contribution to the limited information available on health care utilisation in the growing group of long-term cancer survivors. This study included an unselected group of cancer patients, treated in various general hospitals, and not in centres of excellence or tertiary referral centres in contrast to most randomized trials. Results of a population-based study can more easily be generalized to the general population compared to results of randomized controlled trials. In addition, the large number of participants in this study and the high response rate of this study allow us to extrapolate to the broad population of long-term cancer survivors without disease progression.

Our study provided insight into health care utilisation of long-term cancer patients. Given the fact that the incidence and prevalence of cancer is rising and that long-term cancer survivors visit their medical specialist more often than the general Dutch population, our findings may have implications for health care planning in the near future. Changes in health care, such as less administrative work for the specialist and more efficiency, are probably necessary in order to cope adequately with this increasing demand on the system. Nurse practitioners and specialized oncology nurses will become even more crucial in the near future in order to be able to deal with this increasing workload. Furthermore, studies are being performed to change the standard aftercare programs, which are identical for all patients, into 'tailor-made' care programs. This could also alter the demand on the medical specialist.

Acknowledgement

The authors want to thank all patients for their participation in the study. Furthermore, they want to thank Rotary Tilburg Triborch, the regional Interzol clinical study group for Heamato-oncology, and the Comprehensive Cancer Centre South for financially supporting the study.

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General discussion

Introduction

The aim of this project was to measure QOL, treatment-related dysfunctions and health care utilisation among long-term cancer survivors and to compare our findings to general Dutch population norms. In the first part of this chapter, the main findings of the separate studies will be summarized according to tumour type. Subsequently, potential implications of the findings for clinical practice will be discussed. Finally, some general methodological considerations on study design, recruitment strategies and measurement approaches of our studies will be made, combined with recommendations for future research.

Main findings and implications for clinical practice

Breast cancer

Our systematic review of the literature on long-term breast cancer survivors revealed that these patients experienced a good overall QOL (**Chapter 1**). However, almost all studies reported that breast cancer survivors experienced problems such as, for example, a thick and painful arm and problems with sexual functioning. Current medical condition, amount of social support and current income level were strong positive predictors of QOL, whereas use of adjuvant chemotherapy emerged as a negative predictor.

Results from our study of long-term breast cancer survivors showed that survivors experienced posttraumatic growth (**Chapter 2**). In addition, the majority of patients reported benefit finding from their experience with cancer, which was moderately positively correlated with posttraumatic growth. Women, who stated that their life satisfaction was high, reported higher levels of posttraumatic growth in comparison to women who did not. Radiotherapy was negatively associated with posttraumatic growth. Women with a higher tumour stage at diagnosis experienced less benefit finding in comparison to women with lower tumour stages.

Breast cancer survivors had a similar health status and psychological well-being and a significantly higher satisfaction with life compared to controls of the same age (**Chapter 9**). However, breast cancer survivors visited a medical specialist more often than controls and young breast cancer survivors visited a physical therapist or complementary caregiver more often especially because of fatigue and arm problems. Chemotherapy increased the risk of reporting fatigue by more than five.

Implications for clinical practice:

Psychologists involved in the guidance of cancer patients might learn from the experiences of patients with posttraumatic growth. It may yield important information helpful for counseling.

Breast cancer survivors go more often to a physical therapist compared to population controls. Fortunately, introduction of the sentinel node technique in the late 1990s has resulted in fewer women with axillary lymph node dissection and related arm problems and increased health care utilisation [1]. However, long-term consequences of the sentinel node technique are unclear.

Treatment with chemotherapy increased the risk of feeling fatigued even 10 years after diagnosis. The question is whether this finding, which is supported by other studies, should be weighed against the tendency to broaden the indication for (adjuvant) chemotherapy. In addition, multidisciplinary revalidation programs, such as the Dutch program 'Herstel en Balans' ('Recovery and Balance'), might be offered to survivors on a regular basis, especially to those feeling tired. A number of studies concluded that 'Herstel en Balans' could reduce fatigue; they will be published in the near future. The patients included in our study did not attend the 'Herstel en Balans' program because this program was not yet available in 1993. The promotion of this revalidation program has been limited and the program was not available in every region of the Netherlands in the beginning. Furthermore, the costs of this program were only partly covered by health insurance companies. Presently this has improved significantly. The revalidation program is geographically and financially adequately accessible nowadays for all patients with cancer. However, the referral to this program still needs to be improved in order to ensure that every cancer patient in the Netherlands is able to follow a rehabilitation program after treatment.

Prostate cancer

The questionnaire that, in our opinion, was most suitable for measurement of QOL among long-term cancer survivors was the Quality of Life-Cancer Survivor (QOL-CS) questionnaire (**Chapter 3**). Since this tool was only available in English and Spanish versions, we developed and validated a Dutch version of this instrument. It appeared that QOL for a group of long-term prostate cancer survivors was adequately measured by the physical, psychological and social well-being subscales of the QOL-CS. In contrast, the subscale spiritual well-being showed a low internal consistency, although the test-retest reliability was good.

Long-term prostate cancer survivors reported comparable QOL combined with lower general health perceptions and better mental health than an age-matched normative population (**Chapter 4**). As expected, incontinence, bowel leakage and erection problems occurred far more often in prostate cancer survivors in comparison to an age-matched normative population (**Chapter 5**). Long-term QOL and prostate-specific problems of prostate cancer survivors appear to vary significantly as a function of the type of primary treatment, which could be expected on the basis of literature.

Prostate cancer survivors visited their medical specialist significantly more often compared to the age-matched general male Dutch population (**Chapter 10**). Patients that were not married had contact with a medical specialist less often. Contact with a psychologist was related to having a university or college degree.

Implications for clinical practice:

It is important for patients to receive adequate information on the occurrence of prostate-specific problems before treatment. In addition, after treatment, there should be appropriate support for these problems. For example, the majority of men with erection problems did not receive treatment for their erection problems. Maybe patients did not feel the need but it is far more likely that they felt uncomfortable talking about their sexual problems with their urologist or general practitioner. Another aspect is the cost of medication for erection problems. Many patients told us that they could not afford to medication and the majority of health insurance companies in the Netherlands do not cover these costs. This issue could be resolved if more insurance companies would include this medication in their insurance coverage.

Given the fact that the incidence and prevalence of cancer are rising and that long-term prostate cancer survivors visit their medical specialist more often than the general Dutch population, our findings may have implications for health care planning in the near future. Changes in health care, such as less administrative work for the specialist and more efficiency, are probably necessary in order to cope adequately with the increasing demand on the system. Nurse practitioners and specialized oncology nurses will become even more crucial in the near future in order to be able to deal with the increasing workload. At the moment, studies are being carried out to investigate the possibility of offering tailor-made follow-up programs to patients. The main goal is to improve the efficiency and quality of follow-up after curative therapy for cancer; in addition, this should reduce the workload of the medical specialist (www.maastro.nl).

Endometrial adenocarcinoma

Long-term endometrial cancer survivors treated with surgery alone had a better QOL than women who underwent surgery and adjuvant radiotherapy, although no differences were found when they were compared with a norm population (**Chapter 6**). Adjuvant radiotherapy was independently and negatively associated with vitality and physical and social well-being.

Survivors of endometrial cancer visited their medical specialist more often compared to the age-matched sample of the general Dutch population (**Chapter 10**). Patients who were not married had contact with a medical specialist less often. Contact with a psychologist was related to having a university or college degree.

Implications for clinical practice:

Although optimization of survival and local control of cancer is the first priority, QOL after treatment is increasingly being recognized as an important aspect of patient care. When different treatment options result in similar survival or survival benefit is unclear, then QOL becomes even more important. Patients in this study were treated 5-10 years ago, when there were no national treatment guidelines with respect to the indication for adjuvant radiotherapy. After the PORTEC trial [2], the indication for radiotherapy was restricted to 'high-intermediate' risk patients (endometrial cancer stage I in the presence of at least two of the following three risk factors: 1) grade 3, 2) age 60 and over, and 3) deep (>50%) myometrial invasion), resulting in a reduction in referral for radiotherapy of endometrial cancer patients in South-eastern Netherlands [3]. The challenge is therefore to select high-risk patients, who would benefit the most from adjuvant therapy, taking into account disease-free and overall survival but also the QOL.

Changes in health care, such as less administrative work for the specialist and more efficiency, are probably necessary in order to cope adequately with the increasing demand on the system. Nurse practitioners and specialized oncology nurses will become even more crucial in the near future in order to be able to deal with the increasing workload. At the moment, studies are being carried out to investigate the possibility of offering tailor-made follow-up programs to patients. The main goal is to improve the efficiency and quality of follow-up after curative therapy for cancer; in addition, this should reduce the workload of the medical specialist (www.maastro.nl).

Hodgkin's lymphoma and Non-Hodgkin's lymphoma

The general health perceptions and vitality levels of non-Hodgkin's lymphoma survivors remained significantly lower than those of general population controls (**Chapter 7**). Patients diagnosed 10-15 years earlier reported better psychological and social well-being than patients diagnosed 5-9 years previously. In addition, patients who received chemotherapy reported significantly worse psychological and social well-being and QOL than patients who were not treated with chemotherapy. Furthermore, survivors faced practical problems with their work and finances.

Hodgkin's lymphoma patients diagnosed 5-9 years ago experienced lower general health, social functioning and mental health levels and felt less vital compared to an age-matched normative population (**Chapter 8**). In addition, patients diagnosed 10-15 years earlier reported lower general health but better physical functioning compared to the age-matched normative population. QOL was better in Hodgkin's lymphoma patients who were diagnosed 10-15 years ago compared to patients who were diagnosed 5-9 years ago. No differences in QOL were found between different treatment methods. Problems obtaining health care or life insurance were infrequent but present; problems obtaining a mortgage were reported more often.

Survivors of Hodgkin's lymphoma visited their general practitioner somewhat more often compared to the age- and sex-matched general Dutch population but this effect was not always statistically significant (**Chapter 10**). In addition, survivors of Hodgkin's and non-Hodgkin's lymphoma visited their medical specialist significantly more often. Patients had contact with a medical specialist less often if they were diagnosed between 10-15 years ago and if they were not married. Contact with a psychologist was related to having a university or college degree.

Implications for clinical practice: The majority of lymphoma survivors experienced a good QOL compared to population controls; however, they reported lower general health perceptions and were less vital. Therefore rehabilitation programs like the Dutch program 'Herstel en Balans' should be offered to lymphoma survivors on a regular basis. It is important to identify those persons in need of extra care.

In addition, a substantial minority of survivors face practical problems with their work and finances that deserve additional attention during the period of rehabilitation. The Dutch Cancer Society pays attention to these problems in one of their information brochures ("Verder leven met kanker"). Information on financial problems after cancer can help survivors in dealing with insurance companies and banks. Information on work-related problems can inform patients and their employers about the different aspects of reintegration, although this is also a responsibility of medical advisors.

Changes in health care, such as less administrative work for the specialist and more efficiency, are probably necessary in order to cope adequately with the increasing demand on the system. Nurse practitioners and specialized oncology nurses will become even more crucial in the near future in order to be able to deal with the increasing workload. At the moment, studies are being carried out to investigate the possibility of offering tailor-made follow-up programs to patients. The main goal is to improve the efficiency and quality of follow-up after curative therapy for cancer; in addition, this should reduce the workload of the medical specialist (www.maastro.nl).

Methodological reflections and implications for future research

Study design

A major strength of our studies, as compared to many other survivorship studies, concerned the population-based sampling frame. We selected *every* patient with a specific type of cancer who was diagnosed in the region of the Comprehensive Cancer Centre South during a specific period of time. Our results are therefore more easily generalized to the general population compared to results of studies that only include a selection of patients from a single and often specialized hospital, e.g. a clinic-based sampling frame.

Due to the cross-sectional design of our study, it is more difficult to draw conclusions about causal relationships. Because baseline differences between treatment groups cannot be excluded as part of the explanation of the differences in QOL between different treatments, our findings need to be verified in population-based longitudinal studies.

Since we excluded patients with proven or likely recurrences, metastasis or new primary tumours it is important to keep in mind that our results can only be generalized to survivors with the best prognosis, namely those who do not show any signs of disease progression. Furthermore it is important to realize that our results can only be generalized to long-term survivors, namely those who survived at least 5 years after diagnosis.

Recruitment strategies

Medical specialists involved in the treatment and follow-up of cancer patients in the region of the Eindhoven Cancer Registry (ECR) were asked to participate in our studies and almost all did. This high participation rate of medical specialists can mainly be explained by two factors. The first is the fact that the Comprehensive Cancer Centre South (CCCS) has active tumour working groups, which means that the participating specialists interact with our research department. Our research plans were presented and discussed in these tumour working groups where after specialists were invited to participate. The second factor that could explain the high participation of medical specialists is the fact that researchers from CCCS coordinated and facilitated the mailing of questionnaires at each hospital, thus reducing the efforts requested of the specialists considerably. This tangible support improved the participation of the specialists and subsequently improved the response rate.

The number of patients responding to our questionnaire was, without exception, high across all of our studies. This may be due to the way in which our questionnaires were sent. Patients received a questionnaire together with a letter to inform them about the study. That letter also asked them to participate in our study and was signed by the patients' own (former) specialist. Along with the questionnaire and the accompanying letter, the patients received a stamped return-envelope in which they could send the completed questionnaire to the CCCS. If patients did not return their questionnaire within two months, a reminder-letter with a new questionnaire was sent.

The geographical region in which our studies were performed lacks an academic hospital or university medical centre which implies that the patients are not asked very often to participate in a study, especially not after completion of treatment. This could also explain the high number of participating patients. Actually, they were relieved that after all of these years someone asked them the right questions and paid attention to their problems; therefore they were willing to cooperate.

Some of the patients we wanted to include in our study could not be included due to unknown addresses. This was mainly due to the long-term nature of this study. Some patients moved after their last annual control visit and their current addresses were therefore unknown. The addresses of patients that were unknown could probably be traced through the administration of general practitioners or the municipal authorities. This could increase the number of included patients significantly.

The majority of non-respondents in our study were of old age. These patients probably experienced some difficulties in completing a self-report questionnaire without assistance. Offering this group some assistance with completing the questionnaire could probably reduce the number of non-respondents. Giving information by telephone or completing the interview by telephone could increase the response of, especially older, patients. Furthermore, patients could be offered house-visits by a research assistant who would help them to fill out the questionnaire.

Measurement approaches

One of the major goals of our studies was to measure QOL among cancer survivors. There is however no consensus over a definition of QOL. It is a broad-ranging concept incorporating physical, psychological, social, and spiritual well-being. According to the World Health Organization (WHO), QOL is a patient's perception of his or her position in life within the context of the culture and value systems in which he or she lives and in relation to his or her goals, expectations, standards, and concerns [4].

An enormous number of different QOL questionnaires exist which can be divided into health related quality of life (HRQL) questionnaires and QOL questionnaires. Most questionnaires are, strictly speaking, HRQL questionnaires. These questionnaires measure the *presence* or *frequency* of behaviors and feelings. In contrast, QOL questionnaires measure the patients' own *perception* of these behaviors and feelings. For example, imagine a fatigued patient who underwent surgery and chemotherapy for breast cancer. On a HRQL questionnaire this patient can fill in that she *feels* fatigued and she can rate *how often* she experiences fatigue. A QOL questionnaire will however ask her how she *perceives* this tiredness. A young breast cancer patient with a job and a busy family life will probably perceive fatigue differently than an older retired woman with no children living at home.

In our studies, we used the QOL-CS because this questionnaire was specifically developed to measure QOL in long-term cancer survivors; we applied the SF-36 questionnaire to measure HRQL. The SF-36 was also used because of the availability of a gender- and age-matched normative sample drawn from a large, random, nationwide normative sample of adults (n=1742) taken from the general Dutch population. This made it possible to compare the HRQL of cancer survivors with that of the general population. The QOL-CS and SF-36 measured different aspects of QOL. This proved to be very useful. Effects that were found with one questionnaire were not always found with the other and this was mainly due to the difference in focus.

In order to use the QOL-CS, we developed and validated a Dutch version of this instrument in a group of prostate cancer survivors. It appeared that QOL was adequately measured by the physical, psychological and social well-being subscales of the QOL-CS and less so by the subscale spiritual well-being. Due to the general nature of its questions, we believe that the use of this questionnaire is not only appropriate for prostate cancer survivors but also for survivors with other types of cancer.

In our study of breast cancer survivors, we also assessed whether patients experienced posttraumatic growth from their experience with cancer. The Perceived Disease Impact Scale was used to measure whether patients found some form of benefit from their cancer experience. Both measures were thus able to measure *positive* effects of cancer and this also proved to be very useful. A majority of the breast cancer survivors indeed experienced posttraumatic growth and benefit finding after cancer. Taken together, we feel strongly that the often reported increased QOL and life satisfaction of cancer patients should not be considered merely as an artifact (e.g. due to response-shift), because there is sufficient reason to hypothesize that such positive changes are real and related to posttraumatic growth and benefit finding.

We selected questionnaires on the basis of the literature and tested the usefulness of the resulting set of questionnaires by sending them to a small subgroup of patients. On the basis of the reactions of these patients, we composed our final set of questionnaires. However, the reactions of these patients were rather limited, they did not give us much information to help improve our set of questionnaires. After analyzing our final research data, we noticed that our questionnaires included an insufficient number of questions on radiotherapy-related complaints after treatment for endometrial cancer. We believe that the use of focus groups could resolve this problem due to the interaction between patients and researchers.

Implications for future research at the CCCS

The cross-sectional studies in this thesis gave us the following valuable information on the physical and psychological well-being among long-term cancer survivors; QOL in general is good among long-term survivors. However, a number of patients experience problems related to having had cancer; like sexual problems, arm problems, fatigue and financial problems. However, to be able to draw conclusions about causal relationships, one would like to know baseline characteristics of patients. Therefore, studies that are currently being planned in new populations of cancer survivors in the CCCS region will probably also include longitudinal cohorts to be followed in the future.

The studies described in this thesis only included disease-free survivors as far as certain. Patients with apparent or presumed disease progression were excluded due to a number of reasons. One of them was the lack of sufficient information in the cancer registry on tumor and treatment in patients with disease progression. However, by not including patients with disease progression, important information on the QOL of these patients is lost. To solve this issue, registrars of the cancer registry are now trying to collect additional information about date, type (recurrence, metastases) and treatment of progression, in order to report on the QOL of these patients. Hopefully we will be able to report on the QOL among patients with disease progression in the near future.

The literature on QOL among long-term cancer survivors is rapidly increasing. This has resulted in new initiatives to design specific questionnaires focused on QOL issues of *long-term* cancer survivors. Because QOL was adequately measured by the physical, psychological and social well-being subscales of the QOL-CS but less so by the subscale spiritual well-being we are considering the use of a different questionnaire in our future studies. Recently, the Impact of Cancer (IOC) questionnaire was developed and evaluated among long-term survivors of breast cancer, prostate cancer, colorectal cancer and lymphoma [5] by Zebrack and Ganz et al. Future work is necessary to confirm the factor structure, responsiveness and further validation of the instrument. In addition, careful translation into Dutch and validation of this questionnaire will show if it is appropriate for use in Dutch long-term cancer survivors.

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Samenvatting (Summary in Dutch)

Stijgende prevalentie van kanker

Door de steeds vroegere opsporing van kanker en de verbeterde behandeling is het aantal personen dat kanker overleeft de afgelopen jaren sterk toegenomen. Verbetering van de overleving van kankerpatiënten is zeer belangrijk in de kankerbestrijding, maar het uiteindelijke succes van de behandeling is mede afhankelijk van het al of niet optreden van nadelige lange termijn effecten, met andere woorden van de kwaliteit van leven van de (ex-)kankerpatiënt. Gezondheidsaantastende lange termijn effecten, en daardoor een eventuele verminderde kwaliteit van leven, zullen naar verwachting leiden tot een toename in allerlei zorggebruik. Daarom is het van belang om de mogelijke negatieve lange termijn effecten van kanker, kwaliteit van leven, en het daarbij behorend zorggebruik te onderzoeken. Dit soort onderzoek kan belangrijke informatie opleveren over mogelijke bijwerkingen van vroegere behandelingen waardoor late complicaties eventueel kunnen worden verminderd. Bovendien kan dit soort onderzoek belangrijke informatie opleveren over medische en psychosociale behoeften van patiënten en de voorspellers hiervan.

Studies naar kwaliteit van leven bij overlevenden van kanker

Sinds de afgelopen twee decennia is er meer aandacht voor kwaliteit van leven (KvL) van kankerpatiënten. KvL is de perceptie van een individu op zijn of haar positie in het leven, binnen de context van de cultuur waarin hij of zij leeft en tegen de achtergrond van zijn of haar doelen en verwachtingen.

Een toenemend aantal studies beschrijft de impact van de diagnose kanker en de behandeling daarvan op de KvL tijdens en kort na de behandeling. Er wordt echter minder aandacht besteed aan KvL van lange termijn overlevenden. Volgens de definitie van de 'American Cancer Society' is een lange termijn overlevende iemand die 5 jaar na diagnose nog in leven is.

Het is aannemelijk dat bijwerkingen van kanker en de behandeling daarvan op korte termijn verschillend zijn van de bijwerkingen op lange termijn al of niet samenhangend met het verouderingsproces. Sommige bijwerkingen zullen in de loop van de tijd verdwijnen, anderen zullen wellicht pas later ontstaan. Met dit in gedachten zijn we ons onderzoek naar lange termijn effecten van kanker, kwaliteit van leven en zorggebruik gestart onder een grote groep lange termijn overlevenden van kanker. Het was ons doel om KvL, eventuele negatieve bijwerkingen van kanker en de behandeling, en het specifieke zorggebruik in kaart te brengen bij kankerpatiënten die hun ziekte langdurig overleefden en te vergelijken met de algemene Nederlandse populatie.

Borstkanker

De meeste studies over KvL van lange termijn overlevenden van kanker richten zich op borstkanker patiënten. In een systematische review (**Hoofdstuk 1**) werden gepubliceerde artikelen meegenomen als ze KvL beschreven van vrouwen die tenminste 5 jaar eerder werden gediagnosticeerd met borstkanker. Tien artikelen voldeden aan onze selectiecriteria. De methodologische kwaliteit van die studies, uitgevoerd tussen 1997 en 2004, was hoog. De meeste studies rapporteerden dat borstkankerpatiënten een goede KvL hadden. Echter, bijna alle studies rapporteerden ook dat patiënten bepaalde problemen ervaren na kanker (b.v. een dikke en pijnlijke arm en seksuele problemen). De huidige lichamelijke conditie, de hoeveelheid sociale steun en het huidige inkomen bleken sterke positieve voorspellers van KvL te zijn terwijl het gebruik van adjuvante chemotherapie juist een negatieve voorspeller was.

Bovenstaande studie liet zien dat de meerderheid van de borstkankerpatiënten een goede KvL had. In **hoofdstuk 2** evalueerden we daarom posttraumatische groei, welzijn en het ervaren van positieve effecten als gevolg van kanker. Verder keken we naar de interactie van deze drie variabelen. We deden dit met behulp van een gerandomiseerde steekproef van borstkankerpatiënten die 10 jaar geleden werden gediagnosticeerd en die nu ziektevrij waren. Verwacht werd dat vrouwen posttraumatische groei zouden hebben doorgemaakt en dat ze niet alleen negatieven maar ook positieve effecten als gevolg van kanker zouden hebben ervaren. Uit de kankerregistratie van het Integraal Kankercentrum Zuid (IKZ) werden alle vrouwen geselecteerd die in 1993 werden gediagnosticeerd met borstkanker in zes ziekenhuizen uit de regio van het IKZ. Zelfgerapporteerde gezondheidsstatus en psychisch welzijn waren vergelijkbaar met vrouwen met dezelfde leeftijd uit de algemene populatie. De tevredenheid met het leven was hoger onder borstkankeroverlevenden. Verder vonden we posttraumatische groei in de volgende domeinen: 'relaties met anderen', 'persoonlijke sterkte' en 'waardering van het leven'. Het aantal patiënten dat positieve effecten van hun ziekte rapporteerde was hoog (79%, n=145). Zowel vrouwen die positieve effecten van hun ziekte rapporteerden als vrouwen die tevreden waren met hun leven rapporteerden meer posttraumatische groei in vergelijking met vrouwen die dat niet ervaren. Radiotherapie vertoonde een negatieve samenhang met posttraumatische groei. Vrouwen met een hoger ziektestadium bij diagnose ervaren minder positieve effecten van hun ziekte dan vrouwen met een lager ziektestadium bij diagnose. Het is van belang te beseffen dat niet iedere patiënt positieve effecten van kanker ervaart en dat positieve effecten ook zeker niet gedurende het hele ziektetraject optreden.

Prostaatkanker

Een vragenlijst die uitermate geschikt is om KvL in lange termijn overlevenden van kanker te meten is de 'Quality of Life -Cancer Survivor (QOL-CS) questionnaire'. Deze vragenlijst was alleen beschikbaar in het Engels en Spaans. Een Nederlandse versie van de QOL-CS werd daarom ontwikkeld en gevalideerd (**Hoofdstuk 3**). Met behulp van de kankerregistratie van het IKZ werden alle patiënten geselecteerd die tussen 1994 en 1998 (5-10 jaar na diagnose) prostaatkanker kregen in de regio van het IKZ, dit waren 784 patiënten. Om de test-hertest betrouwbaarheid van de vragenlijst te testen kregen 109 deelnemers van deze totale groep na twee maanden een tweede vragenlijst, 103 (94%) patiënten vulden deze vragenlijst in. In een groep lange termijn overlevenden van prostaatkanker werd de KvL adequaat gemeten door de subschalen lichamelijk-, psychologisch- en sociaal welzijn. De subschaal spiritueel welzijn vertoonde echter minder interne consistentie, hoewel de test-hertest betrouwbaarheid goed te noemen was. Dit kan veroorzaakt worden door culturele en sekse verschillen omdat de lijst oorspronkelijk ontwikkeld is om de KvL te meten van Amerikaanse ovariumkanker overlevenden.

Met behulp van bovenstaande vragenlijst en de SF-36 vragenlijst hebben we KvL gemeten bij Nederlandse lange termijn overlevenden van prostaat kanker en vergeleken met een normgroep uit de algemene Nederlandse populatie met dezelfde leeftijd (**Hoofdstuk 4**). Verwacht werd dat de KvL van deze twee groepen ongeveer gelijk zou zijn. De kankerregistratie van het IKZ werd wederom gebruikt om alle patiënten te selecteren die tussen 1994 en 1998 prostaatkanker kregen in de regio van het IKZ. Negenhonderd vierenzestig patiënten ontvingen onze vragenlijst; 780 (81%) personen reageerden. Patiënten die prostaatkanker langdurig overleefden rapporteerden een vergelijkbare KvL in vergelijking tot mannen uit de normpopulatie maar rapporteerden een slechtere algemene gezondheid. Patiënten die geopereerd waren functioneerden lichamelijk het beste, gevolgd door patiënten met een afwachtend beleid en patiënten die waren behandeld met radiotherapie. Patiënten die waren behandeld met hormoontherapie functioneerden lichamelijk het slechtst. Omdat deze verschillen tussen patiënten hoogst waarschijnlijk gedeeltelijk al voor aanvang van de behandeling bestonden moeten deze bevindingen worden geverifieerd in longitudinale studies voordat men definitieve conclusies kan trekken.

In dezelfde groep patiënten onderzochten we ook de lange termijn effecten van kanker en de behandeling daarvan op darm-, plas- en seksuele klachten en we vergeleken de frequentie van deze klachten met die in een referentiegroep (**Hoofdstuk 5**). Tussen januari 2003 en mei 2004 ontving de referentiegroep van mannen uit de algemene Nederlandse populatie van dezelfde leeftijd zonder kanker dezelfde vragenlijsten; 3892 (81%) van de mannen reageerden hierop. Prostaatkankeroverlevenden hebben vaker problemen met het krijgen van erecties (67% t.o.v. 18%), zijn vaker incontinent (33% t.o.v. 4 %) en hebben meer darmproblemen (9% t.o.v. 2%) dan mannen met gelijke leeftijd zonder kanker. Na een radicale prostatectomie kwamen plasproblemen het vaakste voor en darmproblemen kwamen het meest frequent voor na radiotherapie. Omdat deze problemen jaren na de behandeling nog steeds vóórkomen en omdat de patiënt blijkens hierop vaak niet voorbereid is dienen urologen patiënten adequate informatie te geven over dit onderwerp voor aanvang van de behandeling. Indien patiënten een keuzemogelijkheid bij de behandeling hebben kunnen ze deze factoren mee laten wegen bij het maken van deze keuze. Indien er geen keuzemogelijkheid is kan een patiënt zich aan de hand van deze informatie voorbereiden op eventuele toekomstige negatieve neveneffecten. Ook na de behandeling moet er voldoende aandacht zijn voor deze neveneffecten.

Baarmoederkanker

In **hoofdstuk 6** werd KvL van lange termijn overlevenden van baarmoederkanker vergeleken met een vrouwelijke normpopulatie. Met behulp van de kankerregistratie van het IKZ werden alle vrouwen geselecteerd die tussen 1994 en 1998 werden gediagnosticeerd met baarmoederkanker in de regio van het IKZ. In totaal ontvingen 462 patiënten een vragenlijst; 305 (75%) patiënten vulden de vragenlijst in. Voor deze studie werden alleen de data van patiënten geanalyseerd die waren gediagnosticeerd met stadium I of II en die chirurgisch behandeld waren of chirurgisch in combinatie met adjuvante radiotherapie (N=264). De vrouwen die adjuvante radiotherapie hadden gehad rapporteerden lagere scores op alle subschalen van onze KvL vragenlijsten, hoewel dit verschil niet altijd statistisch significant was. Adjuvante radiotherapie vertoonde een onafhankelijk en negatief verband met vitaliteit en lichamelijk en sociaal welzijn. Er werden geen significante verschillen gevonden tussen beide behandelgroepen in vergelijking tot de normpopulatie. Deze resultaten geven gynaecologen en patiënten extra informatie voor het maken van een goed geïnformeerde behandelkeuze over adjuvante radiotherapie of om te anticiperen op mogelijke lange termijn effecten van deze tumor en de behandeling daarvan.

Lymfeklierkanker

Twee studies betroffen patiënten met lymfeklierkanker. De veronderstelling was dat de KvL van lymfeklierkanker overlevenden vergelijkbaar was met dat van de normpopulatie. Verder werd verwacht dat lymfeklierkanker patiënten problemen zouden hebben op financieel vlak. Het doel van de deze studies was het documenteren van lange termijn effecten van lymfeklierkanker en de behandeling daarvan op KvL en maatschappelijke problematiek (**Hoofdstuk 7**). Met behulp van de kankerregistratie werden alle patiënten geselecteerd die tussen 1989 en 1998 (5-15 jaar na diagnose) gediagnosticeerd waren met het non-Hodgkin lymfoom in de regio van het IKZ. In totaal ontvingen 360 patiënten een vragenlijst via hun behandelend specialist; 294 (82%) patiënten namen deel. Patiënten die behandeld waren met chemotherapie rapporteerden een significant lagere KvL, vooral een lager psychisch en sociaal welzijn, in vergelijking tot patiënten die niet waren behandeld met chemotherapie. Radiotherapie en een afwachtend beleid hadden geen significante invloed op KvL. Patiënten die tussen de 10 en 15 jaar geleden waren gediagnosticeerd rapporteerden een beter psychisch en sociaal welzijn dan wanneer ze 5 tot 9 jaar geleden gediagnosticeerd waren. Er was een significant negatief verband tussen co-morbiditeit en lichamelijk welzijn. In vergelijking met een normpopulatie met dezelfde leeftijd rapporteerden de non-Hodgkin lymfoom overlevenden een slechtere algemene gezondheid, minder vitaliteit en meer lichamelijke pijn. Praktische problemen vanwege kanker werden gerapporteerd in verband met werk (41%), het afsluiten van een ziektekostenverzekering (6%), levensverzekering (15%) en hypotheek (22%). Vijf tot 15 jaar na diagnose bleek de algemene gezondheidsperceptie en het niveau van vitaliteit nog steeds lager dan dat van de algemene populatie. Bovendien hebben patiënten met het non-Hodgkin lymfoom problemen met werk en financiën waaraan aandacht besteed zou moeten worden tijdens de periode van herstel.

In een studie onder overlevenden van het Hodgkin lymfoom (**Hoofdstuk 8**) werden alle patiënten geselecteerd die tussen 1989 en 1998 gediagnosticeerd waren in de regio van het IKZ. In totaal ontvingen 164 patiënten een vragenlijst; 132 patiënten (80%) vulden deze in. De KvL van patiënten die tussen de 10 en 15 jaar geleden werden gediagnosticeerd was beter dan die van patiënten die tussen de 5 en 9 jaar geleden de ziekte kregen. Patiënten die tussen de 5 en 9 jaar geleden werden gediagnosticeerd rapporteerden een lagere algemene gezondheid, sociaal functioneren en mentale gezondheid en voelden zich minder vitaal in vergelijking tot de normgroep uit de algemene populatie. Patiënten die tussen de 10 en 15 jaar geleden waren gediagnosticeerd hadden een slechtere algemene gezondheid maar functioneerden fysiek beter vergeleken met de normgroep. Er werden geen verschillen gevonden in KvL tussen de verschillende behandelmethodes. Veranderingen in de werksituatie (zoals pensioen, meer of minder werken en arbeidsongeschiktheid) werden door 31% van de patiënten gerapporteerd. Problemen met het afsluiten van zorgverzekeringen en levensverzekeringen kwamen niet vaak voor (respectievelijk 11 en 13%); problemen met het afsluiten van een hypotheek werden vaker gemeld (33%). Wanneer deze percentages worden berekend bij de mensen die daadwerkelijk hebben geprobeerd om een verzekering of hypotheek af te sluiten zijn de problemen groter (respectievelijk 25, 38 en 63%). De KvL van patiënten die het Hodgkin lymfoom langdurig overleefden is enigszins lager in vergelijking tot de normgroep uit de algemene populatie. Bovendien bleken ex-patiënten nog specifieke (financiële) problemen te hebben in de jaren na diagnose.

Zorggebruik

Van alle kankerpatiënten uit bovenstaande studies werd het zorggebruik gemeten. Verwacht werd dat dit zorggebruik, vanwege de nadelige lange termijn effecten van kanker en de behandeling daarvan, hoger zou zijn dan het zorggebruik van de algemene Nederlandse populatie. Dit resulteerde in twee artikelen. In **hoofdstuk 9** werd het, zelfgerapporteerde zorggebruik van borstkankerpatiënten, die 10 jaar geleden werden gediagnosticeerd, vergeleken met het zorggebruik van een normpopulatie. Bovendien werd er gezocht naar voorspellers van zorggebruik. Hiertoe werden de gegevens van de onderzoekspopulatie zoals beschreven in hoofdstuk 2 gebruikt. Het aantal vrouwen (79%) dat in de afgelopen 12 maanden een specialist bezocht was significant hoger in vergelijking met de normgroep (53%). Jonge borstkankerpatiënten (45-54 jaar op het moment van het invullen van de vragenlijst) bezochten bovendien vaker een fysiotherapeut (56%) of alternatief genezer (26%) dan de controle groep (respectievelijk 29 en 13%). Spontaan gerapporteerde problemen, zoals vermoeidheid en arm klachten als gevolg van kanker, en co-morbiditeit lieten een sterk verband zien met zorggebruik. We kunnen concluderen dat lange termijn overlevenden van borstkanker vaker een specialist, fysiotherapeut en alternatief genezer bezochten dan de normgroep. Verder maken jonge borstkankerpatiënten het meest frequent gebruik van zorg, samenhangend met vermoeidheid en armklachten.

Gebruik makend van de gegevens van de populatie kankeroverlevenden uit de hoofdstukken 4-8 wordt het zelfgerapporteerde zorggebruik van lange termijn overlevenden van kanker vergeleken met een normgroep met dezelfde leeftijd en wordt er ook gekeken naar voorspellers van zorggebruik **(hoofdstuk 10)**. Ex-kankerpatiënten bezochten hun medisch specialist significant vaker dan de algemene populatie. De huisarts werd ook vaker bezocht maar dit verschil was alleen significant voor patiënten met het Hodgkin lymfoom. Patiënten die waren gediagnosticeerd met baarmoederkanker hadden het minst vaak contact met hun specialist. Ook patiënten die tussen de 10 en 15 jaar geleden waren gediagnosticeerd en alleenstaanden bezochten de specialist minder vaak. Mensen met een hoger opleidingsniveau hadden vaker contact met een psycholoog. Op basis van dit onderzoek mogen we concluderen dat patiënten, 5-15 jaar na diagnose, meer gebruik maken van de zorg dan de algemene Nederlandse populatie. Veranderingen in de gezondheidszorg, zoals minder administratieve taken voor de specialist en meer efficiëntie zijn waarschijnlijk nodig om adequaat om te kunnen gaan met de stijgende werkdruk in de zorg. Nurse practitioners en oncologie verpleegkundigen zullen in de nabije toekomst nog belangrijker worden om met deze stijgende werkdruk om te kunnen gaan.

Discussie

In de algemene discussie (**General discussion**) van dit proefschrift worden de belangrijkste bevindingen van het onderzoek samengevat per tumor. Verder worden de mogelijke implicaties hiervan voor de klinische praktijk besproken. Als laatste worden ook nog algemene methodologische overwegingen besproken wat betreft studie opzet, inclusie en meetmethoden, gecombineerd met aanbevelingen voor toekomstig onderzoek.

Het doel van dit project was het meten van KvL, bijwerkingen van kanker en behandeling en zorggebruik bij kankerpatiënten die hun ziekte langdurig overleefden en om dat te vergelijken met de algemene Nederlandse populatie, voor zover mogelijk. De KvL van de meeste mensen die kanker langdurig overleefden (en bij wie geen ziekteprogressie was vastgesteld) bleek goed te zijn. Globaal gezien was de KvL vergelijkbaar met de algemene Nederlandse populatie. Veel ex-patiënten rapporteren echter nog lichamelijke klachten gerelateerd aan de diagnose en behandeling van kanker. De belangrijkste aanbevelingen uit dit proefschrift luiden als volgt: rekening houden met KvL bij het maken van een behandelkeuze, patiënten beter informeren over de mogelijke bijwerkingen van de behandeling, na afloop van de behandeling de bijwerkingen (zoals seksuele problemen) bespreekbaar maken en doorverwijzing naar het revalidatieprogramma 'Herstel en Balans' stimuleren. Verder moet er voor worden gezorgd dat mannen die zijn behandeld voor prostaatkanker medicatie voor het behandelen van hun erectieproblemen vergoed krijgen en tot slot moeten er veranderingen in de gezondheidszorg worden aangebracht (zoals minder administratieve taken voor de specialist en meer efficiëntie) zodat de werkdruk onder specialisten niet nog verder stijgt. Conclusie: onze studies dragen vermoedelijk bij aan een betere kwaliteit van zorg door hulpverleners aan patiënten en ex-patiënten.

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Acknowledgement

Many people have contributed in many ways to the realization of this thesis. I would like to thank them all for their help and friendship.

Mijn speciale dank gaat uit naar mijn promotores Ad Vingerhoets en Jan Willem Coebergh en mijn co-promotor Lonneke van de Poll-Franse.

Ad, jij was het die me vroeg of promoveren niet 'iets voor mij zou zijn' en jij was ook degene die me in contact bracht met het IKZ. Zonder jou zou dit proefschrift er dan ook niet zijn geweest en zou ik nu waarschijnlijk geen onderzoek doen. Bedankt hiervoor en ook bedankt voor het feit dat je me hielp om niet al te veel 'epidemiologisch geïndoctrineerd' te raken. De samenwerking was prettig en je ideeën inspirerend.

Jan Willem, je weet het misschien niet maar in de wandelgangen van het IKZ word jij wel eens de 'trendwatcher' genoemd. Ook met het onderwerp van dit proefschrift had je het weer bij het juiste einde, het zou een 'hot-item' gaan worden. Toen we met dit onderzoek begonnen was er vrijwel niets bekend over de kwaliteit van leven van mensen die hun kanker langdurig overleefden. Sinds de start van ons onderzoek nemen de publicaties op 'pubmed' echter in een sneltreinvaart toe. We waren er op het juiste moment bij en mede daardoor is het onderzoek een succes geworden. Bedankt voor je goede ideeën.

Lonneke, bedankt voor je enthousiasme, je goede ideeën en de vele adviezen, je gezelligheid, je indrukwekkende kennis van de statistiek en niet te vergeten je handigheid met SAS. Eigenlijk zou jouw naam ook op de voorkant van dit boekje moeten staan! Bedankt voor de fijne samenwerking!

Corina en Annelies, ik ben blij dat jullie achter me staan op vrijdag 2 maart. Ik vind het een hele eer dat jullie mijn paranimfen willen zijn. Bedankt voor jullie vriendschap en gezelligheid!

Mijn collega's van het IKZ, en in het bijzonder de afdeling onderzoek, wil ik bedanken voor de prettige werksfeer, de gezellige koffiepauzes, en jullie kennis en adviezen over zowel het doen van onderzoek als over de klinische praktijk. Het is fijn om jullie als collega's te hebben!

Mijn collega's van medische psychologie op de UvT wil ik natuurlijk ook bedanken. De lunchpauzes (stipt om 12 uur) waren altijd een prettige onderbreking van de dag. Al was ik dan officieel niet in dienst van de UvT; ik heb me in jullie midden altijd welkom gevoeld!

Mijn vrienden wil ik natuurlijk ook bedanken. Het samen eten op zaterdagavond, de zwemavonden op donderdag, de bioscoopavondjes in Antwerpen (doen we te weinig!) en natuurlijk ook de gezamenlijke vakanties waren een welkome afwisseling op het schrijven van dit proefschrift. Jullie zijn

zelf niet bezig met promoveren en keken daarom altijd weer lekker nuchter en met een frisse blik tegen de zaken aan, heerlijk!

Lieve pap en mam, bedankt voor alles wat jullie voor mij hebben gedaan. Jullie hebben altijd in me geloofd, nooit een seconde aan mijn capaciteiten getwijfeld (toch?) en me gestimuleerd om voor het hoogst haalbare te gaan. Bedankt voor alle kansen die jullie me hebben gegeven. Mam, ik moet je toch (alweer) gelijk geven. Een goede moeder is inderdaad het halve werk. Toch wil ik hier nog aan toevoegen dat het effect van een goede vader zeker niet onderschat mag worden!

Lieve Jeroen, het laatste plekje van mijn dankwoord is voor jou, omdat ik als geen ander van je hou. Bedankt voor je steun en je vertrouwen in de afgelopen 10 jaar! (En niet te vergeten; de heerlijke maaltijden en het schone huis dat ik iedere dag aantrof als ik thuis kwam van mijn werk!)

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Tilburg, December 2006

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