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Publisher: Routledge

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Nutrition and Cancer

Publication details, including instructions for authors and subscription information:

<http://www.tandfonline.com/loi/hnuc20>

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Version of record first published: 31 Jan 2013.

To cite this article: Xuesong Han, June Stevens & Patrick T. Bradshaw (2013): Body Mass Index, Weight Change, and Survival in Non-Hodgkin Lymphoma Patients in Connecticut Women, *Nutrition and Cancer*, 65:1, 43-50

To link to this article: <http://dx.doi.org/10.1080/01635581.2013.741760>

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Body Mass Index, Weight Change, and Survival in Non-Hodgkin Lymphoma Patients in Connecticut Women

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Evidence is emerging that obesity and weight gain may affect the prognosis of several types of cancer. We investigated the impact of body mass index (BMI) as well as pre-and postdiagnosis weight changes on non-Hodgkin lymphoma (NHL) prognosis. A cohort of 573 female incident NHL cases diagnosed during 1996–2000 in Connecticut was followed for a median of 7.8 yr. Self-reported height and weight at 3 time points before and after diagnosis were collected. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated using proportional hazard models adjusting for factors believed to be associated with overall survival of NHL. Underweight (BMI < 18.5; HR = 2.84; 95% CI = 1.12–7.15) before diagnosis was associated with poorer survival compared to being normal weight (18.5 ≤ BMI < 25). Prediagnosis weight loss (HR = 1.42; 95% CI = 1.02–1.97) and posttreatment weight loss (HR = 1.98; 95% CI = 1.14–3.45) and weight gain (HR = 1.85; 95% CI = 1.04–3.32) were associated with poorer survival. NHL patients who were underweight, lost weight prediagnosis, or change weight after treatment were found to have a poorer survival.

INTRODUCTION

Non-Hodgkin lymphoma (NHL) is the seventh most common cancer in the United States (1). The incidence of non-Hodgkin lymphoma has nearly doubled from 11.1 cases per 100,000 in 1975 to 20.2 cases per 100,000 in 2009 (2), making it one of the most rapidly rising cancers. It is estimated that 70,130 people will be diagnosed with non-Hodgkin lymphoma and 18,940 will die in the United States in the year 2012 (2).

The survival of patients with NHL is relatively poor, with only half surviving through five years after diagnosis. Clinical predictors for NHL survival include age, stage, performance status (a measure of how the disease affects the daily living abilities of the patient), extranodal involvement, and lactate dehydrogenase (LDH) level. Very few studies have examined

the impact of modifiable lifestyle factors on NHL survival. Adiposity, an individual characteristic that can be altered through lifestyle changes, has been shown to be related to risk of NHL (3–10). To the best of our knowledge, only 1 study has examined the relationship between body mass index (BMI) prior to diagnosis and NHL prognosis (11) and found worse survival in obese patients. Weight loss greater than 10% is regarded as one of the “B-symptoms” (systemic symptoms of fever, night sweats, and weight loss that may be present in lymphoma patients) at diagnosis, which has been shown to be associated with worse prognosis and shortened survival (12). Two clinical reports with small number of cases found that weight gain during treatment was associated with better survival among NHL patients using chemotherapy (13,14). To our knowledge, no study has examined the effect of BMI and weight change at pre-and postdiagnosis on NHL prognosis and survival. In this study, we used anthropometric information at three time points before and after diagnosis to examine the relationship of BMI and weight change and overall survival among female NHL patients diagnosed from 1996 to 2000 in Connecticut.

MATERIALS AND METHODS

Study Population

The study population has been described in detail elsewhere (15–17). In brief, a total of 1122 potential female NHL cases aged between 21 and 84 years were identified between 1996 and 2000 through the Yale Comprehensive Cancer Center’s Rapid Case Ascertainment Shared Resource, a component of the Connecticut Tumor Registry (CTR). CTR is the oldest tumor registry in the United States and all hospitals and private pathology laboratories in Connecticut are required by public health legislation to report incident cases to CTR. Among those cases, 167 died before they could be interviewed and 123 were excluded because of doctor refusal, previous diagnosis of cancer except nonmelanoma skin cancer or inability to speak English. Out of 832 eligible cases, 601 gave written consent and completed an in-person interview. Participants had a similar race

Submitted 11 August 2011; accepted in final form 26 August 2012.
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distribution with nonparticipants and were slightly older than nonparticipants (mean ages 67 vs. 62, respectively). Pathology slides or tissue blocks were obtained from the hospitals where the cases had been diagnosed and the specimens were reviewed by 2 independent study pathologists. All NHL cases were classified into histological subtypes according to the World Health Organization (WHO) classification system (18,19).

Vital status for these NHL cases was abstracted at the CTR in mid-2008. Other abstracted follow-up information included date of death, cause of death, most recent follow-up date, and type and date of treatments; B-symptom presence and tumor stage were also obtained from CTR record. Of the 601 cases, 13 were unable to be identified in the CTR system and 13 were found to have a history of cancer except nonmelanoma skin cancer prior to the current diagnosis of NHL. Further excluding 3 cases with missing weight, yielded 573 NHL patients in the final analyses. Of these, 182 had diffuse large B-cell lymphoma (DLBCL), 133 had follicular lymphoma (FL), 63 had chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), 38 had marginal zone B-cell lymphoma, 42 had T/NK-cell lymphoma (T-cell), and the rest 115 had other subtypes. This study was approved by the Human Investigation Committee at Yale University and the Connecticut Department of Public Health.

Exposure Assessment

Trained interviewers administered a standardized, structured questionnaire to obtain demographic information and known or suspected risk factors for NHL through in-person interviews. The median time between diagnosis and interview was 6.4 mo. During the interview, patients were asked about their height without shoes, their usual weight prior to diagnosis (the question attempts to acquire the average weight 1–2 yr before diagnosis without impacts from the disease), weight at the interview and the weight 1 yr prior to the interview. The 3 weights were highly correlated (correlation coefficient 0.88–0.93 and P values < 0.0001). The usual weight prior to diagnosis (mean 154 lbs) was slightly higher than the weight at interview (mean 153 lbs) (P value for paired t -test = 0.1845) and significantly lower than the weight 1 yr prior to the interview (mean 157 lbs) (P value for paired t -test < 0.0001). Additional information on age, race, education, smoking, family history of cancer, and other lifestyle factors before diagnosis was also obtained during the interview.

Statistical Analysis

BMI at each time point was calculated as weight in kilograms divided by squared height in meters (kg/m^2), and classified into 4 categories according to the World Health Organization definition: underweight ($< 18.5 \text{ kg}/\text{m}^2$); normal weight ($18.5\text{--}24.9 \text{ kg}/\text{m}^2$); overweight ($25\text{--}29.9 \text{ kg}/\text{m}^2$); obese ($\geq 30 \text{ kg}/\text{m}^2$). Weight changes between the time points were calculated and categorized as 3 groups: weight loss ($< 0 \text{ kg}$), no change (0 kg) and weight gain ($> 0 \text{ kg}$). We are interested in relationships between 5 BMI or weight change exposures and overall survival of NHL. The 5 exposures include baseline BMI

defined as the usual BMI prior to diagnosis; postdiagnostic BMI before treatment that was calculated with the “weight at interview” among only the subjects interviewed before receiving any treatment ($n = 218$); prediagnostic weight change which was calculated with the “weight one year prior to the interview - usual weight prior to diagnosis” among only the subjects interviewed within 1 yr after diagnosis ($n = 518$); postdiagnostic weight change before treatment which was calculated with “weight at interview - usual weight prior to diagnosis” among subjects who were interviewed before any treatment ($n = 218$); postdiagnostic weight change after treatment that calculated with “weight at interview - usual weight prior to diagnosis” among subjects who were interviewed after a treatment ($n = 282$). Survival analyses were conducted for NHL cases overall and the 3 major NHL subtypes (DLBCL, FL, and CLL/SLL) using the Kaplan-Meier method, where deaths from any cause were events and subjects alive at the end of follow-up were right-censored. Follow-up time was calculated as the time between diagnosis and event/censoring. Log-rank tests were performed to detect the survival difference between categories. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated by fitting Cox proportional hazards models, where normal weight or no weight change was reference group. Age (continuous), education (high school or less, some college, and college graduate or more), stage (I, II, III, IV, and unknown), presence of B-symptoms (yes, no/unknown), initial treatment (none, radiation only, chemotherapy-based regimen, and other) and smoking (never/ever smoked > 100 cigarette) were adjusted as confounding variables. A test for interaction of race (White or other) with BMI and weight change variables was conducted by adding the interaction terms into the model and no interaction effect was found, thus the analyses were not stratified by race. Adjustments for race and the time between diagnosis and interview did not result in material changes ($> 10\%$) for the observed associations when the analyses were performed in the entire cohort and thus were not included in the final models. For weight change variables, we further examined the interaction between baseline weight status and weight change for subjects that had a baseline BMI ≥ 18.5 . The assumption of proportionality of hazards was assessed by test of Schoenfeld residuals and it appeared to be met. Statistical analyses were performed using SAS, version 9.2 (SAS Institute, Cary, NC).

RESULTS

Demographic characteristics for 573 NHL cases are presented in Table 1. Compare to all the female NHL cases diagnosed in Connecticut in 1996–2000 and aged 21–84, our sample has a similar race distribution (percentage of Whites: 95.1% vs. 94.5%) and a younger age (percentage of age below 65: 52.5% vs. 42.8%) (20). The majority of these patients (60%) had stage I or II diseases and 6% had B-symptoms. The most common initial therapy was a chemotherapy-based regimen (52%), followed by observation (35%) and radiation (12%). For those

TABLE 1
Selected demographic characteristics of non-Hodgkin
lymphoma (NHL) cases, Connecticut, 1996–2000

Characteristic	<i>n</i>	%
Age at diagnosis (yr)		
≤45	69	12.0
46–55	111	19.4
56–65	121	21.1
66–75	165	28.8
≥76	107	18.7
Race		
White	545	95.1
Black	18	3.1
Other	10	1.8
Education		
High school or less	246	42.9
Some college	190	33.2
College graduate or more	137	23.9
Family history		
None	124	21.6
Any other cancer	441	77.0
NHL	8	1.4
Cause of death (total death = 252)		
Lymphoma	149	59.1
Other cancers	23	9.1
Cardiovascular disease	26	10.3
Respiratory disease	5	2.0
Nervous system disease	4	1.6
Infectious disease	4	1.6
Accident	4	1.6
Other and nonreported	37	14.7

who received treatment, the median time between diagnosis and treatment was 26 days. During the follow-up period, 252 patients died. Median follow-up time was 3.65 years for the deceased and 9.08 years for the survivors. At baseline before diagnosis, 20% of the patients were obese, 32% were overweight, 46% had normal weight, and the remaining 1% were underweight (Table 2). Nineteen percent of the patients lost weight and 34% gained weight in the year prediagnosis; among those who were interviewed before any treatment, 35% lost weight and 35% gained weight after diagnosis; among those who were interviewed after receiving a treatment, 45% lost weight and 33% gained weight after treatment (Table 2).

NHL patients who were underweight or obese at baseline had poorer survival compared to normal weight and overweight subjects (Fig. 1). NHL patients who were overweight or obese before treatment had the best survival, followed by normal-weight subjects, and underweight patients before treatment had the worst survival (Fig. 1). Those who lost weight either before or after diagnosis, including both before and after treatment,

all had the worst survival compared to those who maintained or gained their weight (Fig. 1). Similar patterns were also seen for the three major subtypes, although the differences were not significant partly because of small sample size in the subtype analyses (figures not shown).

After adjustment for confounding variables, NHL patients who were underweight at baseline had a higher risk of death compared to normal weight subjects and NHL patients who were overweight before treatment had a lower risk of death compared to normal weight subjects (Table 2). Weight loss before diagnosis was associated with 42% increased rate of death compared to subjects with no weight change (Table 2). After treatment, weight loss and weight gain were both associated with a higher risk of death (Table 2). When analyzed by NHL subtype, a higher risk of death was observed among FL patients who were underweight at baseline and who were underweight before treatment. Losing weight in the year before diagnosis was associated with a higher risk of death among CLL/SLL patients (Table 2).

No statistically significant interaction was found between baseline weight status and weight change pre- or postdiagnosis. However, the increased risk of death associated with prediagnostic weight loss was mainly seen in overweight subjects, and the increased risk of death associated with postdiagnostic weight change after treatment was mainly seen in normal weight subjects (Table 3).

DISCUSSION

This study evaluated the relationships of BMI and weight change at different time points and survival of a cohort of female NHL patients in Connecticut women. We found that prior to diagnosis, having a baseline BMI that was underweight was associated with poorer survival after accounting for clinical and demographic variables, and weight loss in the year prediagnosis was also associated with poorer survival. After diagnosis, being overweight before treatment was associated with better survival, and weight change after treatment (either weight loss or weight gain) was associated with poorer survival.

BMI prior to diagnosis was linked to NHL prognosis and survival in another population-based study, in which Geyer et al. (11) followed 1189 NHL patients diagnosed in the United States during 1998–2000 through 2007 and found that being obese (BMI ≥ 30) 1 yr before diagnosis was associated with 1.32 times the risk of death compared to normal weight. We observed a comparable borderline significant hazard ratio of 1.38 observed for baseline obesity before diagnosis.

Obesity probably affects cancer progression and prognosis through multiple biological mechanisms. For example, obesity is a proinflammatory state, and this promotes tumor growth (21,22). Obesity is associated with altered immune function (23), which is implicated in lymphomagenesis. Moreover, obesity is known to induce insulin resistance and elevated insulin levels, and insulin stimulates cell proliferation (24). Excess

TABLE 2
Adjusted hazard ratios (HRs) for death in relation to body mass index (BMI) categories and weight change status for non-Hodgkin lymphoma (NHL) cases, Connecticut, 1996–2000

	NHL overall			DLBCL			FL			CLL/SLL		
	No. deaths/cases	HR	No. deaths/cases	HR	No. deaths/cases	HR	No. deaths/cases	HR	No. deaths/cases	HR	No. deaths/cases	HR
Baseline BMI												
<18.5	5/6	2.84(1.12–7.15)	0/0		3/3	18.72(4.74–73.95)			0/1			
18.5–24.9	111/266	1	36/80	1	18/61	1			20/36			1
25–30	78/185	0.98(0.73–1.31)	27/65	0.70(0.41–1.20)	16/39	1.29(0.63–2.66)			9/18			2.43(0.92–6.42)
≥30	58/116	1.38(0.99–1.93)	21/37	1.77(0.98–3.21)	12/30	1.23(0.54–2.80)			4/8			0.91(0.22–3.81)
BMI before treatment §												
<18.5	6/9	0.98(0.39–2.43)	0/1		4/4	5.79(1.13–29.61)			0/2			
18.5–24.9	48/93	1	8/17	1	6/19	1			16/24			1
25–30	22/67	0.55(0.33–0.92)	1/6		11/28	0.80(0.24–2.65)			4/9			1.53(0.41–5.74)
≥30	17/49	0.62(0.34–1.12)	1/7		3/13	0.56(0.11–2.99)			0/6			
Prediagnostic weight change*												
<0	57/99	1.42(1.02–1.97)	13/24	1.02(0.51–2.02)	11/19	1.34(0.62–2.93)			9/12			6.63(1.59–27.62)
0	107/243	1	37/86	1	20/55	1			15/27			1
>0	73/176	1.04(0.77–1.41)	28/57	1.23(0.73–2.06)	14/45	0.60(0.27–1.32)			9/21			2.67(0.85–8.45)
Postdiagnostic weight change before treatment #												
<0	43/76	1.45(0.84–2.50)	6/15	1.64(0.18–14.76)	7/15	1.36(0.40–4.65)			12/17			1.34(0.34–5.31)
0	24/65	1	2/6	1	6/20	1			7/13			1
>0	26/77	0.99(0.56–1.76)	2/10		11/29	0.92(0.29–2.93)			1/11			
Postdiagnostic weight change after treatment §												
<0	67/126	1.98(1.14–3.45)	31/55	1.42(0.61–3.31)	6/15	1.17(0.20–6.95)			5/8			14.77(0.36–607.47)
0	17/64	1	8/23	1	3/15	1			1/5			1
>0	37/92	1.85(1.04–3.32)	16/39	1.44(0.60–3.49)	8/25	1.22(0.25–5.83)			5/5			1.01(0.04–22.69)

Models were adjusted for age, education, stage, B-symptom, initial treatment and smoking. DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; CLL/SLL = chronic lymphocytic leukemia/small lymphocytic lymphoma.

§ BMI at interview, only cases interviewed before treatment ($n = 218$) were included.

* Weight 1 yr prior to interview-usual weight, only cases interviewed within 1 yr after diagnosis ($n = 518$) were included.

Weight change = weight at interview-usual weight, only cases interviewed before treatment ($n = 218$) were included.

§ Weight change = weight at interview - usual weight, only cases interviewed after treatment ($n = 282$) were included.

TABLE 3

Adjusted hazard ratios (HRs) for death in relation to weight change by baseline weight status for non-Hodgkin lymphoma (NHL) cases, Connecticut, 1996–2000

	Normal weight ($18.5 \leq \text{BMI} < 25$)		Overweight ($25 \leq \text{BMI} < 29.9$)		Obese ($\text{BMI} \geq 30$)	
	No. of deaths/cases	HR	No. of deaths/cases	HR	No. of deaths/cases	HR
Prediagnostic weight change* (P interaction = 0.1800)						
<0	21/41	1.28(0.76–2.13)	23/33	2.51(1.38–4.55)	13/25	0.88(0.44–1.75)
0	55/126	1	22/63	1	26/50	1
>0	27/74	1.08(0.67–1.72)	30/69	1.19(0.68–2.08)	15/31	1.05(0.54–2.04)
Postdiagnostic weight change before treatment# (P interaction = 0.1475)						
<0	20/31	0.94(0.44–2.03)	14/30	2.33(0.84–6.44)	7/12	2.81(0.73–10.81)
0	13/31	1	6/23	1	4/10	1
>0	11/35	0.76(0.33–1.73)	12/25	2.38(0.86–6.61)	3/17	0.52(0.11–2.40)
Postdiagnostic weight change after treatment§ (P interaction = 0.0766)						
<0	29/58	3.49(1.42–8.55)	21/38	2.52(0.72–8.73)	16/29	0.60(0.23–1.54)
0	6/32	1	3/18	1	7/13	1
>0	20/49	3.52(1.39–8.91)	10/28	1.97(0.53–7.29)	7/12	0.67(0.23–1.97)

Models were adjusted for age, education, stage, B-symptom, initial treatment and smoking.

*Weight change = weight 1 yr prior to interview – usual weight. Only cases interviewed within one year after diagnosis ($n = 518$) were included.

Weight change = weight at interview – usual weight. Only cases interviewed before treatment ($n = 218$) were included.

§ Weight change = weight at interview – usual weight. Only cases interviewed after treatment ($n = 282$) were included.

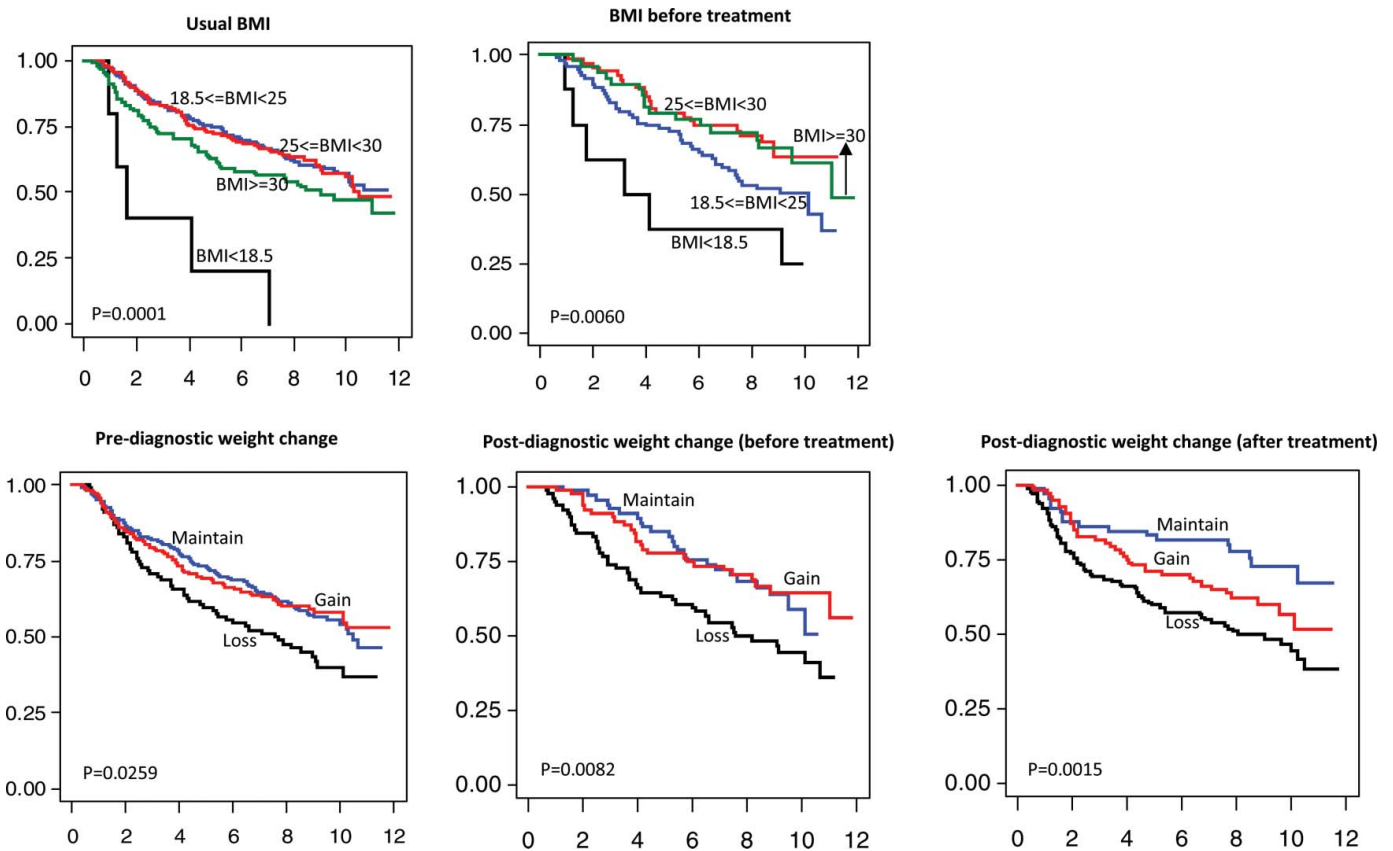


FIG. 1. Kaplan-Meier survival curves for non-Hodgkin lymphoma cases in Connecticut women and log-rank P-values (Color figure available online).

adipose tissue produces estrogen, which stimulates tumor growth and progression (25). Obesity is also associated with altered production of adipokines and other cytokines (e.g., adiponectin, leptin, IL-6, and tumor necrosis factor- α), and these factors can affect cell proliferation and cell survival (21).

We observed a high risk of death among patients who were underweight at baseline. Underweight people may have poor physical stamina, a weak immune system due to malnutrition and increased risk of comorbidities. They are also at risk of overdosing and greater toxicity from chemotherapy (26). Previous studies have linked being underweight to both overall and cancer-specific mortality (27–29), however, to our knowledge our study is the first to show poorer survival in underweight NHL patients. Although the associations observed here were extreme, our result should be viewed with caution because the number of underweight subjects was very small.

Studies examining the impact of overweight/obesity at the time of treatment on outcomes in lymphoma patients have been inconsistent (30), with some studies finding overweight/obesity associated with worse outcomes (31), some finding no association (32,33), and some finding it associated with improved outcomes (34). In our study, we did not have the weight at time of treatment. However, in analysis that limited subjects to only those who were interviewed before receiving any treatments, we were able to explore the relationship between postdiagnostic BMI before treatment and overall survival. We found that subjects who were overweight had significantly lower risk of death compared to normal weight subjects, and obese subjects did not show a worse survival. Our results support the argument that obesity alone does not predict poorer long-term treatment outcomes. Our findings need to be replicated in other populations.

Weight loss was associated with poorer survival compared to weight maintenance in our study. Although weight loss among overweight and obese people has been shown to reduce blood pressure and blood glucose and improve lipid profile and insulin sensitivity (35,36), unintentional weight loss has been linked to higher mortality risk (37) and can be a sign of many diseases including cancer (38–40). Furthermore, studies have shown that weight loss is associated with a decrease in the function aspects of the immune system (23,41,42). Currently immune dysregulation is the only established risk factor for NHL, and decreased immune function may also cause a worse prognosis among NHL patients. However, our study cannot exclude the effect of reverse causality on the observed associations between weight loss and poorer survival. This bias of reverse causality may obscure relationships between obesity, weight change, and mortality (43). The ability to differentiate intentional weight loss from weight loss due to health problems would help in evaluating the impact of reverse causality. Further research will be important to elucidate the true effect of weight loss on survival after cancer diagnosis.

Recent studies have shown that postdiagnosis weight change, both gain and loss, may be associated with a worse prognosis for patients with various cancer types such as breast cancer

(44–46), gastrointestinal cancer (45), and lung cancer (45). Similarly, in patients who already received treatment, we observed that both weight gain and weight loss were associated with reduced survival among NHL patients. Chemotherapy (47), psychological stress (48), and modifications in dietary intake and physical activities after diagnosis all could possibly disturb energy balance and cause weight variations. Two clinical studies from Taiwan and Serbia have examined the relationship between weight change during chemotherapy and survival (13,14), and both found weight gain during the 18-wk treatment regimen was associated with improved survival. However, these studies included a small number of cases (138 in the Taiwan study and 30 in the Serbia study) and did not adjust for other confounding variables or consider NHL subtypes. The Taiwan study did not differentiate weight loss and weight maintenance when making comparisons to weight gain. These clinical studies suggested a beneficial effect of weight gain during chemotherapy. In contrast, our results suggest that a stable weight might be best for cancer survivors. This difference may be due to combining weight losers and weight maintainers in the Taiwan study. Like our studies, none of the studies reviewed here can exclude the effect of reverse causality on the observed associations between weight loss and poorer survival.

The strengths of our study include a population-based sample, nearly complete follow-up, availability of several important clinical features such as disease stage and treatment information, and weight information at multiple time points around diagnosis. Self-reported anthropometric measurements were a potential limitation of our study. Although some studies (49) suggest that self-reported current anthropometric measures are highly correlated with measured values and therefore appropriate for epidemiologic studies, there are also studies showing that underreporting weight is associated with obesity in women (50) and this could bias our results. Differential recall of weight based on cancer severity is possible too and could result in an underestimation of the harmful effect of obesity and an overestimation of the effect of being underweight. Moreover, our results would have had a clearer clinical meaning if the reference time point of the weight assessment questions had been clearly defined as diagnosis or treatment. We had limited power for subtype analysis although notable patterns for NHL subtypes were still observed. We did not collect information on comorbidity and postdiagnostic lifestyle change such as dietary modification, thus were not able to control for the possible confounding effects from it. Finally, the generalizability of our study findings is limited because the population was restricted to women in Connecticut and the study sample included few ethnic minorities. Our findings may not apply to the very severe NHL cases, because 26% of the eligible cases were not enrolled in the study because of the severity of the disease (either they died before they could be interviewed or refused by physicians).

Our study found that being underweight or obese at baseline and weight loss before or after diagnosis was associated with reduced overall survival of NHL. Our findings highlight the

importance of maintaining a healthy body weight before and after developing NHL and avoiding weight fluctuations near the time of treatment. Our results warrant replication from studies of larger populations that include men and other racial and ethnic groups and a more detailed assessment regarding the intent of weight change.

ACKNOWLEDGMENTS

Dr. Han was supported by American Institute for Cancer Research Marilyn Gentry Fellowship. This research was funded by grant CA62006 from the National Cancer Institute (NCI) and by Hull Argall and Anna Grant 22067A from the Yale Cancer Center. This research was approved by the Department of Public Health Human Investigation Committee. Certain data used in this study were obtained from the Connecticut Department of Public Health. The authors assume full responsibility for analyses and interpretation of these data.

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