Changes in health and wellbeing in the years leading up to a cancer diagnosis: a prospective cohort study

Running title: Pre-diagnostic changes in health and wellbeing

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Abstract

Emerging evidence suggests cancer survivors suffer impairments in health and wellbeing that pre-date their diagnosis. This study prospectively examine changes from 4-6y pre-diagnosis to 0-2y post-diagnosis. Data were from 477 cancer survivors and 5,451 cancer-free comparisons participating in the English Longitudinal Study of Ageing. We examined group-by-time interactions for self-rated health, quality of life (QoL), depression, life satisfaction and impairments in mobility, activities of daily living (ADLs) and instrumental ADLs (IADLs). All health and wellbeing markers worsened over time in both groups. A greater decline in cancer survivors' self-rated health was evident as early as 2-4y pre-diagnosis ($p<.001$). Around diagnosis, there were greater declines in IADL impairment ($p<.001$), QoL ($p<.001$), and depression ($p<.001$) in cancer survivors than controls. Mobility and ADL impairments were consistently more prevalent among cancer survivors ($p<.001$) and life satisfaction was consistently lower ($p=.004$), but the rate of change over time did not differ significantly between groups. These results suggest there may be early signs of deterioration in perceived health that precede development of symptoms leading to cancer diagnosis by many years. Some of the impaired wellbeing in cancer patients may be long-standing, while other changes are more acute and may require targeted support following diagnosis.

Key words: cancer, depression, health, physical function, quality of life, wellbeing

Introduction

Recent advances in the detection and treatment of cancer have led to dramatic improvements in survival. Forty years ago, one in four people diagnosed with cancer in the UK would survive for at least 10 years; today, it is one in two (1). Recognising the growing importance of cancer survivorship, increasing research attention has turned to maximising the health and wellbeing of individuals living with and beyond a cancer diagnosis.

A number of studies have shown that cancer survivors suffer impairments in health, physical function, quality of life and psychological wellbeing relative to cancer-free controls (2–9). While limitations relating to data availability have seen most studies concentrate on differences in the post-diagnostic period, deficits in health and wellbeing have also been observed prior to diagnosis. In one of the first studies to include pre-diagnostic data in analyses of changes in health and wellbeing around the time of a cancer diagnosis, we observed differences in self-rated health, physical function, quality of life and psychological wellbeing between cancer cases and controls at all examined time points – including up to two years before the cancer was diagnosed (9). This finding begs the question: how far in advance of a cancer diagnosis do impairments in health and wellbeing become evident? While some pre-existing health deficits may derive from long-standing characteristics that also increase their risk of cancer – for example, limited physical function can result from obesity, which is also a risk factor for certain cancers (10) – others may be caused by undiagnosed cancer making the individual feel unwell. Understanding the trajectories of changes in health and wellbeing in the years leading up to a cancer diagnosis could identify potential 'red flags' for health care professionals that might aid in diagnosing cancer at an earlier stage.

No studies to date have examined changes in health and wellbeing in cancer survivors across multiple pre-diagnostic assessments. Using prospective data from a large, population-based cohort of English older adults, the present study aimed to examine changes in a range of health and wellbeing indices across biennial intervals from 4-6 years pre-cancer diagnosis to 0-2 years post-diagnosis, in cancer survivors and a cancer-free comparison group. We analysed markers of global health, physical function, quality of life and psychological wellbeing to explore how long before a diagnosis of cancer individuals begin to show impairments.

Method

Design and participants

Data were from the English Longitudinal Study of Ageing (ELSA), a longitudinal panel study of men and women aged ≥50 years living in England. The original ELSA sample (*n*=12,099) was recruited from households participating in the Health Survey for England in 1998, 1999 and 2001, and over the years the sample has been periodically refreshed to ensure the full age range is maintained. Comparisons of sociodemographic characteristics with the national census show that the sample is representative of the English population (11). Eight waves of ELSA data have been collected to date, starting in 2002 and every two years since. At the time of analysis, only the first seven waves of data were available. ELSA has received approval from various ethics committees, including the London Multi-Centre Research Ethics Committee (MREC/01/2/91), and full informed consent has been obtained from all participants.

For the current analyses, cancer cases were those who first reported a diagnosis of cancer in waves 4-7. A cancer diagnosis was defined as answering 'yes' to the question: '*Have you ever been told by a doctor or other health professional that you had cancer or any other kind of malignancy*'. Analyses focus on the wave in which the diagnosis was first reported plus the previous three waves – corresponding to data points at 0-2 years post-diagnosis and 0-2, 2-4 and 4-6 years pre-diagnosis. Individuals who reported a cancer diagnosis in waves 1-3, or joined ELSA in a refreshment cohort, were excluded from the analysis because of the absence of sufficient pre-diagnosis data.

The comparison group comprised participants who never reported a cancer diagnosis in any wave and for whom data were available on at least one health or wellbeing outcome for the waves selected to match the pre- and post-diagnosis points. The 'post-diagnosis' time point for controls was set at wave 7, with waves 6, 5, and 4 used as the three corresponding pre-diagnosis waves.

Measures

Self-rated health was assessed using a single item measure that asked participants to rate their general health on a five-point scale from poor (coded 1) to excellent (coded 5).

Mobility impairment was assessed by asking participants if they had any difficulty performing 10 everyday activities (e.g. walking 100 yards, getting up from a chair after sitting for long periods) because of a health problem (yes/no). Data were highly skewed, so we dichotomised responses to distinguish between those reporting any (score of 1 or more) vs. no mobility impairment (score of 0).

Activities of daily living (ADL) impairment was assessed with six questions that asked participants whether a health or memory problem caused them difficulty with the following everyday activities: dressing, walking across a room, bathing or showering, eating, getting in or out of bed, and toileting (yes/no) (12). Because scores were skewed, with the majority of participants reporting no impairment with any of these activities, we dichotomised responses with a score of 1 or more identifying participants with any ADL impairment.

We also assessed impairment with instrumental activities of daily living (IADLs). Whereas ADLs are tasks involved in caring for and moving the body, IADLs are activities that people do once they are up, dressed and put together, and support an independent lifestyle. IADL impairment was assessed by asking whether participants had any difficulty performing seven activities because of a health or memory problem: using a map to figure out how to get around in a strange place, preparing a hot meal, shopping for groceries, making telephone calls, taking medications, doing work around the house or garden, and financial management (yes/no) (13). Scores were dichotomised to distinguish between participants reporting any IADL impairment (score of 1 or more) and those with no IADL impairment (score of 0).

Quality of life was assessed using the CASP-19, a validated scale designed to measure quality of life in older people (14). Items cover four domains: control, autonomy, self-realization and pleasure. Respondents are asked how often each statement (e.g. '*My health stops me from doing things I want to do'*) applies to them on a four-point scale from 0 (often) to 3 (never). Positively worded items were reverse scored and all items summed, with higher scores indicating higher quality of life (possible range: 0-57).

Depressive symptomology was assessed with the eight-item Center for Epidemiologic Studies Depression (CES-D) scale (15), which asks about feelings over the last week (e.g. '*Over the last week have you felt sad*'), with binary response options (yes=1, no=0). Positive items were reverse scored and items summed to create a score ranging from 0-8. Because scores were highly skewed, we used a score of four or higher (an established threshold) to indicate the presence of depressive symptoms (16).

Life satisfaction was assessed using the Satisfaction with Life Scale (SWLS) (17), which asks respondents to indicate their agreement with five statements (e.g. '*The conditions of my life are excellent*'). Responses are given on a seven-point scale from 0 (strongly disagree) to 6 (strongly agree) and summed to produce a total scores between 0 and 30 (higher scores indicate greater satisfaction with life). The SWLS was not included in

ELSA's wave 1 questionnaire, so analyses for this outcome were limited to participants with new cancer diagnoses in waves 5 to 7.

Demographic information controlled for in the current analyses included age, sex, and non-pension wealth quintile (a sensitive indicator of socioeconomic status in this population group (18)), because of known associations between these variables and health and wellbeing outcomes.

Statistical analysis

We compared demographic characteristics of the cancer survivor and comparison groups using *t*-tests (continuous variables) and χ^2 analyses (categorical variables). For our primary analyses, we used repeated-measures analyses of variance (continuous outcomes) and generalised estimating equations (categorical outcomes) to test main effects of group (overall differences between the cancer survivor and comparison groups in self-rated health, mobility impairments, ADL impairments, IADL impairments, quality of life, depressive symptoms and life satisfaction independent of time), main effects of time (changes in these markers of health and wellbeing over time independent of group) and group-by-time interactions (differences in changes in health and wellbeing over time between the cancer survivor and comparison groups). All analyses were adjusted for age, sex, wealth and diagnosis wave.

Results

Sample characteristics

The analysed sample comprised 5,928 men and women, of whom 477 reported a new cancer diagnosis in waves 4-7 and 5,451 did not report a cancer diagnosis in any wave. Sample characteristics are summarised in **Table 1**. In line with data from cancer registries (19), the most prevalent cancers in our sample were breast cancer, prostate cancer, colorectal cancer, and melanoma and other skin cancers. The cancer diagnosis group was slightly older (71.4 [SD 8.0] vs. 69.8 [7.9] years; $p<.001$), and had a marginally more equal sex balance than the comparison group (50.5% vs. 55.0% female, $p=.061$), but the groups did not differ in wealth ($p=.389$).

Global health

Table 2 summarises unadjusted data on all markers of health and wellbeing in the cancer survivor and comparison groups at each time point.

Figure 1 shows the mean self-rated health score for each group at each time point. The cancer survivor group rated their health as significantly poorer than the comparison group overall (*p*<.001). Mean self-rated health declined over time, independent of group (*p*<.001). There was also a significant group-by-time interaction, with mean self-rated health falling more dramatically in the cancer survivor group than in the comparison group (*p*<.001). The groups' ratings of their own health were almost identical 4-6 years before diagnosis, but between each pair of assessment points thereafter (4-6 to 2-4 years pre-diagnosis, 2-4 to 0-2 years pre-diagnosis, and 0-2 years pre-diagnosis to 0-2 years post-diagnosis) the decline in self-rated health was substantially greater in the cancer survivor group (from 3.40 to 2.63 from 4-6 years pre-diagnosis to 0-2 years post-diagnosis) than in the comparison group (from 3.37 to 3.20 over the same time period).

Physical function

Figure 2A shows the proportion with mobility impairments in each group at each time point. Prevalence of mobility impairments was higher in the cancer survivor group than in the comparison group (*p*<.001) and increased over time (*p*<.001). From 2-4 years pre-diagnosis to 0-2 years post-diagnosis, rates of mobility impairment increased more in the cancer survivor group (from 56% to 64%) than in the comparison group (53% to 55%), but the group-by-time interaction did not reach statistical significance (*p*=.064).

Figure 2B shows the proportion with ADL impairments in each group at each time point. ADL impairments were more prevalent in the cancer survivor group than in the comparison group across all times (*p*<.001). The proportion with ADL impairments increased over time (*p*<.001). The group-by-time interaction was not significant (*p*=.697).

Figure 2C shows the proportion with IADL impairments in each group at each time point. A higher proportion of the cancer survivor group than the comparison group had IADL impairments (*p*=.001), and the prevalence of IADL impairments increased over time (*p*<.001). The group-by-time interaction was significant (*p*<.001), with a substantially greater increase in IADL impairments in cancer survivors from 0-2 years pre-diagnosis to 0-2 years post-diagnosis (21% to 30%) than in the comparison group (17% to 18%).

Quality of life

Figure 3 shows the mean quality of life score for each group at each time point. There was no significant group effect (*p*=.252). Independent of group, mean quality of life scores increased slightly from 4-6 to 2-4 years pre-diagnosis, then declined over time (*p*=.048). The group-by-time interaction was significant (*p*<.001). Scores were slightly lower 4-6 years pre-diagnosis in the cancer survivor group than in the comparison group (41.77 vs. 42.52), and were almost identical at 2-4 (42.40 vs. 42.47) and 0-2 years pre-diagnosis (41.90 vs. 41.98). However, from 0-2 years pre-diagnosis to 0-2 years post-diagnosis, mean quality of life declined in the cancer survivor group (from 41.90 to 40.64) and increased slightly in the comparison group (from 41.98 to 42.65).

Psychological wellbeing

Figure 4A shows the proportion with depressive symptoms in each group at each time point. A greater proportion of the cancer survivor group had depressive symptoms (*p*=.002) and overall, the proportion with depressive symptoms increased over time (*p*=.001). There was a significant group-by-time interaction (*p*<.001), with the prevalence of depressive symptoms at 0-2 years pre-diagnosis and 0-2 years post-diagnosis increasing from 14% to 21% in the cancer survivor group, and remaining stable at 12% in the comparison group.

Figure 4B shows the mean life satisfaction score for each group at each time point. Life satisfaction was lower in the cancer survivor group, independent of time (*p*=.004). Scores fluctuated over time, independent of group (*p*=.046). From 0-2 years pre-diagnosis to 0-2 years post-diagnosis, mean life satisfaction decreased from 20.06 to 19.65 in cancer survivors and increased from 20.96 to 21.37 in the comparison group, but the group-by-time interaction was not significant (*p*=.111).

Conclusions

This prospective study examined changes in health and wellbeing from 4-6 years before a diagnosis of cancer to 0-2 years after diagnosis in a large, population-based sample of English older adults. In a previous study, we found that cancer survivors reported poorer health and wellbeing up to two years prior to receiving their diagnosis (9). The present results extend these findings by demonstrating impairments in some markers even further in advance of diagnosis. Self-rated health was comparable in cancer survivors and comparisons 4-6 years before diagnosis, but a greater decline in cancer survivors' self-rated health was evident from 2-4 years prior to diagnosis, with between-groups differences growing ever larger over time. Mobility and ADL impairments were more prevalent among cancer survivors across all times – up to six years prior to diagnosis – and the rate of change over time did not differ significantly between groups, although there was a trend for a greater increase in mobility impairments among cancer survivors from 2-4 years before diagnosis. Similarly, cancer survivors reported poorer life satisfaction at all times and although life satisfaction appeared to decrease in cancer survivors relative to the comparison group around the point of diagnosis, this difference was not statistically significant.

However, not all markers of health and wellbeing showed substantial group differences in the years leading up to diagnosis. The largest changes in cancer survivors' quality of life, depressive symptoms and IADL impairment occurred around the point of diagnosis. Quality of life scores were fairly similar in cancer survivors and the comparison group prior to diagnosis and the groups diverged post-diagnosis such that cancer survivors had lower quality of life. Depressive symptoms were consistently slightly higher among cancer survivors but the difference became much more pronounced after diagnosis. IADL impairment was more prevalent in cancer survivors across all times, and while the difference between groups increased slightly over the lead up to the diagnosis point, the greatest change was seen from the wave immediately before diagnosis to the wave immediately after. In general, data on most health and wellbeing variables followed similar trends over time across groups. Exceptions were quality of life, depressive symptoms and life satisfaction, where a divergence in mean scores/prevalence became obvious following a cancer diagnosis.

Differences in the pattern of results across the range of outcome measures may reflect differences in the way the variables relate to the cancer. It is likely that the sharp increase in depression and declines in quality of life and life satisfaction observed following diagnosis result from stress related to diagnosis and treatment (31), whereas the greater decline in self-rated health in the cancer survivor group in the lead up to diagnosis is likely to be caused by undiagnosed disease making individuals feel unwell. If a decline in perceived health is a warning sign for cancer this could have important implications for diagnosis and prognosis. It is important to continue to encourage people to seek help early if they are feeling unwell. Regularly recording patient's self-rated health at primary care appointments could provide a simple basis for identifying individuals at risk of cancer based on their rate of decline. This could aid in making diagnoses at an earlier stage, which may lead to better outcomes (20–22). However, our finding is at odds with a recent study that observed no significant association between declining self-rated health and risk of developing cancer over 12 years in a cohort of Danish women (23). There is a need for further investigation into the relation between self-rated health and cancer risk to resolve these discrepant findings.

Clinical implications

Health problems that pre-date the cancer diagnosis by a number of years may contribute to the onset of cancer or share a common aetiology. For example, people with impaired mobility tend to be less physically active, which is known to increase risk of developing several cancers (24–27), and disability and cancer share a common risk factor in obesity (28,29). With potentially modifiable risk factors such as obesity, physical activity, diet, smoking and alcohol intake among the leading causes of cancer death (30). health promotion and behaviour change interventions at the general-population level continue to be of critical importance.

More acute changes in depression and quality of life that take place around the time of diagnosis are likely a reaction to the stressful nature of cancer diagnosis and treatment (31). This highlights a need to ensure cancer patients are screened for these risk factors at diagnosis and have access to psychological support. Previous studies have shown that around a quarter of female cancer survivors and one in ten male cancer survivors desire psychological support from healthcare professionals (32) and that providing such support can significantly reduce psychological morbidity in patients undergoing cancer treatment (33). Moreover, given evidence relating psychosocial stress to adverse changes in the cellular immune response at the tumour level (34,35), which may lead to faster disease progression, initiatives aimed at reducing stress and enhancing quality of life may offer significant benefits in terms of disease course.

Study strengths and limitations

This study had several strengths. No other studies have investigated these processes over such a long lead in time or in a sample of this size. Data were drawn from a large sample that was broadly representative of the older English population. The prospective design minimised recall bias, and the inclusion of a cancer-free comparison group allowed for typical changes in health and wellbeing with ageing to be accounted for.

However, results should be considered in light of a number of limitations. Cancer diagnoses were self-reported and it is possible that malignancies diagnosed many years previously were forgotten or not reported, or that benign tumours were mistakenly reported as cancerous; although validation studies comparing self-reports against medical records have generally shown high agreement (36–38). Data were not available on the exact date of diagnosis, which could have been any time over the two years between the last wave at which a participant reported no history of cancer and the wave in which cancer was first reported. Information on stage at diagnosis was not collected, and it is likely that pre-diagnostic changes in health and wellbeing would be more pronounced in individuals diagnosed at a later stage. The sample of cancer survivors was too small to stratify analyses by cancer site, and given the substantial heterogeneity across cancers results would likely vary by site. Our sample of cancer survivors was restricted to those who were alive and sufficiently well to participate in at least one wave of data collection after their diagnosis, so the results may not generalise to individuals with more aggressive cancers.

Future research

The present study has identified alterations in perceptions of health and wellbeing that precede the diagnosis of cancer by several years. The next steps for advancing this research are to establish whether similar trends are observed in patient subgroups, such as men and women, those from higher vs. lower SES levels, those affected by cancer at various sites/organs, and those diagnosed at different stages. While detailed medical data is not routinely available in ELSA or other cohort studies of this type, it may be possible to explore these questions by linking data with information from cancer registries or hospital episode statistics. Such a design would also allow greater accuracy in determining the timing of diagnosis.

Concluding remarks

To summarise, these results indicate that some of the impaired wellbeing in people diagnosed with cancer may be of long standing, evident up to six years prior, rather than being a reaction to diagnosis. Other changes, for example in depression or quality of life, appear to be more acute in nature and may require targeted support around the point of diagnosis. Importantly, there may be early signs of deterioration in perceptions of health that precede the development of symptoms leading to diagnosis by many years. Further research characterising these changes more precisely could lead to fresh ideas about cancer awareness.

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Tables

Table 1 Sample characteristics

	Whole sample (*n*=5928)	**Cancer survivor group (*n*=477)**	**Comparison group (*n*=5451)**
Age in diagnosis wave (mean [SD] years)	69.95 (7.89)	71.41 (8.03)	69.82 (7.86)
Sex			
Male	45.4 (2690)	49.5 (236)	45.0 (2454)
Female	54.6 (3238)	50.5 (241)	55.0 (2997)
Wealth quintile			
1 (poorest)	15.0 (888)	16.8 (80)	14.8 (808)
2	16.7 (989)	14.7 (70)	16.9 (919)
3	22.0 (1304)	24.1 (115)	21.8 (1189)
4	22.5 (1334)	20.8 (99)	22.7 (1235)
5 (richest)	23.8 (1413)	23.7 (113)	23.8 (1300)
Ethnicity			
White	97.0 (5751)	98.5 (470)	96.9 (5281)
Non-white	3.0 (176)	1.5 (7)	3.1 (169)
Cancer site			
Lung	-	6.3 (30)	-
Breast	-	16.1 (77)	-
Colon, bowel or rectum	-	12.8 (61)	-
Lymphoma	-	2.9 (14)	-
Leukaemia	-	0.8 (4)	-
Melanoma and other skin cancers	-	14.0 (67)	-
Prostate	-	16.1 (77)	-
Other/unspecified	-	30.8 (147)	-

Values are percentages (*n*) unless otherwise stated.

SD = standard deviation.

Table 2 Health and wellbeing in the cancer survivor group and comparison group at each time point

	Cancer survivor group (*n*=477)				**Comparison group (*n*=5451)**			
	4-6 years pre-diagnosis	**2-4 years pre-diagnosis**	**0-2 years pre-diagnosis**	**0-2 years post-diagnosis**	**4-6 years pre-diagnosis**	**2-4 years pre-diagnosis**	**0-2 years pre-diagnosis**	**0-2 years post-diagnosis**
Self-rated health (1-5), mean (SD)	3.38 (1.08)	3.39 (1.07)	3.16 (1.08)	2.58 (1.07)	3.36 (1.07)	3.32 (1.07)	3.25 (1.08)	3.20 (1.08)
Mobility impairment, % (*n*)	55.6 (265)	55.8 (266)	60.6 (289)	64.2 (306)	50.6 (2759)	52.9 (2885)	53.1 (2893)	54.6 (2978)
ADL impairment, % (*n*)	19.5 (93)	20.3 (97)	22.6 (108)	26.6 (127)	14.4 (784)	14.5 (791)	16.1 (879)	17.2 (937)
IADL impairment, % (*n*)	17.2 (82)	18.9 (90)	21.0 (100)	30.2 (144)	14.7 (802)	15.8 (861)	17.0 (925)	18.4 (1001)
Quality of life (0-57), mean (SD)	41.81 (8.42)	41.07 (8.68)	40.20 (8.67)	39.31 (8.72)	41.86 (8.43)	41.77 (8.54)	41.40 (8.63)	42.17 (8.62)
Depressive symptoms, % (*n*)	15.8 (74)	13.6 (63)	14.0 (65)	21.0 (95)	12.2 (650)	13.0 (689)	11.5 (612)	11.9 (626)
Life satisfaction (0-30), mean (SD)	19.82 (6.74)	20.18 (6.56)	19.77 (6.68)	19.62 (6.81)	20.57 (6.07)	20.94 (6.18)	20.55 (6.26)	21.03 (6.11)

ADL = activities of daily living; IADL = instrumental activities of daily living.

Valid percentages shown for ease of interpretation.

Figure legends

Figure 1. Global health by group and time.

Figure 1 shows the mean self-rated health (with 95% confidence intervals) for each group at each time point (adjusted for age, sex, wealth and diagnosis wave). *$p<.05$, **$p<.01$, ***$p<.001$ for the difference between the cancer survivor group and comparison group at each time point.

Figure 2. Physical function by group and time.

Figure 2 shows the proportion with (A) mobility impairments, (B) ADL impairments and (C) IADL impairments (with 95% confidence intervals) for each group at each time point (adjusted for age, sex, wealth and diagnosis wave). *$p<.05$, **$p<.01$, ***$p<.001$ for the difference between the cancer survivor group and comparison group at each time point.

Figure 3. Quality of life by group and time.

Figure 3 shows the mean quality of life score (with 95% confidence intervals) for each group at each time point (adjusted for age, sex, wealth and diagnosis wave). Note: the y-axis begins at 37 rather than 0, to allow for easy visibility of results. *$p<.05$, **$p<.01$, ***$p<.001$ for the difference between the cancer survivor group and comparison group at each time point.

Figure 4. Psychological wellbeing by group and time.

Figure 4 shows (A) the proportion with depressive symptoms and (B) the mean life satisfaction score (with 95% confidence intervals) for each group at each time point (adjusted for age, sex, wealth and diagnosis wave). Note: the y-axis for Figure 4B begins at 16.5 rather than 0, to allow for easy visibility of results. *$p<.05$, **$p<.01$, ***$p<.001$ for the difference between the cancer survivor group and comparison group at each time point.