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Original Research Article

Adherence to lifestyle recommendations after non-muscle invasive bladder cancer diagnosis and risk of recurrence

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A B S T R A C T

Background: Patients with non-muscle invasive bladder cancer (NMIBC) are at a high risk of tumor recurrence. It has not been previously investigated if adherence to cancer prevention recommendations lowers the risk of recurrence.

Objectives: We examined whether the standardized lifestyle score measuring adherence to the 2018 World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) cancer prevention recommendations was associated with the risk of recurrence and progression among patients with NMIBC.

Methods: The study population included patients diagnosed with primary NMIBC between 2014 and 2017 from the prospective cohort UroLife. Lifestyle was assessed at baseline ($n = 979$; reflecting the prediagnosis period) and 3-mo postdiagnosis ($n = 885$). The standardized 2018 WCRF/AICR score was constructed based on recommendations for body weight, physical activity, diet, and alcohol intake. We computed multivariable-adjusted HRs and 95% CIs using Cox proportional hazard regression models.

Results: During a median follow-up time of 3.7 y, 320 patients developed ≥1 recurrence(s) and 49 experienced progression. Patients in the highest compared with the lowest tertile of postdiagnosis WCRF/AICR scores had a lower risk of first bladder cancer recurrence (HR: 0.74; 95% CI: 0.56, 0.98). No associations were observed for multiple recurrences (HR: 0.90; 95% CI: 0.70, 1.15) or for the baseline score with either first (HR: 1.07; 95% CI: 0.82, 1.40) or multiple recurrences (HR: 1.04; 95% CI: 0.82, 1.31). Improving lifestyle after diagnosis (per 1-point increase) was not significantly associated with the risk of first or multiple recurrence(s) (HR: 0.87; 95% CI: 0.74, 1.02; HR: 0.93; 95% CI: 0.80, 1.08, respectively). No associations were observed for bladder cancer progression, but the power was limited.

Conclusions: Better adherence to the WCRF/AICR cancer prevention recommendations 3 mo after NMIBC diagnosis, but not before diagnosis, is associated with a decreased risk of first bladder cancer recurrence. More studies evaluating postdiagnosis lifestyles are needed to provide solid support for lifestyle recommendations for cancer survivors.

Keywords: non-muscle invasive bladder cancer, recurrence, lifestyle, body mass index, physical activity, diet, alcohol

Introduction

Patients with non-muscle invasive bladder cancer (NMIBC) have a good 5-y survival (>90%) but are at a high risk of tumor recurrence [1,2]. This necessitates an intensive treatment and follow-up program that imposes a large burden on patients and healthcare resources [3].

To date, only a few studies have investigated whether lifestyle behaviors influence the risk of recurrence and progression in patients with NMIBC. Two meta-analyses of 10 studies concluded that current smokers with NMIBC diagnosis had a 23% to 27% increased risk of recurrence compared with never-smokers [4,5]. Similar, but slightly lower, risk estimates were reported for former smokers [4,5]. Another meta-analysis of 5 cohort studies concluded that obesity was associated with a 2-fold increased risk of recurrence and an 88% increased risk of progression compared with healthy weight patients with NMIBC [6]. Two reviews summarized the evidence for other lifestyle behaviors in

Abbreviations: CIS, carcinoma in situ; EAU, European Association of Urology; GT-UR, gap time – unrestricted; NMIBC, non-muscle invasive bladder cancer; SI, single instillation; SQUASH, Short Questionnaire to Assess Health enhancing physical activity; TURBT, transurethral resection of the bladder tumor; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research.

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relation to NMIBC prognosis [7,8]. They noted that no studies on physical activity have been published to date, and only few studies have evaluated dietary behaviors. An unhealthy ('Western') dietary pattern was associated with increased recurrence risk [9], whereas no associations were observed for fruits and vegetables, several nonalcoholic beverages, and alcohol intake [7,8]. A limitation of these studies is that they only examined single lifestyle behaviors and assessed lifestyle at 1 timepoint.

The current recommendations for cancer survivors emphasize the importance of adopting an overall healthy lifestyle rather than focusing on single lifestyle behaviors. These recommendations are the same as those for the general public to decrease the risk of cancer [10,11]. The 2018 World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) recommendations are to: *1*) achieve and maintain a healthy body weight; *2*) engage in regular physical activity; and *3*) achieve a dietary pattern high in vegetables, fruits, and whole grains while limiting fast foods, red and processed meat, and sugary drinks; and *4*) limiting alcohol consumption. Currently, no study has investigated whether an overall healthy lifestyle consistent with cancer prevention recommendations is associated with the risk of recurrence in patients with NMIBC.

Therefore, we investigated whether adherence to the WCRF/AICR recommendations is associated with the risk of recurrence and progression in patients with NMIBC. Furthermore, we examined whether a change in adherence to these recommendations after NMIBC diagnosis was associated with bladder cancer recurrence and progression.

Methods

Study design and population

We used data from the UroLife study, a prospective multicenter cohort study among patients diagnosed with primary NMIBC [12]. Patients were recruited in 22 hospitals in the Netherlands between May 2014 and April 2017. Eligible patients were identified through the Netherlands Comprehensive Cancer Organization using notification lists of the Pathological Anatomical National Automated Archive (PALGA Foundation). Patients were eligible when they were between 18 and 80 y old, Dutch speaking, diagnosed with a histologically confirmed primary stage Ta, T1, or Tis NMIBC tumor and underwent a transurethral resection of the bladder tumor (TURBT). Exclusion criteria are shown in Figure 1. Approximately 4 wk after diagnosis, the patients were invited to participate in the UroLife study. Patients who agreed to participate provided written informed consent. Data were collected through questionnaires approximately 6 wk, 3, 15, and 51 mo after diagnosis. In our current analyses, we only used data collected at 6 wk and 3 mo after diagnosis because 50% of all first recurrences occurred before the completion of the 15-mo questionnaires. Ethical approval was provided by the Committee for Human Research region Arnhem-Nijmegen (CMO 2013-494).

Lifestyle assessment

Information on body weight, physical activity, and diet was collected via self-reported web-based or paper-and-pencil-based questionnaires at baseline (enrollment 6 wk postdiagnosis) and at follow-up (3 mo postdiagnosis). Data collected at baseline were used to calculate the baseline lifestyle, while data collected at follow-up was used to calculate the postdiagnosis lifestyle score. BMI was calculated from current body weight (assessed at baseline and follow-up) and height (only assessed at baseline). Waist circumference was measured with a tape sent to the participants and was only available at follow-up. Physical activity was assessed using the validated Short Questionnaire to Assess Health enhancing physical activity (SQUASH) [13–19]. Participants were asked to report their average time (days per week, hours and minutes per day) spent walking, cycling, gardening, odd jobs, sports, household activities, and work [15]. The reference period was a normal week in the months before diagnosis (baseline) or the previous 3 mo (follow-up). Total minutes per week of moderate-to-vigorous physical activity were calculated based on summing leisure time (cycling, gardening, odd jobs, and sports with a metabolic equivalent value ≥ 3) and commuting (walking and cycling) activities but not household and work activities. Dietary intake was assessed using a 163-item validated semiquantitative FFQ developed by Wageningen University [20–22]. The reference period was the previous year (baseline) or the previous month (follow-up). In the baseline FFQ, fruit and vegetable intake were queried separately for summer and winter. To limit seasonal variability between baseline and follow-up, we calculated baseline fruit and vegetable intake based on reported intake in the season that matched the season of follow-up assessment. To assess the amount of food and beverage intake, we combined the frequencies of intake with portions based on standard portion sizes and household measures [20]. Intakes of dietary fiber and alcohol were calculated based on the 2011 Dutch Food Composition Database [23].

Lifestyle score

Overall lifestyle was assessed with the standardized 2018 WCRF/AICR score that reflects concordance with the WCRF/AICR cancer prevention recommendations [24,25]. The score includes recommendations concerning body weight, physical activity, diet, and alcohol intake (Table 1). Participants were allocated points for meeting, partially meeting, or not meeting each recommendation (maximum 1 point per recommendation), using cutoffs defined in the standardized scoring system. A total score was calculated by summing the points for each recommendation (range 0–7), with higher scores indicating better adherence to the WCRF/AICR recommendations. Our primary exposure was the 3-mo postdiagnosis lifestyle score, as patients can make changes to their postdiagnosis, but not baseline, lifestyle.

Outcome assessment

Information on recurrence and progression was collected from medical records by trained registrars from the Netherlands Cancer Registry in February/March 2021. Recurrence was defined as the first new bladder tumor after being tumor-free. The definition of being tumor-free differs by the presence of (concomitant) carcinoma in situ. In the case of Ta and T1 tumors, being tumor-free was defined by the date of radical TURBT (either primary TURBT or re-TURBT). In case of (concomitant) carcinoma in situ, being tumor-free was defined by the date of the first tumor-negative cystoscopy after TURBT. Progression was defined as the first occurrence of stage or grade progression or local or distant metastasis [27]. Patients were censored at *1*) last contact between the patient and urologist, *2*) radical cystectomy in the absence of recurrence/progression, *3*) diagnosis of another type of cancer with metastasis, or *4*) progression to muscle invasive bladder cancer (only in multiple recurrence analyses), whichever came first.

Covariate assessment

Sociodemographic information was self-reported at baseline. Smoking status (never, former, current) was reported at baseline (reflecting prediagnosis smoking) and follow-up (reflecting postdiagnosis smoking). The presence of 14 comorbidities at baseline was

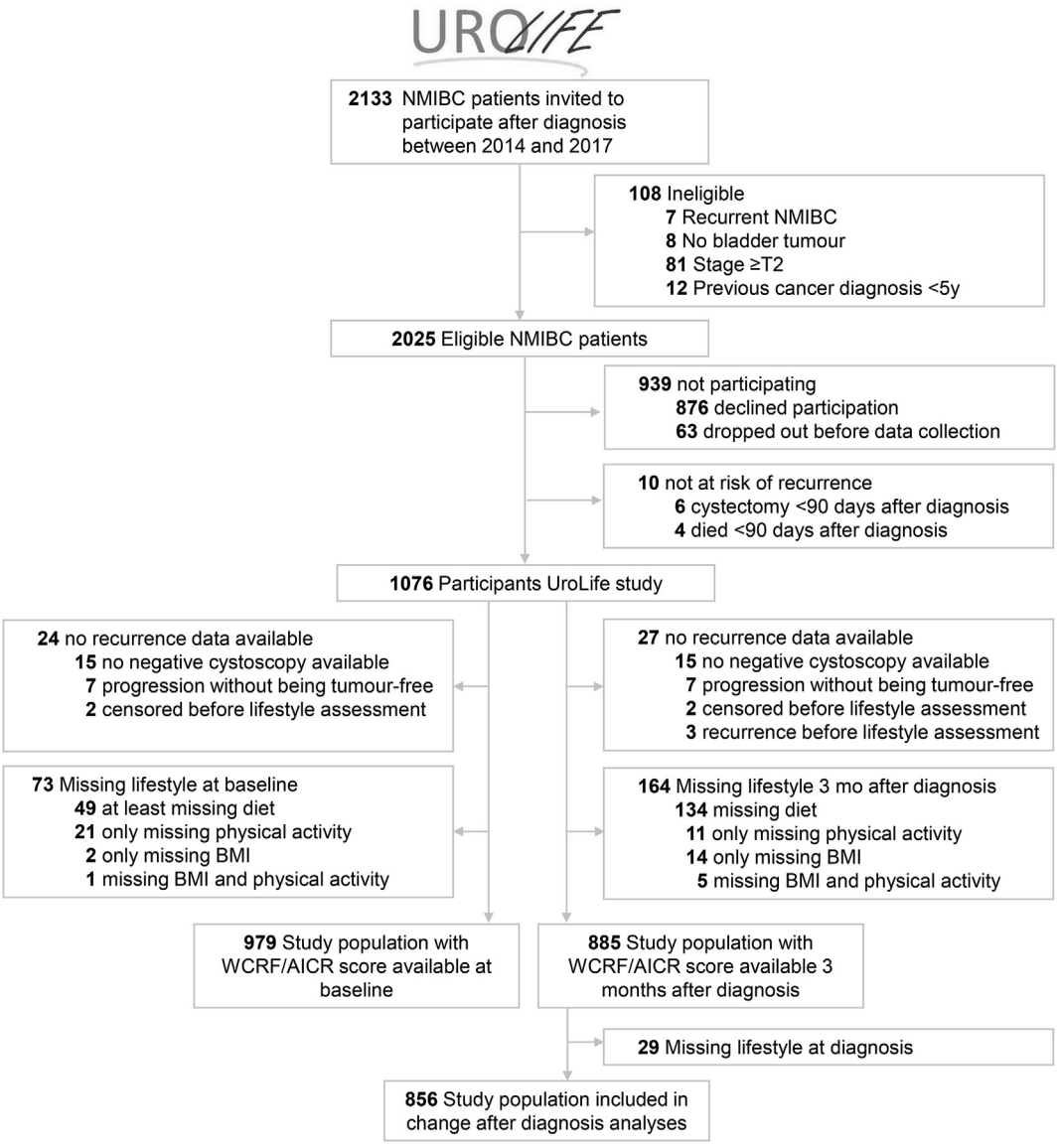

FIGURE 1. Flowchart representing patient selection for the current study. Abbreviations: NMIBC, non-muscle invasive bladder cancer; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research.

evaluated using an adapted version of the Self-administered Comorbidity Questionnaire [28]. Clinical data, such as tumor characteristics and treatment, were retrieved from medical records by data managers of the Netherlands Cancer Registry. Participants were divided into low, intermediate, and high-risk groups according to the European Association of Urology (EAU) guidelines based on stage, grade, concomitant carcinoma in situ, and focality [29], without considering the tumor size (not available) and the recurrent nature of the tumor (only primary tumors included).

Statistical analyses

The first recurrence was the primary endpoint; multiple recurrences and progression were used as secondary endpoints. Cox proportional hazard regression models were used to calculate HRs and 95% CIs with follow-up time in days as the underlying time metric. For recurrence, follow-up time started after baseline or follow-up questionnaire completion, respectively, or at the first day of being tumor-free, whichever came last. For progression, follow-up time began at the completion of the baseline or follow-up questionnaire, respectively. In addition, we analyzed multiple recurrences with an extended Cox model for recurrent event data (gap time – unrestricted [GT-UR] model with a random effect) [30,31]. As the recurrence-specific baseline hazards were similar for all recurrence numbers, we selected a model with a common baseline hazard; analysis time was reset at each recurrence. The GT-UR model has a slightly different HR interpretation compared with the well-known Cox model; HRs are the increase or decrease in recurrence risk since the last event (either primary tumor or previous recurrence).

The WCRF/AICR score was categorized into tertiles because no generally accepted cutoffs for the overall WCRF/AICR score exist and to ensure we had sufficient participants in each group. The tertiles with the lowest scores, indicating a lifestyle least consistent with the recommendations, were the reference groups for all analyses. To test for linear trends, the median score of each tertile was assigned to all participants within that category and entered as a continuous variable in the Cox models. Continuous analyses were conducted for 1-point increments. The models used to evaluate the baseline WCRF/AICR

TABLE 1
World Cancer Research Fund/American Institute of Cancer Research (WCRF/AICR) recommendations and adherence in patients with non-muscle invasive bladder cancer[1]

2018 WCRF/AICR recommendations	Operationalization of recommendations	Score	Adherence	
			At diagnosis	Postdiagnosis
			$n = 979$ (%)	$n = 885$ (%)
1. Be a healthy weight [2]	BMI (kg/m^2)			
	18.5 to <25	0.5	330 (34%)	294 (33%)
	25 to <30	0.25	460 (47%)	411 (46%)
	<18.5 or ≥30	0	189 (19%)	180 (20%)
	Waist circumference (cm)			
	<94 M and <80 F	0.5	-	199 (23%)
	94 to <102 M and 80 to <88 F	0.25	-	251 (29%)
	≥102 M and ≥88 F	0	-	429 (49%)
2. Be physically active	Moderate-to-vigorous PA[3] (min/wk)			
	≥150	1	823 (84%)	700 (79%)
	75–150	0.5	63 (6.4%)	65 (7.3%)
	<75	0	93 (9.5%)	120 (14%)
3. Eat a diet rich in wholegrains, vegetables, fruit, and beans	Fruit and vegetables (g/d) [4]			
	≥400	0.5	161 (16%)	82 (9%)
	200 to <400	0.25	428 (44%)	378 (43%)
	<200	0	390 (40%)	425 (48%)
	Total dietary fiber (g/d)			
	≥30	0.5	145 (15%)	139 (16%)
	15 to <30	0.25	706 (72%)	640 (72%)
	<15	0	128 (13%)	106 (12%)
4. Limit consumption of fast foods and other processed foods high in fat, starches or sugars	Percent of total kcal from ultraprocessed foods [5]			
	Tertile 1 (<26.7 energy%)	1	327 (33%)	226 (26%)
	Tertile 2 (≥26.7 to <36.36 energy%)	0.5	327 (33%)	294 (33%)
	Tertile 3 (≥36.36 energy%)	0	325 (33%)	365 (41%)
5. Limit consumption of red and processed meat	Red (g/wk) and processed meat (g/wk) [6]			
	Red meat ≤500 and processed meat <21	1	60 (6.1%)	79 (9%)
	Red meat ≤500 and processed meat 21 to <100	0.5	117 (12%)	129 (15%)
	Red meat >500 or processed meat ≥100	0	802 (82%)	677 (76%)
6. Limit consumption of sugar -sweetened drinks	Sugary drink (g/d) [7]			
	0	1	153 (16%)	199 (22%)
	>0 to ≤250	0.5	524 (54%)	453 (51%)
	>250	0	302 (31%)	233 (26%)
7. Limit alcohol consumption	Ethanol (g/d) [8]			
	0	1	157 (16%)	184 (21%)
	>0 to ≤10	0.5	314 (32%)	268 (30%)
	>10	0	508 (52%)	433 (49%)

Abbreviations: F, female; M, male; PA, physical activity.

[1] Following the standardized scoring system of the 2018 WCRF/AICR recommendations [24,25].

[2] Waist circumference was only available at 3-mo postdiagnosis. Therefore, waist circumference is excluded from the baseline and change scores. When data are only available for BMI, the subscore is doubled to retain the 0–1 point total range for the component.

[3] Moderate-to-vigorous physical activity includes leisure time (cycling, gardening, odd jobs, and sports with a metabolic equivalent value ≥ 3) and commuting (walking and cycling) activities.

[4] Fruits and vegetables excluding potatoes (starchy staple food) and juices.

[5] An adapted ultraprocessed food (aUPF) variable was created based on the NOVA classification on food processing [26]. The definition of aUPF was altered to exclude food items already included in other components of the score and to be in line with the definitions from the WCRF/AICR 2018 Third Expert Report and national guidelines. Calculated as energy intake from aUPF versus total energy intake; cutoffs were determined by cohort-specific tertiles at baseline. Ultra-processed foods included ready-to-eat/heat foods (e.g., French fries, pizza, soups, meat substitutes, cooking sauces, potato products, and fishfingers/fried fish), refined grains (e.g., white bread, pancakes, rice, pasta, and ready-to-eat breakfast cereals), snacks, sweets, and desserts (e.g., cakes, biscuits, confectionary, savory snacks, custard or pudding, ice cream, sugar added to coffee/tea, and diet drinks), spreads and sauces (e.g., peanut butter, chocolate spread, cream cheese, potato salad, mayonnaise, tomato ketchup), and some fats (hard margarine, solid cooking fats, frying fats). Not included were yogurt, soft margarine, liquid cooking fats, brown/whole meal bread, sugary drinks, and processed meat.

[6] Red meat included raw pork, beef, minced meat, fresh sausages, fresh hamburgers, liver, and game meat/other red meat. Processed meat included ready-to-eat/heat sausages, cold cuts/ham, and liver sausage/pate.

[7] Sugary drinks included sugar-sweetened soft drinks, sweet dairy drinks, and fruit juices. Not included were diet drinks, tea/coffee with added sugar, and alcohol-free beer. Consumption of up to 250 g/mo was defined as zero intake [25].

[8] Alcohol intake was based on alcoholic drinks (excluding alcohol-free beer). One drink corresponded to 10 g of ethanol. Consumption of up to 1 drink/mo was defined as zero intake [25]. Part of the alcohol subscore was based on national recommendations (limit to ≤10 g/d) [25].

scores were adjusted for age at baseline, sex, education level, comorbidities at baseline, EAU risk group, baseline smoking status, baseline energy intake, and initial treatment. In the models of postdiagnosis scores, we included the same covariates as in the analyses of baseline scores, except that smoking status and energy intake were obtained from the follow-up questionnaires. As waist circumference was included in the postdiagnosis score but not in the baseline score (not available), we also performed a sensitivity analysis in which the postdiagnosis score was calculated without including waist circumference. We also explored whether the associations between postdiagnosis lifestyle scores and risk of recurrence were modified by age, sex, postdiagnosis smoking status, EAU risk group, and initial treatment. The proportional hazards assumption was tested using Schoenfeld's global test. No statistically significant violations of this assumption were detected.

In addition, we evaluated the relative importance of each of the components of the postdiagnosis WCRF/AICR score for prognosis. First, we alternately subtracted 1 component at a time from the original score and included this component as a covariate in the model. Second, we performed analyses for each component separately by using the subscores of body weight, physical activity, diet, and alcohol while mutually adjusting for the other components.

For the change-after-diagnosis analyses, we calculated the difference between postdiagnosis and baseline lifestyle scores. The group with a change in lifestyle score of 0 served as the reference in the categorical models. Change models were adjusted for the same covariates as the postdiagnosis models, with the addition of baseline lifestyle score.

All analyses were performed in R version 3.6.2. The Cox models were fitted using the survival package v3.2.11 and the GT-UR models were fitted using the coxme package v2.2.16. P values ≤ 0.05 were considered statistically significant.

Results

Of the 2133 invited patients, 2025 were eligible, and 1076 (53%) agreed to participate (Figure 1). The final sample sizes were 979 for the baseline, 885 for the postdiagnosis, and 856 for the change-after-diagnosis analyses. The baseline characteristics of the study population are listed in Table 2. The mean age at NMIBC diagnosis was 67 y, 80% were male, and 76% had stage Ta disease. Regarding treatment, 50% of the participants underwent TURBT with or without a single instillation, 22% received chemotherapy instillations, and 28% BCG instillations. Participants included in the current analysis did not differ from invited nonparticipants with respect to age, sex, tumor stage, and tumor grade (data not shown). Lifestyle (both at baseline and 3-mo postdiagnosis) was suboptimal (Table 1 and 2). Although physical activity levels were generally high, adherence to dietary recommendations was low, 65% were overweight or obese, and 24% smoked at diagnosis.

During a median (IQR) follow-up time of 3.7 (1.6–4.4) y, 320 (36%) of the 885 patients developed $\geq$1 recurrence(s) of bladder cancer after completion of the follow-up questionnaires. A total of 120 (14%) of those patients developed $\geq$2 recurrences. Progression occurred in 49 (6%) of the participants.

Lifestyles at baseline

Highest vs. lowest baseline lifestyle scores were not associated with a lower risk of recurrence (Figure 2). The multivariable HRs were 1.07 (95% CI: 0.82, 1.40) for the first recurrence and 1.04 (95% CI: 0.82, 1.31) for multiple recurrences, respectively. Each 1-point increment in the WCRF/AICR score was associated with an HR for progression of 1.00 (95% CI: 0.72, 1.39) (Supplementary Table 1).

Postdiagnosis lifestyle

Highest vs. lowest postdiagnosis lifestyle scores were associated with a decreased risk of first recurrence (Figure 2). The multivariable HRs were 0.74 (95% CI: 0.56, 0.98) for the first recurrence and 0.90 (95% CI: 0.70, 1.15) for multiple recurrences, respectively. Each 1-point increment in the lifestyle score was associated with an HR for progression of 0.93 (95% CI: 0.68, 1.27) (Supplementary Table 1). There was little evidence of confounding by clinical characteristics, smoking status, and treatment compared with the model only accounting for age at diagnosis and sex because HRs were comparable between both models (Supplementary Table 1). In sensitivity analyses omitting waist circumference from the postdiagnosis score, HRs were similar to our main analyses, although statistically nonsignificant (Supplementary Table 2).

We found no statistically significant effect modification of the associations between postdiagnosis lifestyle score and the first recurrence by age, sex, smoking status, level of education, comorbidity at diagnosis, EAU risk group, stage, or initial treatment (Figure 3). Our effect estimates for each 1-point increment in the WCRF/AICR score did not change meaningfully when each component of the score was alternately removed (Supplementary Table 3). Body weight, physical activity, dietary, and alcohol subscores were not associated with recurrence risk (Supplementary Table 4).

Changes in lifestyle after diagnosis

The mean WCRF/AICR score was 3.3 at baseline and postdiagnosis. While the mean score remained constant over time, 284 participants increased their score after diagnosis, of which 124 increased their score by >0.5 points. The largest changes observed were a decreased consumption of red and processed meat and fruit and vegetables, as previously described in detail [32].

Each 1-point increase in the score after diagnosis tended to be associated with a lower risk of first recurrence ($HR_{highest\ vs\ lowest}$: 0.87; 95% CI: 0.74, 1.02; P for trend = 0.10), although the association was not statistically significant. No associations were observed for multiple recurrences and progression (Supplementary Table 5).

Discussion

In this prospective study among patients diagnosed with primary NMIBC, better adherence to the 2018 WCRF/AICR lifestyle recommendations 3 mo after diagnosis was associated with a decreased risk of first bladder cancer recurrence. The same tendency was observed for an improvement in the WCRF/AICR lifestyle score after diagnosis, although these associations were statistically nonsignificant. Lifestyle at baseline was not associated with recurrence risk. No associations were observed for multiple recurrence and bladder cancer progression.

To our knowledge, we are first to examine the association between an overall healthy lifestyle score and recurrence among patients with NMIBC. Several studies have examined BMI, and only few studies have examined other single lifestyle behaviors in relation to NMIBC prognosis [7,8]. These studies among patients with NMIBC concluded that obesity and an unhealthy ('Western') dietary pattern were associated with an increased risk of recurrence and progression [6,9]. No

TABLE 2
Population characteristics of patients with non-muscle invasive bladder cancer at baseline (n = 979) and 3 mo postdiagnosis (n = 885)

	Baseline			Postdiagnosis		
	WCRF/AICR score			WCRF/AICR score		
	0–2.75	3.0–3.5	3.75–7.0	0–2.75	3.0–3.5	3.75–7.0
n	330	339	310	324	293	268
Age at baseline, y	65 (58, 71)	68 (63, 72)	68 (62, 74)	66 (59, 72)	68 (63, 73)	68 (62, 72)
Men	279 (85%)	276 (81%)	231 (75%)	269 (83%)	233 (80%)	202 (75%)
Education						
Low	163 (49%)	171 (50%)	148 (48%)	163 (50%)	138 (47%)	120 (45%)
Intermediate	91 (28%)	87 (26%)	81 (26%)	87 (27%)	79 (27%)	72 (27%)
High	76 (23%)	81 (24%)	81 (26%)	74 (23%)	76 (26%)	76 (28%)
Stage						
Tis	8 (2.4%)	11 (3.2%)	5 (1.6%)	10 (3%)	7 (2.4%)	6 (2.2%)
Ta	258 (78%)	256 (76%)	235 (76%)	244 (75%)	216 (74%)	210 (78%)
T1	64 (19%)	72 (21%)	70 (23%)	70 (22%)	70 (24%)	52 (19%)
Grade[1]						
Low	220 (67%)	215 (64%)	195 (63%)	206 (64%)	183 (63%)	173 (65%)
High	108 (33%)	123 (36%)	115 (37%)	118 (36%)	108 (37%)	94 (35%)
Concomitant CIS	15 (4.5%)	30 (8.8%)	26 (8.4%)	18 (6%)	27 (9.2%)	17 (6.3%)
Multifocal tumor[2]	100 (30%)	98 (29%)	92 (30%)	111 (34%)	79 (27%)	75 (28%)
EAU risk group						
Low	48 (15%)	61 (18%)	66 (21%)	46 (14%)	58 (20%)	50 (19%)
Intermediate	157 (48%)	141 (42%)	118 (38%)	141 (44%)	112 (38%)	114 (43%)
High	125 (38%)	137 (40%)	126 (41%)	137 (42%)	123 (42%)	104 (39%)
Initial treatment						
TURBT only	74 (22%)	63 (19%)	53 (17%)	53 (16%)	57 (19%)	55 (21%)
TURBT + single instillation[3]	109 (33%)	100 (29%)	98 (32%)	104 (32%)	90 (31%)	84 (31%)
TURBT + Chemotherapy instillations	76 (23%)	77 (23%)	68 (22%)	81 (25%)	59 (20%)	56 (21%)
TURBT + BCG	71 (22%)	99 (29%)	91 (29%)	86 (27%)	87 (30%)	73 (27%)
Comorbidity at baseline						
0	45 (14%)	52 (15%)	53 (17%)	45 (14%)	44 (15%)	44 (16%)
1	75 (23%)	82 (24%)	87 (28%)	79 (24%)	76 (26%)	73 (27%)
≥2	210 (64%)	205 (60%)	170 (55%)	200 (62%)	173 (59%)	151 (56%)
Smoking status [4]						
Never	54 (16%)	54 (16%)	63 (20%)	45 (14%)	60 (20%)	52 (19%)
Former	188 (57%)	211 (62%)	173 (56%)	220 (68%)	198 (68%)	170 (63%)
Current	88 (27%)	74 (22%)	74 (24%)	59 (18%)	35 (12%)	46 (17%)
WCRF/AICR scores [4,5]	2.32 (0.43)	3.28 (0.20)	4.24 (0.53)	2.28 (0.43)	3.26 (0.20)	4.28 (0.55)
BMI [4], kg/m^2	28.3 (26.0, 31.1)	26.3 (24.6, 28.4)	24.5 (23.1, 26.7)	27.8 (25.7, 31.0)	26.4 (24.4, 28.4)	24.6 (22.9, 27.0)
Physical activity [4], min/wk	360 (120, 851)	630 (312, 1080)	630 (300, 1080)	270 (60, 630)	510 (270, 1020)	550 (240, 960)
Dietary component [4]						
Fruits and vegetables, g/d	176 (114, 265)	250 (174, 346)	300 (202, 418)	162 (106, 229)	224 (147, 287)	269 (174, 379)
Dietary fiber, g/d	20 (16, 25)	22 (17, 26)	23 (18, 30)	20 (16, 24)	21 (17, 25)	23 (19, 29)
Processed foods, energy%	37 (30, 43)	31 (25, 37)	26 (21, 34)	37 (32, 43)	34 (26, 41)	30 (23, 36)
Red and processed meat, g/wk	729 (562, 962)	703 (519, 896)	542 (339, 797)	673 (493, 848)	606 (439, 806)	503 (297, 733)
Sugary drink, g/d	253 (72, 417)	110 (26, 257)	49 (7, 178)	196 (57, 406)	101 (19, 216)	32 (0, 165)
Alcohol intake [4]						
Nondrinker [6]	28 (9.0%)	39 (12%)	90 (29%)	32 (10%)	55 (19%)	97 (36%)
Alcohol among drinkers, g/d	16 (8, 29)	13 (5, 24)	11 (5, 25)	14 (7, 25)	14 (6,27)	10 (4, 24)
Alcohol among all, g/d	14 (4, 27)	11 (3, 22)	6 (0, 18)	13 (4, 24)	11 (2, 24)	4 (0, 14)
Total energy intake [4], kcal/d	2356 (1934, 2714)	2213 (1729, 2589)	2117 (1726, 2526)	2138 (1708, 2547)	2,020 (1658, 2472)	2,011 (1637, 2414)

Abbreviations: CIS, carcinoma in situ; EAU, the European Association of Urology; TURBT, transurethral resection of the bladder tumor; WCRF/AICR, World Cancer Research Fund/American Institute of Cancer Research.

Values are medians (IQRs) or n (%), except where indicated otherwise.

[1] Data of 3 participants were missing/unknown.

[2] Data were missing/unknown for 7 participants at baseline and 6 participants postdiagnosis.

[3] Single chemotherapy instillation within 1 d after TURBT.

[4] Variables derived from questionnaires corresponding to baseline or postdiagnosis lifestyle assessment.

[5] mean ± SD

[6] Alcohol intake of up to 10 g/mo was defined as zero intake [25].

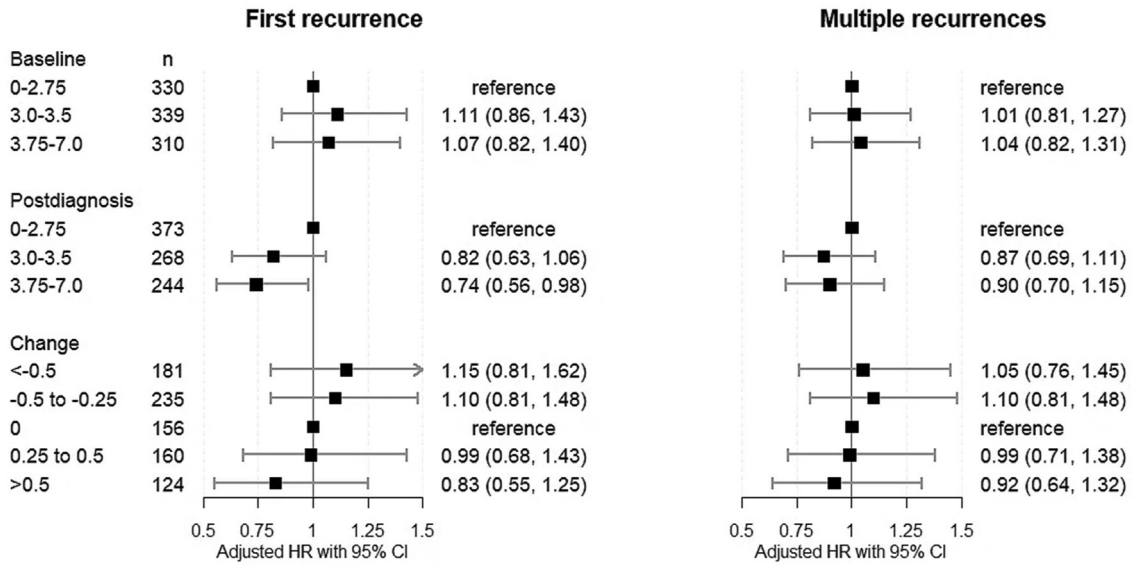

FIGURE 2. Multivariable HRs and 95% CIs of first recurrence and multiple recurrences for the baseline or 3-mo postdiagnosis WCRF/AICR lifestyle scores and the change after NMIBC diagnosis. Cox proportional hazards models were adjusted for age at baseline, sex, education, postdiagnosis smoking status, comorbidities at baseline, postdiagnosis energy intake, EAU risk group (based on tumor characteristics), and initial treatment. Range change score <-0.5: -2.25 to -0.75; and >0.5: 0.75 to 3.25. Abbreviations: EAU, European Association of Urology; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research.

associations were observed for fruit and vegetables [33], several sugary drinks [34], and alcohol intake [34], while no studies on physical activity and recurrence have been published to date. The current study found no associations with recurrence risk for the subscores for body weight, physical activity, diet, and alcohol. Several studies have showed that an overall healthy lifestyle score in the general population impacts the incidence of several cancer types [35,36], but only 2 previous studies, both conducted among colorectal cancer survivors, assessed the associations with cancer recurrence [37,38]. One study concluded that a healthy lifestyle after diagnosis was associated with a lower risk of recurrence [38], whereas the other reported a null finding [37]. Given the lack of studies on lifestyle and cancer recurrence, further studies exploring this association are warranted.

The inconsistent associations with recurrence for baseline and postdiagnosis lifestyle might be explained by the recurrence mechanisms of NMIBC [39] of which some might be altered by lifestyle. A healthy lifestyle after diagnosis, but not necessarily before diagnosis, could impact reimplantation of tumor cells after TURBT and/or impact field cancerization (early genetic changes in a bladder epithelium field). A healthy lifestyle after diagnosis may prevent tumor reimplantation by immune-stimulating effects or occurrence of new bladder tumors from the bladder epithelium with early genetic changes. Furthermore, a healthy lifestyle after diagnosis may also improve the treatment response to BCG therapy by enhancing the immune-stimulating effect of BCG therapy [39]. The inconsistent associations cannot be explained by the inclusion of waist circumference in the postdiagnosis score, as omitting the waist circumference from the postdiagnosis score showed similar HRs as for our main analyses (although HRs were not statistically significant anymore).

We observed no associations between the postdiagnosis score and the risk of multiple recurrences. We had expected to find similar HRs compared to our analyses regarding the risk of first recurrence, but with narrower 95% CIs, because we had more power by including all recurrences that occurred during follow-up. We hypothesize that the risk of recurrence in people experiencing multiple recurrence cannot be altered by lifestyle. However, with our current sample size, we had insufficient power to test whether associations differ for patients experiencing 1 compared with multiple recurrences. Furthermore, we had limited statistical power for the outcome progression, which may explain why no associations were observed for stage/grade progression. Additional larger, population-based studies among patients with NMIBC should also include multiple recurrences and progressions as outcomes to further examine the role of lifestyle in the management of recurrence and progression risk.

For cancer patients and their caregivers, it is important to know whether changing one's lifestyle after diagnosis can lower the risk of recurrence. This was the first study that examined the association between changes in overall lifestyle after NMIBC diagnosis and recurrence. An improvement in lifestyle score after diagnosis may be associated with a lower risk of recurrence. However, associations for the change-after-diagnosis analyses were not statistically significant in the current study. Additional studies are needed to further examine whether a healthy lifestyle after NMIBC diagnosis and changes therein can impact the prognosis. Even if adherence to the WCRF/AICR cancer prevention recommendations is not associated with cancer recurrence, a healthy lifestyle may still be beneficial for cancer survivors as body weight, diet, and physical activity are key modifiable risk factors for managing cardiovascular risk profiles, risk of second cancer, and mortality among cancer survivors [35–38,40–42].

Our study has several limitations. First, although we used the previously validated questionnaires for Dutch populations [13,15,20–22], our self-reported lifestyle data may be subject to measurement errors. However, this likely minimally impacted the results because measurement error is expected to be similar in patients with and without events. Second, the baseline lifestyle was assessed 6 wk after diagnosis and may have been influenced by the cancer itself. However, we think this is unlikely because NMIBC is an early-stage cancer that either causes mild complaints (blood in the urine, irritation during voiding, or

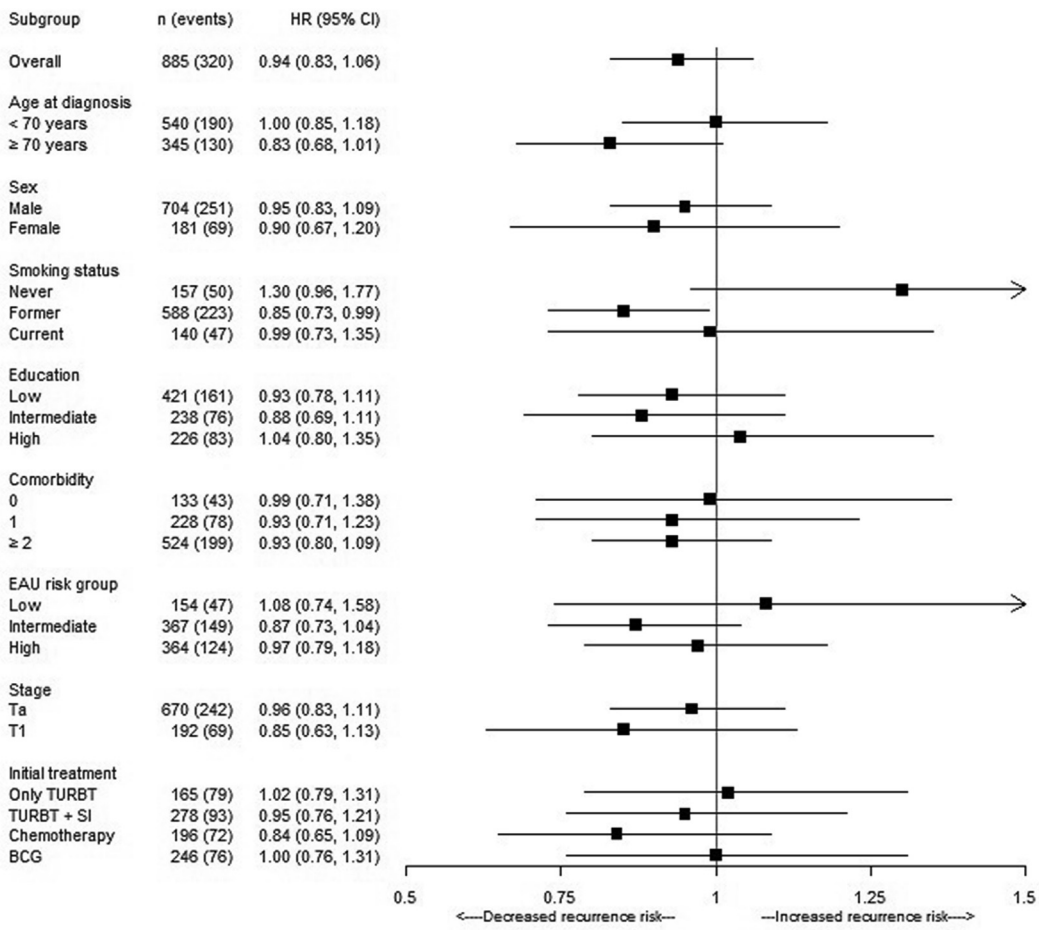

FIGURE 3. Multivariable HRs and 95% CIs of first recurrence per 1-point increase in the postdiagnosis WCRF/AICR lifestyle score, stratified by age at diagnosis, sex, smoking status, EAU risk group, and initial treatment. Cox proportional hazards models were adjusted for age at baseline, sex, education, postdiagnosis smoking status, comorbidities at baseline, postdiagnosis energy intake, EAU risk group (based on stage, grade, CIS, multifocality), and initial treatment (TURBT only, single instillation, chemotherapy, BCG), except in models stratified by these variables. Abbreviations: IS, carcinoma in situ; EAU, European Association of Urology; SI, single instillation (of chemotherapy); TURBT, transurethral resection of the bladder tumor; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research.

frequent voiding) or no complaints at all. Postdiagnosis lifestyle was assessed 3 mo after NMIBC diagnosis and might be affected by treatment and/or does not reflect the lifestyle later during the cancer trajectory. However, adjustment for treatment did not change our risk estimates, and we previously found that the lifestyle was relatively stable between 3 and 15 mo after NMIBC diagnosis [32]. Third, we did not perform competing risk analyses, although death could prevent a recurrence diagnosis. As only 72 people died without recurrence within 5 years after diagnosis, it seems unlikely that our observed associations would be affected by the competing risk of death. Fourth, we had limited statistical power for the outcome progression. Finally, as with all observational studies, we cannot eliminate the possibility of residual confounding even though we were able to control for clinical characteristics, cancer treatment, and smoking status in our analyses.

Strengths of the current study include its prospective design and the use of a validated, comprehensive FFQ. Furthermore, a unique feature of our study was the ability to evaluate changes in lifestyle after diagnosis due to the repeated assessment of lifestyle factors. Patients with NMIBC included in the current analysis did not differ from eligible invited nonparticipants with respect to age, sex, and tumor characteristics, but we do not know whether they differed in lifestyle. It should be noted that ~10% of our study population was excluded from the postdiagnosis analyses, as they only completed the baseline questionnaires. They had slightly lower WCRF/AICR scores at baseline than those who completed questionnaires at both timepoints (3.0 vs. 3.3).

In conclusion, better adherence 3 mo after NMIBC diagnosis, but not before diagnosis, to the 2018 WCRF/AICR cancer prevention recommendations on diet, physical activity, and body fatness was associated with a lower risk of first recurrence. No associations were observed for the risk of multiple recurrences and stage/grade progression. Additional studies evaluating postdiagnosis diet and lifestyle are needed to provide solid support for lifestyle recommendations for cancer survivors.

Conflict of intrest

The authors declare no conflict of interest. The funding sources had no role in the study design and conduct, data analysis, or manuscript preparation.

Data Availability

Data described in the manuscript, code book, and analytic code will be made available upon request pending application to and approval from the corresponding author AV.

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Author contributions

The authors' responsibilities were as follows — AV, EK, LALMK, MvZ: designed the research; MvZ, JH: conducted the research; JAW, KKHA: provided subjects or clinical data; MvZ performed statistical analysis; MvZ wrote the draft manuscript; MvZ, AV: had primary responsibility for the final content; and all authors: read and approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2022.12.022.

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