Brief Report

Cross-sectional and longitudinal associations of adherence to WCRF/AICR cancer prevention recommendations with health-related quality of life in breast cancer survivors. Health-EpiGEICAM study

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ABSTRACT

Objectives: Adherence to healthy lifestyle recommendations has been reported to improve health-related quality of life (HRQL) in breast cancer (BC) patients, but the influence of long-term behavioral changes remains unknown. We evaluated the association between adherence to the 2018 World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) cancer prevention recommendations and HRQL both, at BC diagnosis and the change 7−12 years later.
Design: Prospective cohort study.
Settings and participants: A total of 406 breast cancer survivors, from the EpiGEICAM study, were recruited in 16 Spanish hospitals.
Measurements: Epidemiological, clinical, dietary, physical activity and HRQL information was collected both at recruitment and 7−12 years later. A 7-item score to measure compliance with recommendations was assessed

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according to the 2018 WCRF/AICR scoring criteria. HRQL was evaluated using SF-36 questionnaire. Linear mixed models for longitudinal data were used to assess the cross-sectional and longitudinal association between adherence score and the physical and mental component summary scores.

Results: At diagnosis, for each unit increase in WCRF/AICR score adherence, the HRQL physical domain increased 0.78 points (95%CI: −0.04 to 1.60; *P* trend:0.06). The mean change in physical HRQL from diagnosis to follow-up per unit increase in within-subject adherence score was 0.73 points (95%CI: −0.18 to 1.65; *P* trend: 0.12). For the mental domain, no association was observed with compliance with the recommendations at diagnosis, nor with changes in adherence over time.

Conclusions: Our results suggest that Increased adherence to WCRF/AICR cancer prevention recommendations over time could contribute to slightly improved long-term physical HRQoL in BC survivors.

1. Introduction

Breast cancer (BC) is the most prevalent tumor in Spain, excluding non-melanoma skin cancer [1]. Both, the cancer diagnosis itself and treatment-related side effects can lead to physical and psychosocial problems that compromise HRQL of survivors [2,3]. In 2018, the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) updated its 10 cancer prevention recommendations [4]. The latest advises cancer survivors to follow these recommendations, as far as possible, after the acute stage of treatment. Adherence to these guidelines has been associated with improved HRQL [5–7], as well as higher arm symptom scores [8] in BC survivors. However, these studies conducted cross-sectional analyses, which are prone to reverse causation bias.

Motivation to make positive behavior changes in cancer survivors may decline over time [9]. According to the European Society for Medical Oncology, there is a lack of longitudinal studies providing detailed information on behavioral and lifestyle factors to understand how these factors interact and impact long-term survivorship experience [3]. To the best of our knowledge, no previous studies have evaluated the longitudinal association between compliance with WCRF/AICR recommendations and HRQL in BC survivors.

In the context of the EpiGEICAM case-control study, our group has reported the impact of a recent diagnosis of BC on HRQL [10], as well as the association between the WCRF/AICR recommendations and the risk of this tumor [11]. Subsequently, the degree of adherence to these recommendations was explored in the long-term BC survivors [12]. In the present study, we sought to evaluate the association between adherence to the 2018 WCRF/AICR cancer prevention recommendations and physical and mental HRQL domains at BC diagnosis, and in a longitudinal way, how changes in adherence to these recommendations are associated with changes in HRQL 7–12 years after diagnosis.

2. Methods

2.1. Study population

EpiGEICAM is a multicentre case-control study on incident female BC and individually matched controls conducted between 2006 and 2011 in nine Spanish regions. The study design has been previously described [13]. Briefly, 1,017 BC cases and 1,017 controls were recruited from the oncology departments of 23 hospitals, members of the GEICAM Spanish Breast Cancer Research Group (https://www.geicam.org/). Cases had to be histologically confirmed, between 18 and 70 years old, with no history of BC, and able to answer an epidemiological questionnaire.

Subsequently, in 2017, BC survivors from the EpiGEICAM study were contacted again and invited to participate in the Health-EpiGEICAM study, whose main objective was to assess the degree of compliance with international recommendations for cancer prevention, and to evaluate its influence on the prognosis and quality of life. Until October 2019, 767 women (75.4%) belonging to 16 participating hospitals could be recontacted.

Written informed consent was obtained from each participant. The study was evaluated and approved by Comité de Ética de Investigación Clinica, Consorci Sanitari de Terrassa (June 28, 2017), and the rest of ethics committes from participant institutions accepted that approval. All procedures were in accordance with the principles of the Helsinki Declaration and its subsequent modifications. Patient information was anonymized and de-identified prior to analysis.

2.2. Data collection

All BC patients answered an epidemiological questionnaire, both at recruitment (EpiGEICAM study) and 7−12 years later (Health-EpiGEI-CAM). These questionnaires included demographic and anthropometric data, gynaecological information, medical history, physical activity and smoking habits. Total minutes of moderate-vigorous physical activity per week were calculated from a section of the questionnaire that specifically asked about each of the activities performed by the participant during the previous year, taking into account the number of times per week they engaged in that activity and the minutes spent in each session. The total minutes of physical activity per week were then calculated by summing the minutes/week in each activity. Dietary habits were reported through a self-administered validated food frequency questionnaire (FFQ), which included 117 food items and that has been validated [14] and used in different populations of Spanish women [12,15]. The responses for each food item were converted to mean daily and weekly intake (in grams) and total energy intake (in kcals/day) using Software ALEVINT [16]. HRQL, at diagnosis and at follow-up, was measured by the Short Form 36 Health Survey (SF-36, version 1) [17,18], validated for Spanish population [19]. The clinical and pathological information, including tumor pathological subtype, stage at diagnosis, treatments received, and evolution of the disease, was collected by the investigators of the participating hospitals. Stage at diagnosis was defined according to the 7th edition of the American Joint Committee on Cancer [AJCC] TNM staging system [20].

2.3. WCRF/AICR score

To calculate the 2018 Standardized-WCRF/AICR score we relied on the guideline provided by Shams-White et al. [21]. This scoring system includes eight of the ten WCRF/AICR recommendations related to weight, physical activity, diet, and breastfeeding (this last optional recommendation was not included in our study due to lack of information). Each recommendation was assigned 1 point, 0.5, or 0 points for full, partial or no compliance, respectively. For the recommendation of "eat a diet rich in wholegrains, vegetables, fruit, and beans" which has two sub-recommendations, the scoring weight was divided equally (0.5 points each) to maintain an overall score of one point. For the recommendation of "be a healthy weight", which also includes two sub-recommendations based on body mass index (BMI) and waist circumference, since we did not have information on waist circumference, BMI points were doubled as recommended [21]. Physical activity cut-off points (150 and 300 min of moderate-vigorous physical activity per week to differentiate partial and full compliance), were based on Spanish national guidelines [22], as

advised by the authors of the standard scoring system [21]. For the recommendation of limiting "fast food" we applied the the cut-offs created by these same authors, based on the tertiles of an adapted version of the NOVA classification system [21]. Therefore, the global WCRF/AICR score ranged from 0 (none of the recommendations were met) to 7 (all were fully met). Operationalization, scoring, and adherence to the 2018 WCRF/AICR recommendations, at baseline and at follow-up, are presented in Supplementary Table S1.

2.4. Health related quality of life

The SF-36 is a widely used general HRQL questionnaire comprising 36 items aggregated into eight subscales: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health. In addition, the instrument allows to calculate two summary scores through specific weighted scores combinations: Physical Component Summary and Mental Component Summary. We used the weights recommended for the Spanish population [23]. Following the scoring and coding manual, all the scales were transformed to give scores from 0 to 100 points, with higher scores indicating better HRQL. To obtain Norm-Based Scores, the mean score of the general Spanish female reference population in the corresponding age group was subtracted from the value obtained for each woman [24], and the result was divided by the standard deviation of the population. Then, T-scores were generated by multiplying the result by 10 and adding 50. In this way, values greater than 50 points represent better HRQL than their peers in the general population, and scores lower than 50 represent worse HRQL.

2.5. Statistical analyses

To assess the cross-sectional association of adherence to WCRF/AICR recommendations with HRQL physical and mental domains at BC diagnosis, as well as the longitudinal association between changes in adherence to WCRF/AICR recommendations and changes in HRQL physical and mental domains 7–12 years after diagnosis, we used linear mixed models for longitudinal data [25]. The models are specified in detail in the Supplementary Methods. Briefly, the models included fixed-effects linear terms to estimate the average difference in HRQL score at diagnosis per unit increase in between-participant adherence score (cross-sectional association) and the average change in HRQL score over time per unit increase in within-participant adherence score (longitudinal association), while allowing for random variations in HRQL scores at diagnosis and slopes over time across participants. To allow for nonlinear cross-sectional and longitudinal associations, we replaced the above linear terms with tertile indicators and restricted cubic splines for levels at diagnosis and changes over time in adherence score with knots at the 5th, 50th, and 95th percentiles.

Two models were fitted with increasing degrees of adjustment. The first model adjusted for general participant characteristics, including recruitment region (Galicia, Andalucía, Cataluña, Madrid, Comunidad Valenciana, Aragón, or Castilla-La Mancha), attained educational level (primary or less, high school, or university), parity (nulliparous or parous), menopausal status at diagnosis (pre/perimenopausal or postmenopausal), and status at diagnosis and changes over time in the following time-varying covariates: age (continuous), partner status (no or yes), working status (no or yes), smoking status (non-smoker/former smoker $\geq$12 months ago or smoker/former smoker <12 months ago), total energy intake (<1,500, 1,500–1,999, or $\geq$2,000 kcal/day), number of comorbidities (0, 1, or $\geq$2), and family history of BC (no, second degree only, or first degree). The second model further controlled for clinical characteristics of BC survivors, such as tumor receptor status at diagmosis (hormone receptor-positive and HER2-negative, HER2-positive, or triple negative), AJCC tumor stage at diagnosis (0–I, II, or III–IV), and status at diagnosis and changes over time in the following time-varying covariates: surgery (no, conservative, or mastectomy), chemotherapy (no, ongoing, or finished), radiotherapy (no, ongoing, or finished), hormone therapy (no, ongoing, or finished), targeted therapy (no, ongoing, or finished), lymphedema (no or yes), and recurrent or new primary BC (no, past, or current).

To explore potential heterogeneity of both cross-sectional and longitudinal associations by strata of attained educational level (primary or less, or high school or more), menopausal status at diagnosis, and tumor stage at diagnosis (0–I or II–IV), we included interactions of these covariates with linear terms of levels at diagnosis and changes over time in adherence score in the corresponding linear mixed models. In addition, we evaluated modifications in the longitudinal effect of changes in WCRF/AICR adherence over time by categories of adherence score at diagnosis (1–3.50 or 3.75–6.50 points). Statistical analyses were performed in Stata, version 17 (StataCorp) and graphics were produced in R, version 4 (R Foundation for Statistical Computing).

3. Results

After excluding 79 women who refused to participate in Health-EpiGEICAM study, 241 without clinical and/or epidemiological data, 25 with implausible energy intakes (<750 or >4500 kcal/day), and 16 with missing information on the WCRF/AICR adherence score or HRQL score, either at diagnosis or at follow-up, the final study sample comprised 406 BC participants who had both WCRF/AICR adherence score and HRQL score available either at diagnosis or at follow-up (379 participants with scores available at diagnosis, 371 at follow-up, and 344 at both time points).

Table 1 shows the mean scores in HRQL physical and mental domains at BC diagnosis and 7–12 years later. The physical component improved 7.7 points from baseline to follow-up, approaching that of the general population 7–12 years after diagnosis. At that time, participants with the poorest perceived physical HRQL were the youngest, those receiving hormone therapy, those with lymphedema, and those with active tumor recurrence or second primary BC. The mental component only increased by 3.1 points. Participants with poorer adherence to WCRF/AICR recommendations, smokers, survivors not taking hormone therapy and

Table 1

Physical and mental domains of health-related quality of life at diagnosis of breast cancer and 7–12 years later.

	At breast cancer diagnosis			7–12 years after diagnosis		
	No. (%) of participants	Mean (SD) HRQL score		No. (%) of participants	Mean (SD) HRQL score	
		Physical	Mental		Physical	Mental
Overall	379	40.8 (10.2)	48.0 (13.0)	371	48.5 (9.6)	51.1 (11.0)
WCRF/AICR adherence score						
$\leq$3	105 (27.7)	40.4 (9.9)	46.9 (12.6)	50 (13.5)	46.7 (10.4)	48.6 (11.4)
3.25–4	124 (32.7)	40.3 (10.7)	48.8 (13.7)	114 (30.7)	48.3 (9.5)	52.9 (9.5)
$\geq$4.25	150 (39.6)	41.5 (9.9)	48.1 (12.6)	207 (55.8)	49.0 (9.5)	50.8 (11.6)
General characteristics						
Age (years)						
<50	208 (54.9)	38.8 (10.6)	48.1 (13.8)	52 (14.0)	44.6 (10.3)	49.4 (12.5)

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Table 1 *(continued)*

	At breast cancer diagnosis			7–12 years after diagnosis		
	No. (%) of participants	Mean (SD) HRQL score		No. (%) of participants	Mean (SD) HRQL score	
		Physical	Mental		Physical	Mental
50–59	123 (32.5)	43.1 (8.9)	47.0 (11.7)	154 (41.5)	47.8 (9.7)	50.5 (10.9)
≥60	48 (12.7)	43.7 (9.3)	50.3 (12.0)	165 (44.5)	50.3 (8.9)	52.2 (10.6)
Attained educational level						
Primary or less	135 (35.6)	40.6 (10.3)	48.3 (12.4)	131 (35.3)	48.4 (9.6)	50.2 (11.6)
High school	122 (32.2)	40.7 (9.8)	49.3 (13.3)	122 (32.9)	48.1 (10.0)	51.9 (10.7)
University	122 (32.2)	41.1 (10.5)	46.4 (13.1)	118 (31.8)	48.9 (9.3)	51.4 (10.7)
Partner status						
Without partner	71 (18.9)	41.9 (11.0)	47.4 (12.4)	100 (27.0)	48.7 (9.6)	50.2 (10.8)
With partner	305 (81.1)	40.6 (9.9)	48.1 (13.1)	270 (73.0)	48.4 (9.6)	51.6 (11.0)
Parity						
Nulliparous	65 (17.2)	41.9 (10.8)	47.3 (13.0)	64 (17.3)	46.8 (10.7)	50.7 (12.3)
Parous	314 (82.8)	40.6 (10.0)	48.2 (13.0)	307 (82.7)	48.8 (9.4)	51.2 (10.8)
Working status						
Not working	127 (33.5)	41.9 (9.4)	47.7 (12.7)	226 (60.9)	48.0 (9.9)	50.7 (11.3)
Working	252 (66.5)	40.2 (10.5)	48.2 (13.1)	145 (39.1)	49.3 (9.1)	51.8 (10.6)
Smoking status						
Non-smoker/former ≥12 months	264 (69.8)	40.4 (10.1)	49.1 (12.2)	305 (82.7)	48.7 (9.7)	52.2 (10.7)
Smoker/former <12 months	114 (30.2)	41.7 (10.3)	45.6 (14.2)	64 (17.3)	47.1 (9.3)	46.1 (11.4)
Total energy intake (kcal/day)						
<1,500	91 (24.0)	41.0 (10.2)	48.4 (13.0)	124 (33.4)	47.6 (10.0)	49.9 (11.7)
1,500–1,999	134 (35.4)	41.5 (9.9)	47.7 (12.3)	135 (36.4)	48.4 (9.8)	52.5 (10.4)
≥2,000	154 (40.6)	40.1 (10.4)	48.1 (13.6)	112 (30.2)	49.5 (8.9)	50.8 (10.9)
No. of comorbidities						
0	245 (64.6)	40.8 (10.4)	47.2 (13.7)	70 (18.9)	51.3 (9.4)	52.4 (9.7)
1	85 (22.4)	40.3 (9.7)	50.1 (11.1)	93 (25.1)	48.6 (10.5)	52.4 (9.8)
≥2	49 (12.9)	41.6 (9.7)	48.3 (12.1)	208 (56.1)	47.5 (9.1)	50.1 (11.9)
Family history of breast cancer						
No	271 (71.5)	40.9 (10.2)	47.6 (13.1)	201 (54.2)	49.2 (9.9)	52.0 (10.4)
Second degree only	51 (13.5)	41.1 (10.9)	48.1 (14.5)	56 (15.1)	47.5 (10.3)	51.1 (12.5)
First degree	57 (15.0)	39.8 (9.4)	49.8 (10.9)	114 (30.7)	47.7 (8.7)	49.6 (11.4)
Menopausal status at diagnosis						
Pre/perimenopausal	239 (63.1)	38.9 (10.5)	47.9 (13.7)	231 (62.3)	47.2 (9.9)	49.8 (11.5)
Postmenopausal	140 (36.9)	44.0 (8.7)	48.2 (11.7)	140 (37.7)	50.6 (8.7)	53.2 (9.8)
Clinical variables						
Tumor receptor status at diagnosis						
HR + and HER2−	267 (70.4)	40.9 (9.7)	48.2 (13.1)	263 (70.9)	48.7 (9.5)	51.5 (10.5)
HER2 +	64 (16.9)	40.7 (10.7)	47.2 (12.6)	63 (17.0)	47.8 (9.6)	49.8 (13.0)
Triple negative	48 (12.7)	40.1 (11.9)	48.0 (12.9)	45 (12.1)	48.1 (10.5)	50.6 (11.3)
AJCC tumor stage at diagnosis						
0–I	166 (44.0)	41.0 (9.1)	49.0 (12.4)	167 (45.3)	49.2 (9.1)	51.5 (10.8)
II	160 (42.4)	40.8 (10.8)	47.0 (13.6)	153 (41.5)	47.7 (10.2)	51.5 (10.7)
III–IV	51 (13.5)	40.2 (11.6)	48.0 (12.9)	49 (13.3)	48.7 (9.3)	49.2 (11.9)
Surgery						
No/not yet	77 (20.3)	44.0 (10.9)	44.2 (13.2)	0 (0.0)		
Conservative	210 (55.4)	41.1 (9.9)	48.9 (12.1)	259 (69.8)	48.4 (9.8)	51.6 (10.6)
Mastectomy	92 (24.3)	37.5 (9.2)	49.3 (14.1)	112 (30.2)	48.7 (9.2)	49.9 (11.8)
Chemotherapy						
No/not started	212 (55.9)	40.8 (10.0)	47.8 (13.2)	81 (22.0)	49.2 (9.0)	51.7 (10.7)
Ongoing	137 (36.1)	40.9 (10.7)	48.2 (12.4)	0 (0.0)		
Finished	30 (7.9)	40.1 (8.7)	48.8 (14.0)	287 (78.0)	48.2 (9.8)	50.9 (11.1)
Radiotherapy						
No/not started	299 (79.3)	40.9 (10.4)	47.9 (13.0)	64 (17.3)	49.3 (8.8)	49.7 (11.1)
Ongoing	47 (12.5)	40.4 (9.3)	47.9 (13.5)	0 (0.0)		
Finished	31 (8.2)	40.8 (9.2)	49.0 (12.4)	306 (82.7)	48.3 (9.8)	51.4 (11.0)
Hormone therapy						
No/not started	288 (76.2)	40.4 (10.6)	48.2 (12.9)	68 (18.4)	48.7 (8.8)	48.7 (11.7)
Ongoing	90 (23.8)	42.4 (8.5)	47.6 (13.4)	52 (14.1)	45.5 (10.9)	52.8 (9.5)
Finished	0 (0.0)			250 (67.6)	49.1 (9.5)	51.5 (11.1)
Targeted therapy						
No/not started	379 (100.0)	40.8 (10.2)	48.0 (13.0)	302 (81.8)	49.0 (9.5)	51.5 (10.5)
Ongoing	0 (0.0)			0 (0.0)		
Finished	0 (0.0)			67 (18.2)	46.4 (9.8)	49.5 (13.1)
Lymphedema						
No	379 (100.0)	40.8 (10.2)	48.0 (13.0)	296 (79.8)	49.2 (9.6)	51.9 (10.7)
Yes	0 (0.0)			75 (20.2)	45.6 (9.2)	48.3 (11.9)
Recurrent or new primary breast cancer						
No	379 (100.0)	40.8 (10.2)	48.0 (13.0)	325 (87.6)	48.9 (9.4)	51.1 (11.1)
Past	0 (0.0)			33 (8.9)	47.5 (10.4)	51.2 (10.8)
Current	0 (0.0)			13 (3.5)	40.8 (9.0)	50.4 (10.0)

AJCC, American Joint Committee on Cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; HRQL, health-related quality of life; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research.

Table 2

Cross-sectional association of adherence to WCRF/AICR recommendations with HRQL physical and mental domains at diagnosis of breast cancer*.

	Overall	Tertile of WCRF/AICR adherence score at diagnosis			
		First (1–3)	Second (3.25–4)	Third (4.25–6.50)	*P* for trend[†]
No. of participants	379	105	124	150	
Median WCRF/AICR adherence score at diagnosis	3.75	2.75	3.75	4.75	
HRQL physical score					
Mean (SD) at diagnosis	40.8 (10.2)	40.4 (9.9)	40.3 (10.7)	41.5 (9.9)	
Adjusted mean difference (95% CI)					
Model 1[‡]	0.66 (−0.17 to 1.49)	0.00 (reference)	0.28 (−1.63 to 2.19)	1.76 (−0.21 to 3.73)	0.12
Model 2[§]	0.78 (−0.04 to 1.60)	0.00 (reference)	0.18 (−1.70 to 2.06)	1.59 (−0.35 to 3.53)	0.06
HRQL mental score					
Mean (SD) at diagnosis	48.0 (13.0)	46.9 (12.6)	48.8 (13.7)	48.1 (12.6)	
Adjusted mean difference (95% CI)					
Model 1[‡]	0.21 (−0.88 to 1.29)	0.00 (reference)	−0.05 (−2.52 to 2.41)	0.36 (−2.20 to 2.92)	0.71
Model 2[§]	−0.01 (−1.11 to 1.09)	0.00 (reference)	0.16 (−2.32 to 2.63)	0.05 (−2.51 to 2.62)	0.99

CI, confidence interval; HRQL, health-related quality of life; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research.

[*] Results were obtained from linear mixed models with random between-participant variations in HRQL scores at diagnosis.

[†] *P* value for linear trend across continuous levels of WCRF/AICR adherence score at diagnosis.

[‡] Mean difference per unit increase in WCRF/AICR adherence score at diagnosis, adjusted for recruitment region, attained educational level, parity, menopausal status at diagnosis, age, partner status, working status, smoking status, total energy intake, number of comorbidities, and family history of breast cancer.

[§] Mean difference per unit increase in WCRF/AICR adherence score at diagnosis, further adjusted for tumor receptor status at diagnosis, tumor stage at diagnosis, breast surgery, chemotherapy, radiotherapy, and hormone therapy.

those with lymphedema had poorer mental HRQL 7−12 years after diagnosis.

Table 2 shows the cross-sectional association between adherence to the WCRF/AICR cancer prevention recommendations and the HRQL physical and mental domains at BC diagnosis. The basal score of adherence ranged between 1 and 6.5, with a median of 3.75. Per each unit increase in the adherence score, the physical component increased a mean of 0.78 points (95%CI: −0.04 to 1.60; *P* trend: 0.06). No association was observed between adherence to WCRF/AICR recommendations and the mental domain. The mean physical component score of the women in the upper tertile was 1.59 points higher (95%CI: −0.35 to 3.53) than in the first tertile. This component showed a linear dose-response trend (Fig. 1). When the cross-sectional association was analyzed by subgroups (Supplementary Fig. S1), it was observed that the increase in the HRQL physical score per unit increase in the adherence score was more pronounced in women with a higher educational level and in pre/

perimenopausal women, contrary to what was observed for the mental score, which was higher in participants with a lower educational level and in postmenopausal women.

Table 3 shows the longitudinal association of within-subject changes in adherence to WCRF/AICR recommendations and in HRQL physical and mental domains after diagnosis. The median change in the adherence score over time was 0.50 points. Adherence decreased in 31% of participants, was maintained in 9% and improved in 60% (data not shown). The mean change in the physical component score from diagnosis to follow-up per unit increase in within-subject adherence score was 0.73 points (95%CI: -0.18 to 1.65; *P*trend: 0.12). The mean changes in the mental component score was -0.15 points (95%CI: -1.33 to 1.03; *P*trend: 0.80). Women in the top tertile of adherence showed a within-subject improvement of 0.80 points (95%CI: −1.52 to 3.11) in the physical domain over time, and a non-significant worsening of −0.53 points (95% CI: −3.29 to 2.23) in the mental domain, compared to women in the first
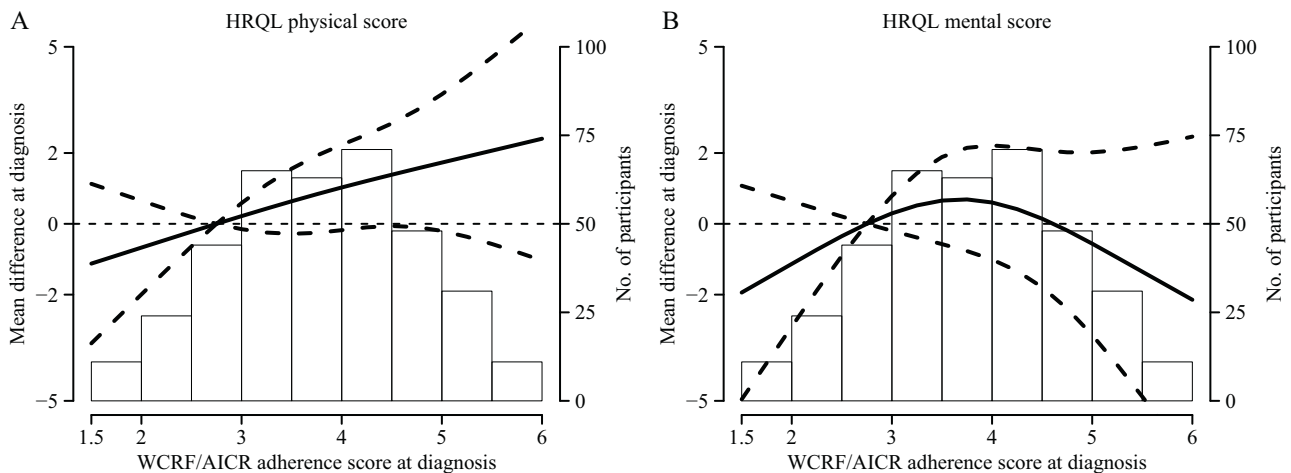
Fig. 1. Cross-sectional trends in HRQL physical (A) and mental (B) domains as a smooth function of adherence to WCRF/AICR recommendations at diagnosis of breast cancer.

Curves represent average cross-sectional differences in HRQL scores at diagnosis (solid lines) and their 95% confidence intervals (dashed lines) based on restricted cubic splines of WCRF/AICR adherence score at diagnosis with knots at the 5th, 50th, and 95th percentiles (2, 3.75, and 5.25 points, respectively). The reference value was set at the 17th percentile of WCRF/AICR adherence score at diagnosis (2.75 points). Results were obtained from linear mixed models with random between-participant variations in HRQL scores at diagnosis, and adjusted for recruitment region, attained educational level, parity, tumor receptor status at diagnosis, menopausal status at diagnosis, age, partner status, working status, smoking status, total energy intake, number of comorbidities, family history of breast cancer, tumor stage, breast surgery, chemotherapy, radiotherapy, and hormone therapy. Histogram represents the frequency distribution of WCRF/AICR adherence score at diagnosis. HRQL, health-related quality of life; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research.

Table 3

Longitudinal association of changes in adherence to WCRF/AICR recommendations with changes in HRQL physical and mental domains 7–12 years after diagnosis of breast cancer*.

	Overall	Tertile of change in WCRF/AICR adherence score over time			
		First (−2.25 to −0.25)	Second (0–0.75)	Third (1–3.75)	P for trend[†]
No. of participants	362	113	115	134	
Median change in WCRF/AICR adherence score over time	0.50	−0.50	0.50	1.50	
HRQL physical score					
Mean (SD) at diagnosis	41.1 (10.1)	42.0 (10.2)	41.9 (9.4)	39.5 (10.5)	
Mean (SD) at 7–12 years	48.3 (9.6)	49.1 (9.8)	48.3 (9.2)	47.7 (9.8)	
Adjusted mean change (95% CI)					
Model 1[‡]	0.61 (−0.31 to 1.53)	0.00 (reference)	−0.66 (−2.91 to 1.60)	0.92 (−1.39 to 3.22)	0.19
Model 2[§]	0.73 (−0.18 to 1.65)	0.00 (reference)	−0.81 (−3.11 to 1.49)	0.80 (−1.52 to 3.11)	0.12
HRQL mental score					
Mean (SD) at diagnosis	48.1 (13.0)	48.1 (13.2)	47.8 (13.6)	48.5 (12.3)	
Mean (SD) at 7–12 years	51.0 (11.1)	50.7 (11.5)	51.7 (10.9)	50.7 (11.0)	
Adjusted mean change (95% CI)					
Model 1[‡]	0.12 (−1.04 to 1.29)	0.00 (reference)	0.43 (−2.34 to 3.19)	0.03 (−2.74 to 2.81)	0.83
Model 2[§]	−0.15 (−1.33 to 1.03)	0.00 (reference)	0.60 (−2.15 to 3.34)	−0.53 (−3.29 to 2.23)	0.80

CI, confidence interval; HRQL, health-related quality of life; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research.

* Results were obtained from linear mixed models with random between-participant variations in both HRQL scores at diagnosis and HRQL changes over time.

[†] P value for linear trend across continuous changes in WCRF/AICR adherence score over time.

[‡] Mean change per unit increase in within-subject WCRF/AICR adherence score over time, adjusted for WCRF/AICR adherence score at diagnosis (either continuous or tertiles), recruitment region, attained educational level, parity, menopausal status at diagnosis, and basal and changes over time in age, partner status, working status, smoking status, total energy intake, number of comorbidities, and family history of breast cancer.

[§] Mean change per unit increase in within-subject WCRF/AICR adherence score over time, further adjusted for tumor receptor status at diagnosis, tumor stage at diagnosis, and basal and changes over time in breast surgery, chemotherapy, radiotherapy, hormone therapy, targeted therapy, lymphedema, and recurrent or new primary breast cancer.

tertile. When exploring the longitudinal trend of both HRQL domains as a smooth function of changes in adherence to WCRF/AICR recommendations 7–12 years after BC diagnosis (Fig. 2), it was observed that the adoption of additional healthy lifestyles over time did imply a slight improvement in the physical, but not mental, domain. No subgroup differences were observed in these associations (Supplementary Fig. S2).

4. Discussion

The results of this study show that, at diagnosis, women with higher adherence to the recommendations had slightly better perception of their physical, but not mental, health, and that survivors who increased their adherence 7−12 years after diagnosis also showed a slight, although not statistically significant, improvement in their physical HRQL, while no changes were observed regarding their mental health.

The better physical health perceived by women with greater adherence to the WCRF/AICR recommendations at diagnosis, may be due to the fact that women with healthy lifestyles are more likely to have better general health, greater physical resilience, or a greater sense of control or empowerment, which contributes to general well-being. However, these women may not have better mental health perception, as the cancer diagnosis and the treatment process can have a significant
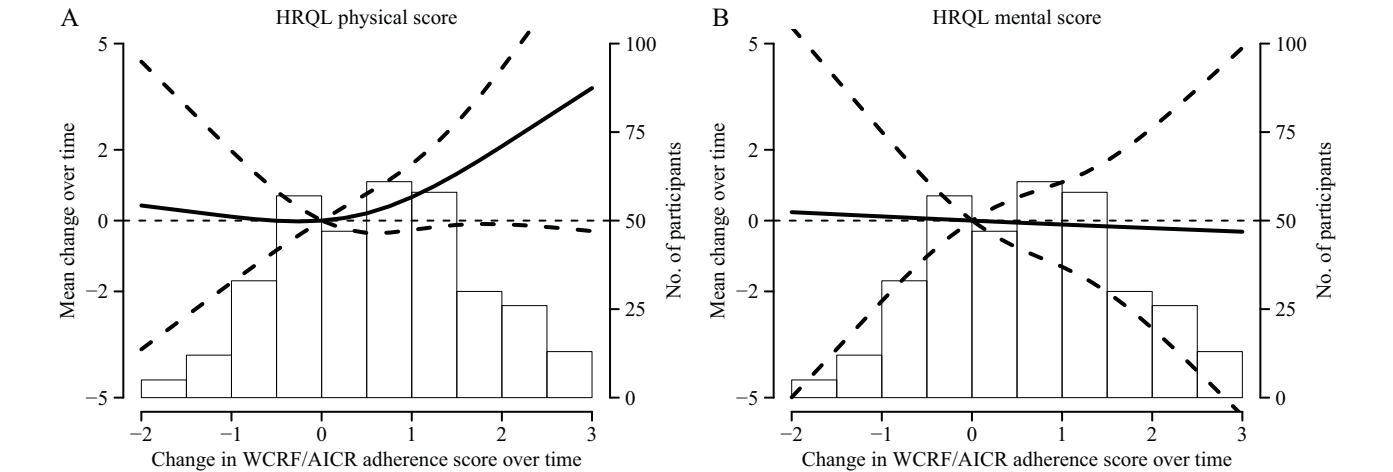
Fig. 2. Longitudinal trends in HRQL physical (A) and mental (B) domains as a smooth function of changes in adherence to WCRF/AICR recommendations 7–12 years after diagnosis of breast cancer.

Curves represent average longitudinal changes in HRQL scores over time (solid lines) and their 95% confidence intervals (dashed lines) based on restricted cubic splines of changes in WCRF/AICR adherence score over time with knots at the 5th, 50th, and 95th percentiles (−1.25, 0.50, and 2.25, respectively) and constrained to be 0 at diagnosis. Results were obtained from linear mixed models with random between-participant variations in both HRQL scores at diagnosis and HRQL changes over time, and adjusted for WCRF/AICR adherence score at diagnosis (restricted cubic splines), recruitment region, attained educational level, parity, menopausal status at diagnosis, tumor receptor status at diagnosis, tumor stage at diagnosis, and basal and changes over time in age, partner status, working status, smoking status, total energy intake, number of comorbidities, family history of breast cancer, breast surgery, chemotherapy, radiotherapy, hormone therapy, targeted therapy, lymphedema, and recurrent or new primary breast cancer. Histogram represents the frequency distribution of changes in WCRF/AICR adherence score over time. HRQL, health-related quality of life; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research.

emotional impact, significantly affecting the mental aspects of HRQL regardless of preventive behaviors [3]. Previous studies have shown that BC survivors with higher adherence to cancer prevention guidelines had better SF-36 physical and mental component summary scores [6], only better physical component [26], less fatigue and better quality of life [5,7], and worse arm symptoms [8].

Regarding subgroup differences, Koh et al. also found higher scores for the physical component associated with higher adherence to American Cancer Society guidelines only among premenopausal BC survivors [26]. Older women who comply with the recommendations may not perceive improvements in their physical HRQL, since their physical condition may already be deteriorated, and they tend to evaluate their health in terms of other people of the same age [27]. However, these women may perceive better mental health, since they cope with diagnosis and treatment with less emotional distress, anxiety, stress, and uncertainty than younger women [28]. The higher mental health scores detected in less educated participants who meet the recommendations may be influenced by greater control and acceptance of the diagnosis, or by a greater resilience acquired by the challenges and adversities previously experienced.

Focusing on the longitudinal association between adherence to WCRF/AICR lifestyle recommendations and HRQL, we have not found similar studies in BC women to compare. The 0.7 point improvement in the HRQL physical component observed in our fully-adjusted model may be relatively small to be considered clinically relevant. In any case, the values of the minimal clinically important difference have been shown to differ depending on the method of estimation (distribution-based method and anchor-based method), disease context, disease severity, study population characteristics, and the observed baseline values and change values [29]. On the other hand, the positive dose-response association detected with physical health, becoming stronger when women adhere to more recommendations over time, reinforces its possible importance for improving survivors' HRQL. This association may be due to the fact that survivors who adopted healthier lifestyles over time were able to strengthen their immune system and general health, thus reducing possible side effects from treatments or other diseases.

The most notable strength of this study lies in its prospective nature and the long follow-up of BC survivors. To our knowledge, this is the first study to evaluate the longitudinal association between global adherence to cancer prevention recommendations and HRQL after BC diagnosis. The 7–12 year follow-up helps ensure that survivors' behavior was not influenced by acute effects of treatments or possible transitory lifestyle changes during the early stages of the disease. On the other hand, adherence to WCRF/AICR cancer prevention recommendations was estimated based on the standard scoring system proposed by Shams-White et al. [21], which facilitates the comparability of results across studies. The SF-36 questionnaire has shown good performance in BC patients [30]. In addition, the availability of population-based reference values for this instrument allows for a richer interpretation of the scores obtained. On the other hand, the use of linear mixed models allowed us to include data from participants with missing data at one or two time points, and the analysis of inter-individual and intra-individual associations from a single model. Finally, we collected comprehensive sociodemographic and clinical characteristics, which allowed us to adjust for many covariates in the analyses.

There are also several limitations to be considered. Between-subject differences and within-subject changes in both, WCRF/AICR adherence score and HRQL mental component score, between diagnosis and follow-up were small, which could explain the modest improvement observed in the physical HRQL per unit increase in the adherence score and the lack of association with mental HRQL. Another important limitation is related to the attrition rate, since of the 767 patients recontacted in the Health-EpiGEICAM study, 10% refused to participate and 37% were excluded due to lack of information or implausible data. When comparing baseline characteristics between women who participated in the follow-up and those who did not, we found that women who did not participate were older, had higher body mass index, lower educational level, more

comorbidities and HER2+ tumors, and more advanced tumor stages. However, no differences were observed in terms of WCRF/AICR adherence score or HRQL at diagnosis (Supplementary Table S2). On the other hand, we have used an overall scoring system that weighs all recommendations equally, without taking into account that some recommendations may have a greater impact on the HRQL than others. Measurement errors cannot be ruled out, since a self-reported questionnaire was used that could have led to underreporting (body weight) and overreporting (physical activity, vegetable and fruit consumption) due to socially desirable responses. Finally, despite adjusting for a wide variety of potential confounders, residual confounding could still affect our estimates due to unmeasured variables (e.g., concomitant stressful life events).

5. Conclusions

The results of this study have allowed us to characterize the impact of adopting healthy lifestyles on the HRQL of long-term BC survivors, showing that adherence to more WCRF/AICR cancer prevention recommendations over time could contribute to a slight improvement in their physical HRQL without affecting their mental HRQL. These women would benefit from increasing adherence to these recommendations regardless of their baseline level of adherence. Given the growing number of women surviving BC, it is increasingly necessary to publicize and disseminate these lifestyle recommendations among them, to improve not only their physical health, but also other important BC outcomes and other pathologies that share the same risk factors.

Author contributions

M.P., Mi.M. and B.P.-G. designed the study; M.P., L.R. and S.B. adquired funding and have primary responsibility for the final content; A. G.-Z., S.A., M.B.-V., B.B., JM.B.-C., L.P., A.A., JI.C., Mo.M., JA.G.-S., C.O., P.S.-R., A.A.L., S.G, J.B., A.O. and Mi.M. acquired data; M.P., S.B. and L.R. contributed to the project administration and supervision; V.L., N.FL.-B., E.R.-M. and R.P.-B. contributed to data curation; V.L. and R.P.-B. conducted statistical analyses; V.L., R.P.-B and N.FL.-B. wrote the original draft. All authors read and approved the final manuscript.

Funding statement

Ethical standards

The study was approved by by Comité de Ética de Investigación Clinica, Consorci Sanitari de Terrassa (June 28, 2017), and the rest of ethics committes from participant institutions accepted that approval. All participants provided written informed consent.

Conflicts of interest

A.G.-Z. has received advisory/consultancy from AstraZeneca, Novartis, MSD, Pierre-Fabre, Exact Science and Menarini-Stemline; speaker bureau/expert testimony from Roche, AstraZeneca, Novartis, MSD, Pfizer and Menarini-Stemline; research grant/funding from Pfizer; travel/accommodation/expenses from Roche, Novartis and Pfizer. M.B.-V. honoraria for speaker bureaus from Novartis, Pfizer, Ipsen, and Advanced Accelerator Applications (AAA); support for attending meetings or travel from Novartis, Pfizer and Ipsen; and participation on advisory boards from Pfizer and Ipsen. B.B. reported receiving fees for medical education as consulting or advisory role with MSD, Roche, Pierre Fabre, Novartis,

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