



Characteristics of Cancer Survivors and Women With No Cancer History in the Nurses' Health Study: Prevalence of Risk Factors for Cognitive Decline

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INTRODUCTION

With longer survival rates for many common cancers, there is increased interest in the impact of cancer and cancer treatment on health in aging, especially cognitive function [1-3]. However, as emphasized by the International Cognition and Cancer Task Force (ICCTF), it can be difficult to interpret research on cancer/cancer treatment in survivors versus healthy subjects without better understanding the underlying risk factor profile for cognitive decline across these groups (i.e., independent of their cancer or cancer treatment) [4, 5]. Evaluating basic characteristics of cancer survivors, and of those with no cancer history, in terms of risk factor profiles for cognitive decline, will allow proper inference and help to disentangle effects of cancer itself/cancer treatment versus underlying risk factor profiles.

In this paper, we sought to compare the characteristics, in terms of known risk factors for cognitive impairment, of different groups of cancer survivors, including breast, colorectal, and uterine, as well as individuals with no history of cancer, in the Nurses' Health Study (NHS). A secondary objective was to assess the influence of both chemotherapy treatment and elapsed time since cancer diagnosis on health/lifestyle characteristics, since patients may change their behavior subsequent to diagnosis.

As lead investigator of the project, I developed an analysis plan, wrote SAS programs to perform the analyses, created tables summarizing key findings, and drafted the manuscript describing the findings. During the process, I received guidance from Dr. Francine Grodstein who reviewed each stage of the research. The following authors provided edits while finalizing the manuscript for submission to a peer-reviewed journal: Cecilia Samieri (Channing), Wendy Y. Chen (Channing/Dana Farber Cancer Institute DFCI), Michelle D. Holmes (Channing), Charles S. Fuchs (Channing/ DFCI) and Sanne Schagen (Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital). In addition, Cecilia Samieri provided some technical assistance in writing the SAS analysis programs.

METHODS

Study population

The NHS was established in 1976 when 121,700 female registered nurses from 11 U.S. states, aged 30-55 years old, completed a mailed questionnaire about health and lifestyle factors. Follow-up questionnaires were sent out every two years thereafter with follow-up rates > 90%. The study protocol was approved by the Institutional Review Board of Brigham and Women's Hospital (Boston, MA). Women included in this present analysis had to be responders to the long version of the questionnaire in 2000 (when they ranged from 55 to 79 years of age), which included a large number of health, lifestyle and psychosocial risk factors for cognitive decline. This analysis includes 6,159 women diagnosed with breast cancer, 876 with colorectal cancer, 602 with uterine cancers, and 94,762 with no report of cancer as of 2000.

Identification of cancer and non-cancer cases

On each biennial questionnaire, nurses were asked to report any diagnosis of cancer and the date of diagnosis. For each reported diagnosis, confirmation was sought from the nurse, and permission was obtained to review her relevant medical records. We considered here women with cancers diagnosed through the 2000 NHS questionnaire.

In particular, breast, colorectal, and uterine cancers were selected for analysis due to their clinical significance; these cancers have the highest survival rates among women and are among the most common cancers affecting older women [6], which make health issues in aging survivors important. Due to differences in prognosis and treatment, and potentially concomitant differences in associated health and lifestyle variables, we distinguished between invasive and in-situ breast cancers when evaluating their characteristics/cognitive risk factor profiles. Information on chemotherapy treatment for invasive breast cancer was based upon self-report or extracted from medical records.

Women with stage IV cancer at diagnosis and those with a diagnosis of any other invasive cancer (aside from non-melanoma skin cancer) were excluded. We also examined cancer-free participants, defined as women with no report of cancers through the 2000 questionnaire.

Assessment of health, lifestyle, and psychosocial factors

For these analyses of characteristics related to cognitive impairment, we chose to use data from the 2000 NHS questionnaire for several reasons. Most importantly, the oldest participants were entering their 70s in 2000 and we included a particularly large spectrum of risk factors for cognitive decline and aging on that questionnaire. Variables of interest included a range of factors that have been shown to be related to cognitive decline in the NHS and elsewhere: (i) socio-demographic factors: age and education [7]; (ii) lifestyle factors: smoking status [8], alcohol intake [9, 10], and recreational physical activity [metabolic equivalents (MET)-hours/week] [11]; (iii) cardiovascular [12-14] and metabolic factors [15, 16]: body mass index, history of type 2 diabetes, high blood pressure, high cholesterol, and myocardial infarction; (iv) medications and vitamin supplements: aspirin use (d/week) [17], ibuprofen use [18], postmenopausal hormone therapy [19], and multivitamin use [20]; and (v) mental health: history of diagnosed depression [21], the mental health index (MHI-5) from the Medical Outcomes Short-Form 36 (SF-36) (range 0-100, with a higher score indicating better mental functioning) [22, 23].

Statistical Analysis

In comparing the prevalence of characteristics across our groups of interest, we standardized by age to control for differences in age across the study groups. Differences in the distributions of variables across groups were tested using chi-square tests for categorical variables and analysis of covariance for continuous variables.

Since cancer diagnosis may modify the behavior of individuals, we performed secondary analyses stratifying cancer groups by time since diagnosis (i.e., number of years between date of cancer diagnosis and 2000), differentiating between more recent diagnosis (arbitrarily defined as <5 years) and more distant diagnosis (defined as ≥ 5 years post-diagnosis).

Finally, we compared risk factors for cognitive decline according to chemotherapy treatment at diagnosis (no chemotherapy versus history of chemotherapy). This analysis was performed only among invasive breast cancer patients, since this was our largest group of cancer survivors and therefore provided the most stable data after subdividing survivors according to treatment. All analyses were performed using SAS Version 9 (SAS Institute Inc., Cary, NC).

RESULTS

We identified 6,159 breast cancer survivors diagnosed through the return of the 2000 NHS questionnaire, which included 5,220 (85%) invasive and 939 (15%) in-situ breast cancers. There were 876 colorectal cancer survivors and 602 uterine cancer survivors. We also identified 94,762 women who had no history of cancer prior to the 2000 questionnaire (Table 1).

Overall, after adjusting for age, the distributions of risk factors for cognitive decline were generally similar across groups of cancer survivors as well as women with no cancer history (Table 1). Specifically, alcohol intake was similar across all groups (range across group: 8-11% prevalence of consuming ≥ 15 g/day), as was history of myocardial infarction (range: 5-7%), regular ibuprofen use (range: 21-26%), and mean SF36 Mental Health Index (range: 79.9-80.4) ($p > 0.05$ for all comparisons).

In this large study, we found statistically significant differences ($p < 0.05$) for each of the following risk factors across our groups of interest: educational attainment (range: 8-12% prevalence of women holding a graduate degree), history of high cholesterol (range: 57-64% prevalence), regular aspirin use (range: 72-79% prevalence of no use), multivitamin use (range: 66-71% prevalence of current use), and history of depression (range: 16-21%). History of postmenopausal hormone therapy was approximately 70% more common in women with invasive breast cancer than in women with no cancer history ($p < 0.0001$). However, as Table 1 shows, absolute differences in most of these variables between the groups were quite modest and not clinically significant (except for use of hormone therapy).

Notably, however, the risk factor profile for uterine cancer survivors tended to differ from all other groups. There was nearly a two-fold higher proportion of uterine cancer survivors with $\text{BMI} \geq 30 \text{ kg/m}^2$ (40%) compared to the other groups (22-24%), and a higher percentage of women with type 2 diabetes (19%) compared to other cancer survivors or those with no cancer history in 2000 (9-11%). Similarly, a history of high blood pressure was more common among uterine cancer survivors (61%) than all other groups (48-52%).

We also stratified cancer groups by the number of years post-diagnosis as of 2000 (Table 2). Though long-term colorectal cancer survivors had a lower percentage of past-smokers than shorter-term survivors (47% versus 57%), and were also somewhat more physically active (47% reporting ≥ 10 met-h/week of physical activity versus 37%), we detected no other qualitatively meaningful differences in risk factor profiles for cognitive decline among past and recently-diagnosed cancer survivor groups. An exception was use of postmenopausal hormone therapy; women more recently diagnosed with invasive or in situ breast cancer were much less likely to use hormone therapy than those diagnosed in the past ($p < 0.0001$).

Finally, we evaluated whether chemotherapy treatment at diagnosis affected the distribution of risk factors for cognitive decline among invasive breast cancer survivors (Table 3). There were few statistically significant differences between the two sub-groups across all risk factors examined ($p > 0.05$), apart from age, such that patients who did not receive chemotherapy at diagnosis were older (mean 69.3 years) than those who received chemotherapy (mean 65.2 years). Additionally, for postmenopausal hormone therapy, we found a statistically significant difference in use ($p = 0.003$) between women who were treated with chemotherapy (65% prevalence of hormone use) and those not given chemotherapy (69%), although the absolute difference was small and not clinically significant.

DISCUSSION

We assessed risk factors for cognitive decline across groups of cancer survivors and women with no cancer history, with the goal of describing the characteristics and underlying risk profiles for cognitive decline in cancer survivors, given the scientific and clinical interest in cancer and cognitive health. To our knowledge, no previous research has carefully examined characteristics of cancer survivors and women with no cancer history in terms of their cognitive risk factor profile; it can be difficult to interpret existing studies of measured cognitive function in these groups without better understanding potential differences in relevant health and lifestyle characteristics. We found that breast and colorectal cancer survivors, as well as women with no cancer history demonstrated similar profiles across virtually all cognitive risk factors examined. Furthermore, the distribution of risk factors for cognitive decline generally did not vary with

chemotherapy status among invasive breast cancer survivors. This suggests that scientifically, any observed differences in studies of cognitive decline across women with cancer versus no cancer, are likely due to the cancer itself or to treatment. Moreover, clinically, advice regarding cognitive decline post-diagnosis (e.g. demographic, lifestyle, and psychosocial factors) should be similar among breast and colorectal cancer survivors compared to women with no cancer history, and therefore do not require any different level of consideration specifically in cancer patients (unless, of course, cancer itself or cancer treatment are risk factors for cognitive decline, the topic of future research in our cohort). We did find fairly consistent differences in use of postmenopausal hormone therapy depending on breast cancer status; however, it is controversial whether hormone therapy is related to cognitive function [27].

However, we found some differences in distributions of BMI and related risk factors between uterine cancer survivors versus all other groups. Uterine cancer is the fourth leading cancer affecting women in the United States [28]. Our analyses demonstrate that uterine cancer survivors have a unique distribution of risk factors for cognitive decline, particularly with respect to high BMI, type 2 diabetes, and high blood pressure – all strong risk factors for cognitive decline [7-23]. The distinctive risk factor profile of uterine cancer survivors suggests that consideration must be taken to carefully control for confounding factors in examinations of cognitive decline utilizing this group. It further suggests that development of any endeavors aimed to minimize cognitive dysfunction among uterine cancer survivors should be tailored to the underlying risk factor distribution of the group.

Lastly, we observed, in general, that risk factor profiles for cognitive decline did not readily change with time elapsed since cancer diagnosis. This is consistent with research suggesting few long-term modifications to health behaviors following cancer diagnosis [29-31]. A study using data from the National Health Interview Survey showed that among 7,384 cancer survivors, there were no differences in smoking status, physical activity and alcohol consumption by time since diagnosis [32]. Thus, our results suggest that studies which do not have information on cognitive risk factors from cancer survivors at multiple time points following diagnosis may not be inducing any substantial bias.

A major strength of the study includes the large number of participants in the NHS cohort. The prospective nature of the cohort and availability of information on cognitive risk factors at multiple time points also enabled us to evaluate a comprehensive list of risk factors for cognitive decline, and to consider whether time since cancer diagnosis might impact the cognitive risk factor profile. There are also limitations to consider. The self-reported information could contain some random misclassification; this would tend to bias our results toward the null and might cause a slight underestimation of differences between various risk factors for cognitive decline across these cancer and non-cancer groups. However, we have established that many of the self-reported variables in this cohort of nurses are highly valid.

In summary, to our knowledge, this is the first study to assess the distributions of risk factors for cognitive decline across different groups of cancer survivors as well as a population of women with no cancer history. Though we found uterine cancer survivors to have a unique cognitive risk factor profile, breast and colorectal cancer survivors as well as women with no cancer history demonstrated similar distributions with respect to most major risk factors for cognitive decline in older age. Furthermore, these distributions did not readily change with chemotherapy status or with elapsed time post-diagnosis. This is important in interpreting existing and future research on cancer, cancer treatment and measured cognition, and in discussing future risk of cognitive decline in these groups. Long survivorships now experienced by breast, uterine, and colorectal cancer patients underscore the importance of addressing survivorship issues such as cognitive health.

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Table 1: Risk factors for cognitive decline across breast cancer (invasive and *in-situ*), colorectal cancer, uterine cancer and cancer-free groups - age-standardized

	Breast cancer (invasive) (n=5220)	Breast cancer (in-situ) (n=939)	Colorectal cancer (n=876)	Uterine cancer (n=602)	Cancer-free (n=94762)
Socio-demographic factors					
Age, y, mean (SD) ^a	67.9(6.9)	66.4(6.8)	70.1(6.4)	69.1(6.7)	66.0(7.2)
Age at diagnosis, y, mean(SD) ^{a, b}	59.4(9.0)	59.6(8.4)	62.8(8.3)	60.7(7.5)	-----
Highest level of education, % ^b					
- Nursing degree	69	68	72	74	70
- Bachelors degree	21	20	19	18	20
- Graduate degree	10	12	9	8	10
Lifestyle factors					
Smoking, % ^c					
- Never	43	43	41	53	48
- Past	49	49	51	41	43
- Current	8	8	8	6	9
Alcohol intake, g/day, % ^b					
- None	41	39	42	48	43
- 1-14.9	50	50	49	44	49
- ≥15	9	11	9	8	9
Physical activity, met-h/week, % ^b					
- <10	52	53	57	60	50
- ≥10	48	47	43	40	50
Cardiovascular & metabolic factors					
BMI, kg/m ² , % ^b					
- ≤24.9	43	44	45	30	42

Table 1. (continued)

	Breast cancer (invasive) (n=5220)	Breast cancer (in-situ) (n=939)	Colorectal cancer (n=876)	Uterine cancer (n=602)	Cancer-free (n=94762)
- 25-29.9	35	33	32	31	34
- ≥30	22	23	23	40	24
History of type 2 diabetes, % ^c	10	10	11	19	9
History of high blood pressure, % ^c	48	48	52	61	48
History of high cholesterol, % ^c	60	62	59	64	57
History of myocardial infarction, % ^c	6	7	7	5	6
Medication and supplement use					
Post-menopausal hormone use, % ^b					
- Pre-menopausal	1	1	2	0	5
- Postmenopausal/Past or Current use of hormone therapy	38	30	26	33	22
- Postmenopausal/Never used hormone therapy	62	68	72	66	73
Aspirin use, d/week, % ^b					
- Non-user	76	79	75	72	73
- 1-3	9	7	9	12	10
- 4-7	16	14	17	16	18
Ibuprofen use, % ^b	25	26	21	26	26
Multivitamin use, % ^b	71	70	66	67	67

Table 1. (continued)

	Breast cancer (invasive) (n=5220)	Breast cancer (in-situ) (n=939)	Colorectal cancer (n=876)	Uterine cancer (n=602)	Cancer-free (n=94762)
Psychosocial factors					
History of depression, % ^b	21	19	16	18	18
SF36 Mental Health Index, mean(SD) ^b	80.3(13.5)	80.2(13.3)	80.3(12.4)	79.9(12.5)	80.4(13.4)
Berkman-Syme social network index,% ^b					
- 0-2 social networks	22	19	25	26	22
- 3-4 social networks	78	81	75	74	78

^a Value is not age adjusted

^b Calculated among non-missing values

^c Missing data grouped with referent category

Table 2: Risk factors for cognitive decline across breast cancer (invasive and *in-situ*), colorectal cancer, uterine cancer and cancer-free groups by number of years post-diagnosis- age-standardized

Years since diagnosis	Breast cancer (invasive)		Breast cancer (in-situ)		Colorectal cancer		Uterine cancer	
	<5yrs (n=1807)	≥5 yrs (n=3413)	<5yrs (n=385)	≥5 yrs (n=554)	<5yrs (n=362)	≥5 yrs (n=514)	<5yrs (n=202)	≥5 yrs (n=400)
Socio-demographic factors								
Age, y, mean(SD) ^a	67.4(6.9)	68.1(6.9)	66.0(6.8)	66.6(6.9)	69.4(6.5)	70.6(6.3)	66.9(6.7)	70.2(6.4)
Age at diagnosis, y, mean(SD) ^{a, b}	65.4(7.0)	56.3(8.3)	64.2(6.9)	56.4(7.9)	67.4(6.7)	59.5(7.7)	64.9(6.7)	58.5(6.9)
Highest level of education, % ^b								
- RN degree	68	70	71	68	75	72	70	77
- Bachelors degree	22	20	18	20	16	21	23	15
- Graduate degree	10	10	11	12	9	7	6	8
Lifestyle factors								
Smoking, % ^c								
- Never	44	43	45	41	35	44	52	54
- Past	49	48	48	50	57	47	43	38
- Current	8	8	7	9	8	8	5	7
Alcohol intake, g/day, % ^b								
- None	40	40	39	40	39	46	51	47
- 1-14.9	50	50	53	48	51	47	41	44
- ≥15	10	9	9	11	10	7	8	9
Physical activity, met-h/week, % ^b								
- <10	53	50	51	54	63	53	56	59
- ≥10	47	50	49	46	37	47	44	41
Cardiovascular & metabolic factors								
BMI, kg/m ² , % ^b								
- <24.9	42	44	47	41	44	45	28	31

Table 2. (continued)

Years since diagnosis	Breast cancer (invasive)		Breast cancer (in-situ)		Colorectal cancer		Uterine cancer	
	<5yrs (n=1807)	≥5 yrs (n=3413)	<5yrs (n=385)	≥5 yrs (n=554)	<5yrs (n=362)	≥5 yrs (n=514)	<5yrs (n=202)	≥5 yrs (n=400)
- 25-29.9	35	35	26	38	35	29	32	32
- 30+	23	21	26	21	21	26	41	37
History of Type II diabetes, % ^c	10	11	8	11	10	13	16	21
History of high blood pressure, % ^c	50	48	49	48	51	56	59	62
History of high cholesterol, % ^c	56	62	60	66	60	60	66	65
History of myocardial infarction, % ^c	5	6	8	6	7	8	5	6
Medication and supplement use								
Post-menopausal hormone use, % ^b								
- Premenopausal	1	1	1	1	2	1	0	0
- Postmenopausal/Past or current hormone use	25	45	21	37	29	26	31	34
- Postmenopausal/Never used hormone therapy	75	54	78	62	69	73	69	66
Aspirin use, d/week, % ^b								
- Non-user	76	75	77	80	76	73	70	73
- 1-3	9	9	6	7	8	9	14	10
- 4-7	15	16	16	13	17	18	16	16
Ibuprofen use, % ^b	26	24	24	27	19	21	28	25
Multivitamin use, % ^b	72	70	73	68	69	64	70	64

Table 2. (continued)

	Breast cancer (invasive)		Breast cancer (in-situ)		Colorectal cancer		Uterine cancer	
	<5yrs (n=1807)	≥5 yrs (n=3413)	<5yrs (n=385)	≥5 yrs (n=554)	<5yrs (n=362)	≥5 yrs (n=514)	<5yrs (n=202)	≥5 yrs (n=400)
Psychosocial factors								
History of depression, % ^b	21	21	17	20	16	17	19	18
SF36 Mental Health Index, mean(SD) ^b	80.4(13.9)	80.2(13.3)	80.3(11.2)	80.1(12.5)	80.1(10.6)	80.2(11.7)	80.2(9.2)	80.1(12.1)
Berkman-Syme social network index, % ^b								
- 0-2 social networks	23	22	22	19	26	24	23	26
- 3-4 social networks	77	78	78	81	74	76	77	74

^a Value is not age adjusted

^b Calculated among non-missing values

^c Missing data grouped with referent category

Table 3: Risk factors for cognitive decline among invasive breast cancer patients by treatment status - age standardized

	No chemotherapy (n=2198)	Chemotherapy (n=1443)
Socio-demographic factors		
Age, y, mean(SD) ^a	69.2(6.6)	65.2(6.9)
Age at diagnosis, y, mean(SD) ^{a, b}	62.9(7.4)	57.9(8.5)
Highest level of education, % ^b		
- RN degree	69	69
- Bachelors degree	21	21
- Graduate degree	10	10
Lifestyle factors		
Smoking, % ^c		
- Never	44	45
- Past	49	48
- Current	7	8
Alcohol intake, g/day, % ^b		
- None	43	43
- 1-14.9	47	48
- ≥15	9	10
Physical activity, met-h/week, % ^b		
- <10	51	53
- ≥10	49	47
Cardiovascular & metabolic factors		
BMI, kg/m ² , % ^b		
- ≤24.9	44	43
- 25-29.9	35	37

Table 3. (continued)

	No chemotherapy (n=2198)	Chemotherapy (n=1443)
- ≥ 30	21	20
History of Type II diabetes, % ^c	11	11
History of high blood pressure, % ^c	51	50
History of high cholesterol, % ^c	61	61
History of myocardial infarction, % ^c	6	6
Medication and supplement use		
Post-menopausal hormone use, % ^b		
- Premenopausal	1	0
- Postmenopausal/Past or current use of hormone therapy	69	65
- Postmenopausal/Never used hormone therapy	30	35
Aspirin use, d/week, % ^b		
- Non-user	75	75
- 1-3	9	9
- 4-7	16	15
Ibuprofen use, % ^b	25	24
Multivitamin use, % ^b	71	72
Psychosocial factors		
History of depression, % ^b	21	21
SF36 Mental Health Index, mean(SD) ^b	80.8(13.2)	79.9(13.8)

Table 3. (continued)

	No chemotherapy (n=2198)	Chemotherapy (n=1443)
Berkman-Syme social network index,% ^b		
- 0-2 social networks	22	21
- 3-4 social networks	78	79

^a Value is not age adjusted

^b Calculated among non-missing values

^c Missing data grouped with referent category