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Adherence to cancer prevention recommendations and risk of breast cancer in situ in the United Kingdom Biobank

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Abstract

A health-conscious lifestyle may protect against breast cancer in situ. However, breast cancer in situ is mainly detected by screening, and many studies lack information on screening participation. Thus, we evaluated the association between prediagnostic lifestyle and risk of breast cancer in situ, accounting for screening participation at recruitment. A score reflecting the adherence to the World Cancer Research Fund/American Institute for Cancer Research cancer prevention recommendations was constructed, using the recommendations on healthy body weight, physical activity, consumption of plant-based foods, red and processed meat, alcohol and avoidance of sugar. Cox proportional hazards regression models were used to investigate the association between the lifestyle score and breast cancer in situ risk, while accounting for important confounders. The lifestyle score was not significantly associated with breast cancer in situ risk ($HR_{continuous} = 0.96$, 95% CI = 0.91-1.03) in the overall cohort. In participants not reporting dietary changes in the past 5 years, the lifestyle score was inversely associated with breast cancer in situ risk ($HR_{continuous} = 0.92$, 95% CI = 0.85-0.99). In those reporting dietary changes in the past 5 years due to illness or other reasons, the lifestyle score was not associated with breast cancer in situ risk ($HR_{continuous} = 1.04$, 95% CI = 0.94-1.15). Lifestyle was inversely associated with breast cancer in situ risk in women not reporting recent changes in their dietary habits. This inverse association is consistent with inverse associations reported in previous studies. Our findings suggest that breast cancer in situ and invasive breast cancer share a similar risk factor profile.

KEYWORDS
breast cancer in situ, cancer, cohort, lifestyle, prevention, score

What's new?

Breast cancer in situ accounts for approximately one-fifth of breast cancers. While lifestyle factors likely contribute to this relatively high incidence, the relationship between breast cancer in situ and lifestyle remains unclear. In this analysis of data from the UK Biobank, higher lifestyle

Abbreviations: AICR, American Institute for Cancer Research; BMI, body mass index; CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio; UK, United Kingdom; WCRF, World Cancer Research Fund.

score was inversely associated with breast cancer in situ risk. The inverse relationship was notably prominent among women who lacked changes in dietary habits within the past 5 years. The findings suggest that a healthy lifestyle lowers breast cancer in situ risk and highlight similarities in risk factor profile between breast cancer in situ and invasive disease.

1 | INTRODUCTION

The incidence of breast cancer in situ has been increasing for the past couple of decades, with most studies attributing this increase to the widespread adoption of mammography use.[1] Women with breast cancer in situ rarely report symptoms and thus most breast cancer in situ tumors are detected through organized or opportunistic breast cancer screening.[2] Breast cancer in situ nowadays accounts for approximately 20% of all breast cancers (overall estimate, depending on country and study year) diagnosed via mammography.[3] Despite the observed increase in its incidence, however, little is known about potentially modifiable risk factors for breast cancer in situ.

Few studies so far have investigated the association between individual modifiable lifestyle factors and breast cancer in situ risk. Alcohol intake and smoking were associated with a nonstatistically significant increased risk for breast cancer in situ in postmenopausal women.[4] Higher body mass index (BMI) has been linked with a statistically significant decreased risk for breast cancer in situ in premenopausal women.[5] Conflicting findings have been reported on the relationship between physical activity and breast cancer in situ. No association was observed in two studies,[6,7] while one indicated an inverse association.[8]

When focusing on individual lifestyle factors and their association with health outcomes, the potential synergistic or agonistic effect between them that could modify the overall association between lifestyle and disease risk may be overlooked. To overcome this, a commonly used approach in nutritional epidemiology is to translate the health-promoting nutrition/ lifestyle recommendations from health organizations or combine multiple lifestyle factors into scores and use them when investigating the association with health outcomes.[9-12] When investigating the risk for cancer, the cancer prevention recommendations issued by the World Cancer Research Fund and the American Institute for Cancer Research (WCRF/AICR) have been widely used and linked to lower risk for various cancers.[13-16]

To date, the only comprehensive analysis on prediagnostic lifestyle, using the WCRF/AICR cancer prevention recommendations and breast cancer in situ risk, examining the association in the European Prospective Investigation into Nutrition and Cancer (EPIC) cohort, showed an inverse association with lifestyle limited to women recruited via breast cancer screening programs in selected study centers.[17] However, due to the lack of comprehensive assessment of breast cancer screening attendance in the EPIC study, it was impossible to look into this association in all women, who had a mammogram.

In this study, we examined the association between prediagnostic lifestyle, operationalized as an adherence score to established cancer prevention recommendations and breast cancer in situ risk in the United Kingdom (UK) Biobank cohort, adjusting for self-reported breast cancer screening attendance at study recruitment.

2 | METHODS

2.1 | Study population and data collection

The UK Biobank cohort is a large, population-based prospective study. Between 2006 and 2010, over 500 000 participants entered the study throughout the UK, covering various settings to provide socioeconomic, ethnic and residential heterogeneity. Detailed information on the study design, methods and rationale of the cohort has been previously reported.[18] We conducted this study under application number 55149 using the UK Biobank Resource.

In the present study, only female participants of the UK Biobank were included. Women with prevalent cancers at study enrollment ($n = 18\,448$), women who withdrew their consent to participate in the study ($n = 54$), women who were pregnant or unsure of their pregnancy status at study enrollment ($n = 366$) and women with missing data on any of the lifestyle factors relevant for the cancer prevention recommendations (see below in detail, $n = 21\,667$) were excluded. Therefore, 232 848 women were included in the final analytical sample.

2.2 | Exposure assessment

At the UK Biobank assessment centers, participants provided medical, dietary and lifestyle data, including information on alcohol use, smoking status, physical activity, education, reproductive history, hormone use and previous illnesses via a touchscreen questionnaire. Physical measurements were also taken, and participants provided blood and urine samples.

The touchscreen questionnaire asked about the frequency of food consumption over the past year via 29 questions. The following items were assessed: cooked vegetables, salad/raw vegetables, fresh fruit, dried fruit, oily fish, other fish, processed meats, poultry, beef, lamb, pork, cheese, salt added to food, tea and water. Additionally, the touchscreen questionnaire included questions on the type of milk and spread most commonly consumed, number of slices and type of bread most commonly consumed, number of bowls and type of breakfast cereal most commonly consumed, cups of coffee and type most commonly consumed. Finally, it inquired about the avoidance of specific food groups (eggs or foods containing eggs, dairy products, wheat products, sugar or foods/drinks containing sugar), the age when the participant last ate meat, the preferred temperature of hot drinks, changes in diet in the past 5 years and variation in diet.

The touchscreen questionnaire also asked participants to estimate the number of days in a typical week they engage in moderate and vigorous physical activity, as well as the typical duration of these activities (in minutes; separate questions for moderate and vigorous activities) on a typical day.

2.3 | Adherence to cancer prevention recommendations

We constructed a score reflecting adherence to the WCRF/AICR cancer prevention recommendations. Of the eight recommendations utilized in the standardized scoring system,[19] we used those reflecting healthy body weight, physical activity, consumption of plant-based foods, red and processed meat and alcohol for the construction of the score in our study. Due to the lack of information on the consumption of sugary drinks in the complete UK Biobank cohort, we constructed a binary variable to reflect self-reported avoidance of sugar, based on the question "Which of the following do you never eat?," with possible answers including eggs or foods containing eggs, dairy products, wheat products, sugar or foods/drinks containing sugar. Due to the lack of detailed information on all food groups contributing fiber to the diet, a partial fiber score was created, as previously reported.[20] In short, the fiber contribution from bread, breakfast cereal, fruit and vegetables was estimated by multiplying the fiber content by the frequency of consumption for each food, taking into account the different fiber content of various bread and breakfast cereal types. The fiber contribution from bread, breakfast cereal, fruit and vegetables was then summed to get a daily partial fiber score. The cancer prevention recommendations on breastfeeding, supplement use and the consumption of highly processed foods, as well as the one relevant for cancer survivors were not utilized due to the lack of detailed information.

We based our scoring as much as possible on the standardized scoring system proposed recently by a group including researchers from the WCRF and the AICR.[11] Detailed information on the scoring of individual components used in the present study can be found in Table S1. The scoring was constructed such that each recommendation contributed equally to the total lifestyle score. The score ranged from 0 to 6, with higher scores reflecting greater adherence to the cancer prevention recommendations. The score was additionally categorized into three groups: low adherence (<2 points), moderate adherence (2-4 points) and high adherence (≥4 points).

2.4 | Case ascertainment

Cohort participants were followed using record linkage and incident cancer cases were identified through national cancer registries. First primary incident breast cancer in situ cases were coded according to the 10th Revision of the International Classification of Disease (D05, ICD-10). In analyses focusing on the subtypes of breast cancer in situ, subtypes were defined based on ICD-10 codes as follows: intraductal carcinoma in situ (D05.1), lobular carcinoma in situ (D05.0), other carcinoma in situ of the breast or unspecified carcinoma in situ (D05.7 and D05.9, respectively). Women diagnosed with more than one subtype on the same date, were not considered in the stratified analyses by subtypes, but were included in the overall analyses.

2.5 | Statistical analyses

Baseline categorical data were expressed as percentages and continuous data as mean and SD.

To explore the association between the cancer prevention recommendations and breast cancer in situ risk, we applied Cox proportional hazards regression. Entry time was participants' age at recruitment in the study and exit time was the age when participants were diagnosed with cancer (breast cancer in situ or other cancer), died, were lost to follow-up or were censored at the end of the follow-up period, whichever came first. All analyses were stratified by age at recruitment (5-year intervals), Townsend Deprivation Index (used as adjustment for the socio-economic status of the study participants; quintiles) and recruitment region (10 regions). The results were presented as hazard ratios (HR) and their corresponding 95% confidence intervals (CI). Regarding adjustment for confounding, Model 1 was conditioned on the highest level of attained education (none of the above, Certificate of Secondary Education [CSEs]/General Certificate of Education Ordinary level [O-levels]/General Certificate of Secondary Education [GCSEs] or equivalent, National Vocational Qualification [NVQ]/Higher National Diploma [HND]/Higher National Certificate [HNC]/General Certificate of Education Advanced level [A-levels]/General Certificate of Education Advanced Supplementary level [AS-levels] or equivalent, Other professional qualifications, College/University degree, Prefer not to answer/Missing) and smoking status (never, past, current, prefer not to answer/missing); Model 2 was additionally adjusted for age at menarche (< 13 years, ≥ 13 years, missing), age at first full-term pregnancy (nulliparous, < 25 years, ≥ 25 years, missing), menopausal status (premenopausal, postmenopausal [also including surgical postmenopausal], prefer not to answer/missing), ever use of oral contraceptive pills (yes, no, prefer not to answer/do not know/missing) and ever use of menopausal hormone therapy (yes, no, prefer not to answer/do not know/missing); Model 3 was further adjusted for first degree family history for breast cancer (no, yes, prefer not to answer/do not know/missing), breast cancer screening attendance (no, yes, prefer not to answer/do not know/missing) and time since last screening (never, less than a year, 1-3 years, >4 years, prefer not to answer/do not know/missing).

In UK Biobank, the availability of self-reported information on dietary changes in the past 5 years allowed us to classify participants according to dietary changes and investigate the association separately in those groups. Information on breast cancer screening attendance prior to study recruitment allowed not only for confounder adjustment as described above but also for stratification of the analyses by breast cancer screening attendance (no, yes, prefer not to answer/do not know/missing). Further a priori selected stratifications

TABLE 1 Baseline characteristics of the study population, overall and by self-reported dietary changes in the past 5 years

	Total (n = 232 848)	No dietary changes in the past 5 years (n = 137 479)	Dietary changes in the past 5 years, due to illness or other reasons (n = 94 981)	Prefer not to answer/ unknown/missing (n = 388)
WCRF/AICR lifestyle score including sugar, mean (SD)	2.96 (1.03)	2.93 (1.04)	3.00 (1.03)	2.57 (1.03)
Age at recruitment, mean (SD)	56.01 (8.01)	55.96 (8.11)	56.10 (7.87)	55.51 (8.50)
Highest level of attained education, %				
None of the following	15.08	14.49	15.88	27.84
CSEs/O-levels/GCSEs or equivalent	28.06	28.86	26.93	20.62
NVQ/HND/HNC/A-levels/AS-levels or equivalent	14.85	14.32	15.60	18.04
Other professional qualifications	30.04	29.92	30.27	16.75
College/university degree	10.87	11.40	10.13	6.44
Prefer not to answer/missing	1.10	1.01	1.20	10.31
Smoking status, %				
Never smokers	59.64	60.75	58.04	60.57
Former smokers	31.36	30.04	33.30	25.00
Current smokers	8.72	8.96	8.36	11.08
Prefer not to answer/missing	0.28	0.25	0.29	3.35
Menopausal status, %				
Premenopausal	25.15	26.53	23.15	24.74
Postmenopausal	70.95	69.72	72.75	66.75
Prefer not to answer/missing	3.90	3.75	4.11	8.51
Ever use of oral contraceptive pills, %				
Yes	81.89	81.84	82.01	71.65
Do not know/prefer not to answer/missing	0.23	0.22	0.24	3.61
Ever use of menopausal hormone therapy, %				
Yes	37.46	35.67	40.06	35.05
Do not know/prefer not to answer/missing	0.29	0.25	0.34	2.06
Age at menarche, %				
<13 years	37.84	36.22	40.18	35.05
≥13 years	59.42	60.94	57.25	55.41
Do not know/prefer not to answer/missing	2.74	2.84	2.57	9.54
Age at first full-term pregnancy, %				
Nulliparous	18.93	19.18	18.56	21.13
<25 years	29.74	27.91	32.37	36.86
≥25 years	51.25	52.84	49.00	41.49
Unknown/missing	0.08	0.08	0.08	0.52
First degree family history for breast cancer, %				
Yes	10.73	10.80	10.63	9.02
Do not know/prefer not to answer/missing	1.69	1.54	1.89	3.09
Breast cancer screening participation prior to recruitment, %				
Yes	78.39	77.66	79.48	73.45
Do not know/prefer not to answer/missing	0.15	0.14	0.15	1.55

(Continues)

TABLE 1 (Continued)

	Total (n = 232 848)	No dietary changes in the past 5 years (n = 137 479)	Dietary changes in the past 5 years, due to illness or other reasons (n = 94 981)	Prefer not to answer/ unknown/missing (n = 388)
Overall health rating (self-reported), %				
Poor	3.45	2.18	5.27	8.25
Fair	18.13	14.98	22.62	36.34
Good	59.95	61.45	57.84	45.62
Excellent	18.16	21.14	13.90	5.41
Prefer not to answer/do not know/missing	0.31	0.26	0.38	4.38
Prevalent health conditions at recruitment, %[a]				
No	82.93	87.10	76.92	74.23
Yes	17.07	12.90	23.08	25.77

Abbreviations: A-level, General Certificate of Education Advanced level; AS-levels, General Certificate of Education Advanced Supplementary level; CSE, Certificate of Secondary Education; HNC, Higher National Certificate; HND, Higher National Diploma; GCSE, General Certificate of Secondary Education; NVQ, National Vocational Qualification; O-level, General Certificate of Education Ordinary level.
[a]Including self-reported gastric reflux, gastric/stomach ulcer, irritable bowel syndrome, Crohn's disease, ulcerative colitis, coeliac disease, diabetes and cardiovascular disease.

TABLE 2 Lifestyle score and its association with breast cancer in situ risk, overall and by selected characteristics

		HR (95% CI)		
	Cases/noncases	Model 1[a]	Model 2	Model 3
WCRF/AICR lifestyle score, continuous	957/231 891	0.97 (0.91-1.03)	0.97 (0.91-1.03)	0.96 (0.91-1.03)
WCRF/AICR lifestyle score, low adherence	156/35 669	Ref.	Ref.	Ref.
WCRF/AICR lifestyle score, moderate adherence	621/150 047	0.92 (0.77-1.10)	0.92 (0.77-1.10)	0.92 (0.77-1.09)
WCRF/AICR lifestyle score, high adherence	180/46 175	0.86 (0.69-1.07)	0.86 (0.69-1.06)	0.85 (0.68-1.05)
Intraductal carcinoma in situ, WCRF/AICR lifestyle score, continuous[b]	841/232 007	0.98 (0.92-1.05)	0.98 (0.92-1.05)	0.98 (0.91-1.04)
Lobular carcinoma in situ, WCRF/AICR lifestyle score, continuous	60/232 788	0.93 (0.72-1.19)	0.93 (0.72-1.19)	0.92 (0.72-1.17)
Other carcinoma in situ or unspecified carcinoma in situ, WCRF/AICR lifestyle score, continuous	48/232 800	0.88 (0.67-1.16)	0.88 (0.67-1.17)	0.89 (0.67-1.17)
Menopausal status at recruitment				
Premenopausal	244/58 317	1.00 (0.88-1.14)	1.01 (0.89-1.14)	1.00 (0.88-1.13)
Postmenopausal (including surgical menopause)	685/164 517	0.97 (0.90-1.04)	0.96 (0.90-1.04)	0.96 (0.89-1.03)
Prefer not to answer/missing/not sure	28/9057	0.79 (0.54-1.16)	0.80 (0.54-1.18)	0.81 (0.55-1.20)
Smoking status at recruitment				
Never	595/138 286	0.96 (0.89-1.04)	0.97 (0.89-1.05)	0.96 (0.89-1.04)
Ever	361/92 965	0.98 (0.88-1.08)	0.98 (0.88-1.08)	0.97 (0.88-1.07)
Prefer not to answer/do not know/missing	1/640	—	—	—
Ever had breast cancer screening, reported at recruitment				
No	158/49 805	0.92 (0.78-1.07)	0.92 (0.79-1.07)	0.92 (0.79-1.07)
Yes	798/181 741	0.98 (0.91-1.04)	0.98 (0.91-1.04)	0.98 (0.91-1.04)
Prefer not to answer/do not know/missing	1/345	—	—	—

Abbreviations: CI, confidence interval; HR, hazard ratio; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research.
[a]Model 1 adjusted for highest level of attained education and smoking status; Model 2 further adjusted for age at menarche, age at first full-term pregnancy, menopausal status, ever use of oral contraceptive pills and ever use of menopausal hormone therapy; Model 3 further adjusted for first degree family history for breast cancer, breast cancer screening attendance and time since last screening. The WCRF/AICR lifestyle score was considered as a continuous variable in the stratified analyses. Stratified analyses were not adjusted for the stratifying variable. Stratified analyses by breast cancer screening attendance were additionally not adjusted for time since last screening.
[b]Some women (n = 8) diagnosed with more than one subtype of breast cancer in situ simultaneously were not shown in the stratified analyses by subtype. The subtypes of breast cancer in situ were defined based on ICD-10 codes as follows: Intraductal carcinoma in situ (D05.1), lobular carcinoma in situ (D05.0), other carcinoma in situ of the breast or unspecified carcinoma in situ (D05.7 and D05.9, respectively).

TABLE 3 Lifestyle score and its association with breast cancer in situ risk by reported dietary changes in the past 5 years, overall and by selected characteristics

	No dietary changes in the past 5 years (n = 137 479)				Dietary changes in the past 5 years (n = 94 981)			
		HR (95% CI)				HR (95% CI)		
	Cases/noncases	Model 1[a]	Model 2	Model 3	Cases/noncases	Model 1	Model 2	Model 3
WCRF/AICR lifestyle score, continuous	578/136 901	0.92 (0.85-1.00)	0.92 (0.85-1.00)	0.92 (0.85-0.99)	379/94 602	1.05 (0.95-1.16)	1.04 (0.94-1.15)	1.04 (0.94-1.15)
WCRF/AICR lifestyle score, low adherence	101/22 093	Ref.	Ref.	Ref.	55/13 477	Ref.	Ref.	Ref.
WCRF/AICR lifestyle score, moderate adherence	391/88 555	0.95 (0.76-1.19)	0.96 (0.77-1.19)	0.94 (0.76-1.18)	230/61 246	0.88 (0.65-1.18)	0.87 (0.65-1.17)	0.87 (0.65-1.17)
WCRF/AICR lifestyle score, high adherence	86/26 253	0.70 (0.52-0.94)	0.70 (0.52-0.94)	0.69 (0.51-0.92)	94/19 879	1.09 (0.78-1.52)	1.08 (0.77-1.51)	1.07 (0.77-1.50)
Menopausal status at recruitment								
Premenopausal	164/36 316	0.99 (0.85-1.15)	0.99 (0.85-1.15)	0.97 (0.83-1.14)	80/21 905	1.01 (0.81-1.26)	1.00 (0.80-1.26)	1.00 (0.80-1.25)
Postmenopausal (including surgical menopause)	395/95 452	0.91 (0.82-1.00)	0.91 (0.82-1.00)	0.90 (0.82-0.99)	290/68 806	1.05 (0.94-1.17)	1.05 (0.94-1.17)	1.04 (0.93-1.17)
Prefer not to answer/missing/not sure	19/5133	0.73 (0.44-1.20)	0.68 (0.41-1.13)	0.66 (0.38-1.13)	9/3891	1.44 (0.69-3.00)	1.45 (0.64-3.27)	1.38 (0.56-3.39)
Smoking status at recruitment								
Never	364/83 153	0.94 (0.85-1.04)	0.94 (0.85-1.04)	0.94 (0.85-1.04)	231/54 898	1.00 (0.88-1.14)	1.00 (0.88-1.13)	0.99 (0.87-1.13)
Ever	213/53 401	0.89 (0.78-1.01)	0.88 (0.77-1.01)	0.88 (0.77-1.00)	148/39 424	1.13 (0.96-1.32)	1.13 (0.96-1.32)	1.12 (0.96-1.32)
Prefer not to answer/do not know/missing	1/347	—	—	—	0/280	—	—	—
Ever had breast cancer screening, reported at recruitment								
No	96/30 421	0.89 (0.72-1.08)	0.90 (0.73-1.10)	0.89 (0.73-1.09)	62/19 287	0.98 (0.77-1.26)	0.96 (0.75-1.24)	0.97 (0.75-1.24)
Yes	481/106 282	0.93 (0.85-1.01)	0.93 (0.85-1.01)	0.93 (0.85-1.01)	317/75 174	1.06 (0.95-1.18)	1.06 (0.95-1.18)	1.06 (0.95-1.18)
Prefer not to answer/do not know/missing	1/198	—	—	—	0/141	—	—	—

Abbreviations: CI, confidence interval; HR, hazard ratio; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research.

[a]Model 1 adjusted for highest level of attained education and smoking status; Model 2 further adjusted for age at menarche, age at first full-term pregnancy, menopausal status, ever use of oral contraceptive pills and ever use of menopausal hormone therapy; Model 3 further adjusted for first degree family history for breast cancer, breast cancer screening attendance and time since last screening. The WCRF/AICR lifestyle score was considered as a continuous variable in the stratified analyses. Stratified analyses were not adjusted for the stratifying variable. Stratified analyses by breast cancer screening attendance were additionally not adjusted for time since last screening.

were conducted for smoking, menopausal status, self-reported overall health and prevalence of selected chronic diseases at study recruitment.

For each model, adherence to the cancer prevention recommendations was assessed via the lifestyle score as (a) continuous and (b) categorized based on the level of adherence to the cancer prevention recommendations, as described above. For categorical analyses, the reference category was set as the first category, reflecting low adherence.

All statistical analyses were conducted using Stata version 15 (StataCorp, Texas). All statistical tests were two-sided, and *P*-values <.05 were considered statistically significant.

3 | RESULTS

A description of the study population is shown in Table 1. Of all study participants, 137 479 did not report dietary changes in the past 5 years, whereas 94 981 did. Those who did not report dietary changes in the past 5 years were slightly more educated and more likely to have never smoked, compared to those who reported dietary changes in the past 5 years.

After a mean follow-up time of 6.9 years, 957 breast cancer in situ cases were diagnosed. The association between the lifestyle score

TABLE 4 Individual components of the lifestyle score and their association with breast cancer in situ risk

	Total (n = 232 848)		No dietary changes in the past 5 years (n = 137 479)		Dietary changes in the past 5 years (n = 94 981)	
	Cases/noncases	HR (95% CI)	Cases/noncases	HR (95% CI)	Cases/noncases	HR (95% CI)
Body mass index						
0	244/54 886	Ref.	116/26 571	Ref.	128/28 133	Ref.
0.25	336/85 065	0.89 (0.74-1.09)	207/49 095	0.98 (0.75-1.28)	129/35 850	0.78 (0.58-1.05)
0.5	377/91 940	0.94 (0.74-1.20)	255/61 235	1.02 (0.74-1.40)	122/30 619	0.84 (0.57-1.25)
Waist circumference						
0	348/82 128	Ref.	179/41 746	Ref.	169/40 149	Ref.
0.25	238/58 348	1.03 (0.84-1.25)	152/34 518	1.04 (0.80-1.35)	86/23 767	1.00 (0.73-1.37)
0.5	371/91 415	1.01 (0.81-1.26)	247/60 637	0.95 (0.71-1.26)	124/30 686	1.10 (0.77-1.59)
Physical activity						
0	366/80 758	Ref.	222/47 484	Ref.	144/33 094	Ref.
0.5	151/33 755	0.98 (0.81-1.18)	101/19 801	1.09 (0.86-1.38)	50/13 897	0.82 (0.59-1.13)
1	440/117 378	0.82 (0.71-0.95)	255/69 616	0.79 (0.66-0.96)	185/47 611	0.85 (0.68-1.07)
Partial fiber (cohort-based tertiles)						
0	292/77 395	Ref.	194/47 920	Ref.	98/29 303	Ref.
0.25	316/77 230	1.11 (0.92-1.34)	204/45 501	1.13 (0.89-1.42)	112/31 610	1.08 (0.79-1.48)
0.5	349/77 266	1.21 (0.96-1.53)	180/43 480	0.98 (0.72-1.32)	169/33 689	1.61 (1.12-2.32)
Fruit and vegetables						
0	164/40 709	Ref.	116/26 800	Ref.	48/13 820	Ref.
0.25	437/110 213	0.89 (0.72-1.09)	272/66 614	0.88 (0.68-1.13)	165/43 411	0.92 (0.64-1.32)
0.5	356/80 969	0.90 (0.69-1.18)	190/43 487	1.01 (0.72-1.41)	166/37 371	0.80 (0.51-1.25)
Red and processed meat						
0	210/48 949	Ref.	135/29 680	Ref.	75/19 168	Ref.
0.5	259/65 534	0.91 (0.75-1.09)	161/39 682	0.88 (0.70-1.11)	98/25 716	0.95 (0.70-1.29)
1	488/117 408	0.94 (0.79-1.10)	282/67 539	0.90 (0.73-1.11)	206/49 718	1.02 (0.78-1.34)
Alcohol consumption						
0	150/38 270	Ref.	104/25 695	Ref.	46/12 551	Ref.
0.5	710/173 056	1.08 (0.90-1.29)	433/100 843	1.10 (0.88-1.37)	277/71 927	1.07 (0.78-1.48)
1	97/20 565	1.25 (0.96-1.63)	41/10 363	1.05 (0.72-1.53)	56/10 124	1.53 (1.02-2.30)
Sugar avoidance as proxy to sugar-sweetened beverage intake						
0	790/191 058	Ref.	502/117 282	Ref.	288/73 450	Ref.
1	167/40 833	0.96 (0.81-1.14)	76/19 619	0.91 (0.71-1.17)	91/21 152	1.01 (0.80-1.29)

Note: Detailed information on the operationalization of these individual components can be found in Table S1. Adjusted for highest level of attained education, smoking status, age at menarche, age at first full-term pregnancy, menopausal status, ever use of oral contraceptive pills, ever use of menopausal hormone therapy, first degree family history for breast cancer, breast cancer screening attendance and time since last screening.
Abbreviations: CI, confidence interval; HR, hazard ratio.

and breast cancer in situ risk for the overall study population is shown in Table 2. The lifestyle score was not significantly associated with breast cancer in situ risk (HR = 0.96, 95% CI = 0.91-1.03; for one unit of increase in the lifestyle score, $HR_{high\ vs\ low}$ = 0.85, 95% CI = 0.68-1.05; in the fully adjusted models). Prespecified subgroup analyses by smoking, menopausal status, previous breast cancer screening attendance and morphological subtype (Table 2), as well as those by self-reported health rating, dietary changes in the past 5 years and prevalent health conditions at recruitment (Table S2) showed similar associations with those reported in the overall study population.

In participants who did not report dietary changes in the past 5 years, the lifestyle score was inversely associated with breast cancer in situ risk (HR = 0.92, 95% CI = 0.85-0.99; for one unit of increase in the lifestyle score, $HR_{high\ vs\ low}$ = 0.69, 95% CI = 0.51-0.92, in the fully adjusted models; Table 3). This association seemed more pronounced in women who had smoked sometime in their life, while no significant difference was observed in never smokers. No differences were observed by menopausal status and breast cancer screening attendance reported at study recruitment.

When looking at participants who reported dietary changes in the past 5 years, the lifestyle score was not associated with breast cancer in situ risk (HR = 1.04, 95% CI = 0.94-1.15; for one unit of increase in the lifestyle score, $HR_{high\ vs\ low}$ = 1.07, 95% CI = 0.77-1.50; in the fully adjusted models; Table 3). This association did not differ considerably in prespecified subgroup analyses by smoking, menopausal status and breast cancer screening as reported at study recruitment.

Of all the cancer prevention recommendations investigated, a statistically significant association was seen between meeting the physical activity recommendation and breast cancer in situ risk, both in the overall study population and those not reporting dietary changes in the past 5 years (HR = 0.82, 95% CI = 0.71-0.95; HR = 0.79, 95% CI = 0.66-0.96, respectively, in the fully adjusted models; Table 4). Interestingly, a positive association was seen between meeting the fiber and alcohol cancer prevention recommendations and breast cancer in situ risk in women reporting dietary changes in the past 5 years.

Sensitivity analyses excluding participants with <1 year of follow-up did not modify our results (data not shown).

4 | DISCUSSION

In this large prospective study, we investigated the association between adherence to cancer prevention recommendations and the risk of breast cancer in situ. Overall, we did not detect an association between the lifestyle score and breast cancer in situ risk. However, we did observe an inverse association among women, who had not reported dietary changes in the past 5 years.

Our results reported here are comparable to those of a previous analysis conducted using data from the EPIC cohort among women recruited via breast cancer screening programs in selected study centers.[17] Our findings are also in agreement with studies investigating adherence to cancer prevention recommendations and risk for invasive or total (in situ and invasive, as a joint outcome) breast cancer.[15,16,21] While direct comparisons with these studies cannot be made due to differences in the operationalization of adherence to cancer prevention recommendations and endpoints, the similarity of results indicate a common risk factor pattern affecting breast carcinogenesis. To this end, it is notable that mammographic density, a shared intermediate risk factor between in situ and invasive breast tumors, has also been associated with adherence to the WCRF/AICR cancer prevention recommendations.[22]

Of all the individual cancer prevention recommendations investigated, physical activity was statistically significantly associated with breast cancer in situ risk. This inverse association was in line with one published study,[8] but not with two others.[6,7] The lack of statistically significant associations between most of the cancer prevention recommendations investigated and breast cancer in situ risk we observed is consistent with several previous studies failing to detect associations with individual lifestyle factors but reporting significant associations between lifestyle scores and cancer risk.[14,15,17,23] This suggests that a synergistic effect between different lifestyle factors is more strongly linked to the carcinogenesis process, compared to the potential individual effects of lifestyle factors.

In analyses focusing on UK Biobank participants reporting dietary changes in the past 5 years, we observed significant positive associations with breast cancer in situ risk for dietary fiber and alcohol consumption. In both cases, adhering to the respective cancer prevention recommendation was associated with increased breast cancer in situ risk. While this might sound counterintuitive, our results could be attributed to reverse causation. In the UK Biobank study participants reporting dietary changes, better adherence to the cancer prevention recommendations might not reflect lifelong cancer-protective habits, but rather recent changes motivated by health problems or other important reasons. Similar phenomena have been described in the literature in the context of the so-called "sick-quitter effect," that is, a higher proportion of people with impaired health reporting no alcohol consumption.[24]

This study had various strengths. The prospective study design allowed us to establish the time frame between assessment of lifestyle factors and the outcome, while the substantial number of incident breast cancer in situ cases allowed us to perform subgroup analysis. Additionally, information on previous breast cancer screening attendance was available for the vast majority of the study population, thus allowing us to include it as a confounder in the analyses and to perform stratified analysis for this crucial factor in breast cancer in situ detection. Our study also had some limitations. Information on lifestyle habits and breast cancer screening participation was self-reported and only available for all study participants at study recruitment. Therefore, this information may not reflect the long-term habits of the women participating in the UK Biobank. To address this, we performed stratified analyses based on whether participants reported dietary changes in the past 5 years, aiming to capture long-term habits. Dietary assessment was conducted via a short questionnaire, and thus, not all cancer prevention recommendations could be operationalized in our study. Information on total energy intake is not

available for dietary assessment based on the Touchscreen questionnaire, and thus we could not adjust our analyses for it. Additionally, the questionnaire has not been validated for dietary assessment. However, a previous study showed similar consumption for the main food groups over 4 years of follow-up.[20] While our goal was to evaluate the adherence to cancer prevention recommendations in relation to breast cancer in situ risk, we acknowledge that etiology-focused analyses stratifying for the different morphological tumor subtypes are needed. Even though we adjusted our analyses for the most important confounders, the possibility of residual confounding cannot be excluded, as in any observational study.

In conclusion, a lifestyle score reflecting adherence to cancer prevention recommendations was not associated with breast cancer in situ risk in the overall study population. However, an inverse association was observed in women who did not report recent changes in their dietary habits due to illness or other reasons. The inverse association between higher lifestyle score and breast cancer in situ risk in these stratified analyses is consistent with the associations reported previously in the literature. Additional studies with verified information on breast cancer screening participation, before study recruitment, but also during the follow-up period, are required in order to validate our findings.

AUTHOR CONTRIBUTIONS

Conception and design: Nena Karavasiloglou, Tilman Kühn, Sabine Rohrmann. Data acquisition: Nena Karavasiloglou, Sabine Rohrmann. Analyzing the data: Nena Karavasiloglou, Tilman Kühn, Sabine Rohrmann. Interpretation of the data: Nena Karavasiloglou, Giulia Pestoni, Tilman Kühn, Sabine Rohrmann. Drafting the manuscript: Nena Karavasiloglou. Critically revising the manuscript: Nena Karavasiloglou, Giulia Pestoni, Tilman Kühn, Sabine Rohrmann. All authors read and approved the final manuscript. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

This work has been conducted using the UK Biobank Resource (application number 55149). The UK Biobank is an open access resource and bona fide researchers can apply to use the UK Biobank dataset by registering and applying at http://ukbiobank.ac.uk/register-apply/. Further information is available from the corresponding author upon request.

ETHICS STATEMENT

The UK Biobank has ethical approval from the North West Multicentre Research Ethics Committee. All participants provided informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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