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Does use of alternative medicine predict survival from cancer?

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Abstract

This study examines the association between alternative medicines (AM) and cancer survival. A national multicentre study was carried out in Norway in December 1992 to assess the prevalence of AM use among cancer patients. One of the aims of this study was to assess the association between AM and long-time survival. In January 2001, survival data were obtained with a follow-up of 8 years for 515 cancer patients. A total of 112 (22%) assessable patients used AM. During the follow-up period, 350 patients died. Death rates were higher in AM users (79%) than in those who did not use AM (65%). In a Cox regression model adjusted for demographic, disease and treatment factors, the hazard ratio of death for any use of AM compared with no use was 1.30, (95% Confidence Interval (CI) 0.99, 1.70; $P=0.056$), suggesting that AM use may predict a shorter survival. Sensitivity analyses strengthened the negative association between AM use and survival. AM use had the most detrimental effect in patients with an ECOG (Eastern Cooperative Oncology Group) performance status (PS) of 0 (hazard ratio for use = 2.32, 95% CI, 1.44, 3.74, $P=0.001$), when compared with an ECOG PS of 1 or higher. The use of AM seems to predict a shorter survival from cancer. The effect appears predominantly in patients with a good PS.
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Keywords: Alternative medicine; Survival; Prognosis; Performance status

1. Introduction

It is not fully understood why cancer patients use alternative medicines (AM). The inability to cure all cancers, the patient's need for autonomy and active participation, and preferences for "natural" or "holistic" therapy have been suggested as contributing factors [1–4]. It may also be that patients turn to unproven approaches in an attempt to regain control over their health, and avoid helplessness and depression, when given a poor prognosis [5,6]. In addition, there are indications that individuals who seek AM therapies experience higher levels of anxiety than their counterparts [7–9]. Support for this was found in two recent prospective studies of patients with newly diagnosed early-stage breast cancer [9,10]. However, another recent study [11] among patients with a variety of cancer diagnoses did not verify an association between AM use and patients' perceived distress. These authors found that AM use appeared to be a coping strategy in response to patients' hopelessness and despair.

The relationship between patients' use of AM and survival has rarely been studied. A longitudinal study attempting to measure the pattern of AM use and its impact on survival in a heterogenous cancer patient cohort from Northern Norway was reported in 1998 [12]. No overall survival differences between the groups were found, although there was a tendency towards better survival among non-users at 4 months of follow-up. However, this difference could be explained by the more extensive disease found among the AM users.

The aim of the present study was to determine the use of AM in Norwegian cancer patients and to assess any association between AM use and long-time survival. Our hypothesis was that AM use **does** not have any effect on the survival of cancer patients.

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2. Patients and methods

2.1. Project and patients

The Norwegian Board of Health initiated the basic data collection. Data were obtained from all five regional cancer centres in Norway in December 1992. Cancer patients were asked to complete a questionnaire concerning demographic factors, quality of life and use of AM. The participating physicians at each centre reported the medical characteristics and intention of care for all participants. A questionnaire was developed at the University of Tromsø, Norway. It was designed by a consensus of experts and its feasibility was tested in a pilot study of outpatients in the Department of Oncology, University Hospital of Tromsø [13]. This questionnaire had also been applied in a longitudinal study of cancer patients in Tromsø, Norway in 1991 [12].

911 patients with various cancers were invited to take part in the study. Of these, 642 (70%) patients responded and were included in the study [13]. Totally bedridden (Eastern Cooperative Oncology Group (ECOG) 4) patients and those aged over 75 years were excluded due to their limited expected survival. A total of 515 patients comprised the present analyses.

The Regional Ethics Committee (Health region North Norway) approved the project. Permission to store personal information about the patients was granted by the Norwegian Data Inspectorate. Participants were informed that all data would be treated confidentially, and that refusal to participate in the study would not jeopardise their medical treatment.

2.2. Definitions and assessments of AM use

In the questionnaire presented to the patients, AM was defined as any treatment outside of mainstream therapy that had been used to treat their cancer. A multiple-choice list consisting of the best known and frequently used non-proven methods in Norway was presented. Patients also had the opportunity to add other types of alternative therapy in response to an open question.

The following alternative methods were described in the multiple choice questionnaire: Use of biological treatments, herbs, faith healing or healing by hand, homeopathy, reflexology (zone therapy), megadoses of vitamins, diet treatments, injection therapies such as iscador (a mistletoe preparation) and a Norwegian injection therapy called "Nitter therapy". Nitter therapy consists of vitamin B12, gammaglobulins, tranexamic acid, multivitamins and nutritional supplements.

Modalities such as relaxation, psychotherapy, participation in a self-help group or changes in lifestyle activities that were used to reduce distress and to improve the patient's subjective well being were not coded as AM.

In the 50-item questionnaire, two items assessing overall satisfaction with life and physical health had been adapted from a US survey [14] and were validated and had previously been used in large Norwegian studies [15,16]. These questions were: (1) When you think about your life at the moment, would you say that, by and large, you are satisfied with life or are you mostly dissatisfied? (2) At present, do you feel mostly strong and healthy, or tired and worn out? Each question had seven response categories ranging from positive ("very satisfied"/"strong and healthy = 1) to negative ("very dissatisfied"/"tired and worn out" = 7).

Data on the length of survival were obtained by 1 January 2001, from the Norwegian Statistical Registry. Data on the cause of death were available for patients who died before 1 January 1997.

2.3. Analysis of data

The association between AM use and survival was evaluated by using a Cox regression model which included use of AM, gender, age, educational level, ECOG status (0–3, as three dummy variables), disease stage (locoregional or metastatic), treatment type (palliative or curative), time since diagnosis (two dummy variables: less than 3 months before questionnaire completion; more than a year since diagnosis) and questions assessing overall satisfaction with life and physical health (scale of 1–7). Analyses were conducted on Stata 7 (College Station, Texas).

3. Results

Demographic and disease-related factors are described in Table 1, which also compares differences between users of AM and non-users. Use of AM was more common among patients with symptoms related to their cancer, those receiving only palliative treatment, patients with metastatic disease and among those diagnosed with cancer more than three months previously.

The distributions of diagnoses among patients in this study compared with the distribution of diagnoses in the total national cancer population are shown in Table 2. Breast, lung, brain, testicular cancer and malignant lymphomas were more prevalent in the study population than in the general population. Malignant melanomas, kidney and bladder cancers were less prevalent. This discrepancy is explained by the fact that the study population consist of patients referred to specialised cancer centres offering advanced radiotherapy and chemotherapy treatments, and the fact that incidence differs from prevalence due to large differences in survival time between the different cancers.

Patients were classified as users of spiritual methods if they used faith healing or healing by hand, regardless of

Table 1
Characteristics of users and non-users of AM

	Users of AM $n=112$	Non-users of AM $n=403$	Differences P value[a]	Missing values
	n (%)	n (%)		
Sex ($n=515$)				
Female	66 (58.9)	224 (55.6)	0.53	0
Male	46 (41.1)	179 (44.4)		
Age in years ($n=515$)				
15–29	6 (5.4)	25 (6.2)	0.77	0
30–44	26 (23.2)	76 (18.9)		
45–59	41 (36.6)	150 (37.2)		
60–74	39 (34.8)	152 (37.7)		
Education ($n=505$)				
Lower education	59 (54.1)	237 (59.8)	0.28	10
Higher education	50 (45.9)	159 (40.2)		
Stage of disease ($n=503$)				
Localized or regional	39 (34.8)	183 (46.8)	0.02	12
Distant metastases	73 (65.2)	208 (53.2)		
Functional status ($n=515$)				
ECOG = 0	41 (36.6)	201 (49.9)	0.05	0
ECOG = 1	38 (33.9)	109 (27.0)		
ECOG = 2	22 (19.6)	51 (12.7)		
ECOG = 3	11 (9.8)	42 (10.4)		
Type of treatment ($n=462$)				
Curative	32 (32.0)	180 (49.7)	0.002	53
Palliative	68 (68.0)	182 (50.3)		
Months since diagnosis ($n=509$)				
0–3	15 (13.6)	124 (31.1)	0.008	6
3–12	30 (27.3)	87 (21.8)		
>12	65 (59.1)	188 (47.1)		
In-patients'/out-patients' ($n=482$)				
In-patient	58 (56.3)	216 (57.0)	0.90	33
Out-patient	45 (43.7)	163 (43.0)		

AM, alternative medicine; ECOG, Eastern Cooperative Oncology Group.
[a] P value by χ^2.

whether they applied non-spiritual methods as well. While 39% of patients (44/112) used only non-spiritual methods, 61% (68/112) were classified as users of spiritual methods. 58 patients used only one method, whereas 54 patients used two or more methods. The various types of AM used by the 112 patients are shown in Table 3.

During the 8-year follow-up, 350 (68%) died and 165 were still alive. Seventy-nine percent (88/112) of the AM users died, compared with 65% (262/403) of those not reporting AM use (difference between the groups 14%; 95% Confidence Interval (CI): 5, 22%; $\chi^2 = 7.40$; $P = 0.007$).

Table 2
Diagnoses of cancer in the study group compared with national prevalence in Norway

Malignancy	Prevalence of cancer[a] n (%)	Included in the survival analysis n (%)
Breast cancer	20480 (18.5)	138 (26.8)
Malignant lymphomas	4161 (3.8)	59 (11.5)
Gastrointestinal cancer	15004 (13.6)	53 (10.3)
Gynaecological cancer	15885 (14.4)	38 (7.4)
Lung cancer	2326 (2.1)	34 (6.6)
Testicular cancer	2580 (2.3)	37 (7.2)
Brain tumour	1353 (1.2)	30 (5.8)
Prostatic cancer	9209 (8.3)	20 (3.9)
Urological cancer	9312 (8.4)	22 (4.2)
Malignant Melanoma	8511 (7.7)	15 (2.9)
Smaller diagnostic groups	21813 (19.7)	69 (13.4)
Sum	110634 (100)	515 (100)

[a] Prevalence of cancer referring to the number of patients with a diagnosis of cancer from 1953 to 1992 alive on 1 January 1992 were provided by the Cancer Registry of Norway.

Table 3
AM therapies used by Norwegian cancer patients

Therapy	Number of patients using only one AM therapy ($n=58$)	Number of patients using a combination of other AM therapies ($n=54$)
Healing by healer or religious healer	25	43
Homeopathy	5	17
Reflexology	0	7
Herbs/vitamins	6	18
Diets	5	18
Nitter therapy[a]	6	9
Iscador (Mistletoe)	8	16
Others[b]	3	13

[a] Vitamin B12, gamma-globulins, tranexamic acid, multivitamin and nutritional supplement.
[b] Mainly acupuncture or visualisation

Cox regression analyses were conducted for 421 patients for whom a complete data-set on all co-variates were available. All variables except education, ECOG status 2, sex and recent diagnosis were prognostic indicators for survival (Table 4). However, time since diagnosis was highly correlated with treatment type. As treatment type remained predictive when time since diagnosis was removed from the model, but not vice versa, we retained the former. The hazard ratio for any use of AM compared with no use was 1.30 (95% CI 0.99, 1.70; $P = 0.056$) suggesting that AM use predicts a poorer survival (Fig. 1). As AM use was more common in patients with metastatic disease and in those receiving palliative care (Table 1), both of which are associated with poor survival, we conducted sub-group analyses to confirm this result. For patients with metastatic disease ($n=293$); there were 255 deaths (hazard

Table 4
Prognostic factors for survival

$n=421$	Hazard ratio	95% Confidence intervals	P value
AM use	1.30	0.99, 1.70	0.056
Sex	1.04	0.82, 1.32	0.8
Age	1.02	1.01, 1.03	0.001
College	0.90	0.67, 1.22	0.5
ECOG 1	1.69	1.24, 2.30	0.001
ECOG 2	1.10	0.79, 1.53	0.6
ECOG 3	2.55	1.67, 3.89	<0.0005
Disseminated disease	1.91	1.40, 2.61	<0.0005
Palliative treatment	2.34	1.70, 3.22	<0.0005
Quality of life[a]	1.11	1.02, 1.22	0.015

[a] Higher score is worse quality life.

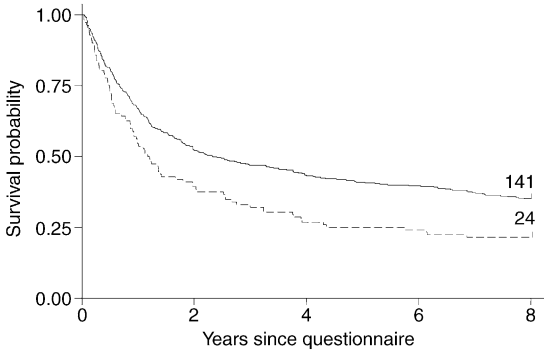

Fig. 1. Survival by use of alternative medicine (AM) (unadjusted analysis). Solid line: no AM use; dashed line: use of AM.

ratio 1.32; 95% CI 1.00, 1.75; $P=0.052$) or for palliative care patients ($n=303$); there were 257 deaths (hazard ratio 1.30; 95% CI 0.99, 1.71; $P=0.059$) thus as in the overall analysis both results showed a trend towards significance.

There was no difference between the type of AM: hazard ratios for non-religious and religious types of AM were both 1.26.

Sensitivity analyses were conducted. Removing non-predictive variables from the model slightly strengthened the association between AM and survival ($n=428$; hazard ratio 1.31; 95% CI 1.01, 1.71; $P=0.044$) as did analysing disease-specific survival at four years ($n=428$; 201 deaths; hazard ratio 1.48; 95% CI 1.09, 2.02; $P=0.012$). The variable for which there was the most missing data was treatment type. Removing this from the model also strengthened the association between AM and survival ($n=480$; hazard ratio 1.33; 95% CI 1.03, 1.72; $P=0.026$).

We then explored by Cox modelling whether the effect of AM on survival was mediated by stage, performance status or intent of treatment. With respect to stage and treatment intent, hazard ratios for AM use were similar for patients with locoregional and disseminated disease and for those receiving palliative and curative treatment. However, AM use appeared as a prognostic indicator only in patients with performance status 0. (Table 5, Figs. 2 and 3).

Table 5
The effect of performance status predicting survival among users and non-users of AM

ECOG	No AM use ratio for use	AM users	Hazard	95% CI	P value
0	201	41	2.32	1.44, 3.74	0.001
1	109	38	1.04	0.66, 1.62	0.876
2	51	22	1.22	0.69, 2.15	0.492
3	42	11	0.97	0.44, 2.16	0.943

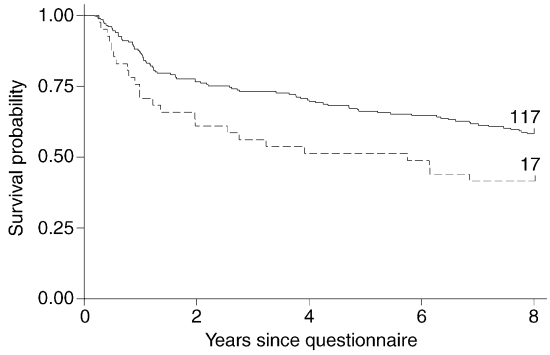

Fig. 2. Survival by use of AM for patients with Eastern Cooperative Oncology Group (ECOG) 0 (unadjusted analysis). Solid line: no AM use; dashed line: use of AM.

4. Discussion

Virtually all studies conducted on cancer patients or healthy individuals show that those who seek AM therapies tend to be female, better educated, of higher socio-economic status and younger than those who do not. These individuals also tend to be more health conscious and to utilise more mainstream medical services. Among cancer patients, most users appear to have non-curative malignant disease and are receiving palliative treatment. It is likely that one of the most important

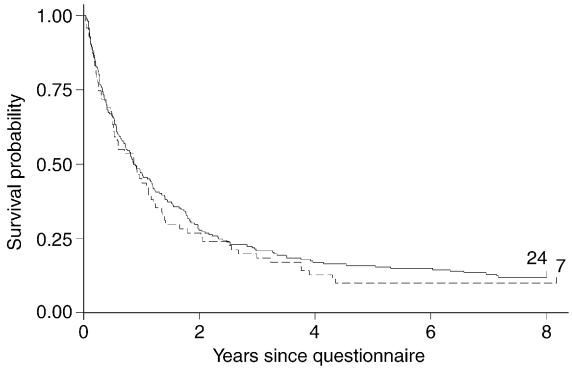

Fig. 3. Survival by use of AM for patients with ECOG 1 or above (unadjusted analysis). Solid line: no AM use; dashed line: use of AM.

reasons for patients with cancer to use unconventional methods is when their cancer cannot be cured by conventional therapy. However, until this study, no one has shown that some users of AM might have a poorer prognosis after adjustment for disease-related negative factors.

As each major Norwegian cancer centre participated in the study, the study population described in this paper is representative of the cancer patient population in Norway.

A possible bias in follow-up studies is the lack of anonymity. Patients may underreport their use of AM because they believe that hospital staff have negative attitudes towards AM. However, a comparative study has found that patients asked anonymously less often answered questions about their use of AM compared with patients in the non-anonymous arm [17]. Follow-up studies can also be flawed by patient drop-out rates, but in this study survival data were available for all patients. Reproducing expected correlations between known prognostic factors such as age, stage of disease, performance status and the different diagnostic groups and survival indicate our study population were representative and not a selective group.

As early as 1984 Cassileth and colleagues suggested that AM use might be a coping strategy to regain hope [18]. Later studies have confirmed this hypothesis [11]. In our previous paper describing this cancer population, AM users perceived that their physicians offered them less hope, compared with non-users of AM [6]. Other authors report higher mental distress levels among users of AM versus non-users. Burstein and colleagues [9] and Carlsson and colleagues [10] found that breast cancer patients who initiated use of AM after breast cancer surgery reported more depression, worse general health and a greater fear of recurrence than other patients. The finding that users of AM reported less hope and more mental distress supports the finding that users have a poorer quality of life. In a large study among patients with advanced malignancies from 12 institutions in 10 countries, Coates and colleagues [19] found that two questions from the European Organisation for Research and Treatment of Cancer Quality of Life C30 questionnaire (EORTC QLQ-30), namely overall physical condition and overall quality of life, independently predicted survival. The finding in our study, that two questions assessing overall satisfaction with life and physical health independently predict a poorer prognosis supports this earlier research. We also believe that perceived hope and feelings of mental distress are closely correlated with patients' satisfaction with life and physical health.

The reason that users of AM tended to have a shorter survival than non-users remains unknown. The association observed in this study cannot, establish a causative relationship between the use of AM and survival, as AM use may act merely as a marker for otherwise undetected prognostic factors. We do not believe that AM treatment directly influences survival because the methods reported by our patients seem rather innocuous. Our patients did not report use of any treatments like Laetrile with known adverse effects. That patients might have adopted other possible harmful treatments in the years following completion of the study is feasible, but not likely. Another possibility is that AM users may fail to use effective conventional treatments. However, in this study, all patients were referred to hospitals, but we cannot rule out the possibility that users of AM may have refused conventional methods of treatment in the later stages of their disease.

Shorter survival among AM users might be explained by patients' correct perception of the gravity of their disease. Indeed, patients may estimate the gravity of their situation more accurate than their physicians. This might explain why, after adjusting for disease-specific parameters, users of AM expressed less hope and more mental distress, and in the end might have a shorter survival than non-users. Studies imply that quality of life ratings add important subjective components to assessments aimed to clarify prognosis [19–21]. Patients' self-reports presumably capture aspects of disease severity that may not be apparent in observer-rated PS or stage of disease. An associated explanation might be that AM is often used for symptom control. Patients with worse symptoms during cancer treatment are more likely to use AM and more severe symptoms might suggest a more aggressive disease. It is a possibility that users of AM hide their symptoms from their physicians and that this is reflected in an assessment of a better ECOG status.

To our knowledge, we are the first to demonstrate a negative correlation between AM use and survival. If patients do perceive the gravity of their disease better than their physicians, and if the use of AM mirrors this fear, we have demonstrated a new reason why we should assess patients' use of AM. We hope that other groups will further evaluate the relationship between prognosis and the use of AM.

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