Smoking and physical inactivity increase cancer prevalence in BRCA-1 and BRCA-2 mutation carriers: results from a retrospective observational analysis

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Abstract

Background The aim of this analysis in a pilot study population was to investigate whether we can verify seemingly harmful lifestyle factors such as nicotine and alcohol indulgence, obesity, and physical inactivity, as well as a low socioeconomic status for increased cancer prevalence in a cohort of BRCA 1 and 2 mutation carriers.

Methods The analysis data are derived from 68 participants of the lifestyle intervention study LIBRE-1, a randomized, prospective trial that aimed to test the feasibility of a lifestyle modification in BRCA 1 and 2 mutation carriers. At study entry, factors such as medical history, lifestyle behavior, and socioeconomic status were retrospectively documented by interview and the current BMI was determined by clinical examination. The baseline measurements were compared within the cohort, and presented alongside reference values for the German population.

Results Study participants indicating a higher physical activity during their adolescence showed a significantly lower cancer prevalence ($p = 0.019$). A significant difference in cancer occurrence was observed in those who smoked prior to the disease, and those who did not smoke ($p < 0.001$). Diseased mutation carriers tended to have a lower BMI compared to non-diseased mutation carriers ($p = 0.079$), whereas non-diseased revealed a significantly higher physical activity level than diseased mutation carriers ($p = 0.046$).

Discussion The present data in this small cohort of 68 mutation carriers suggest that smoking and low physical activity during adolescence are risk factors for developing breast cancer in women with *BRCA1* or *BRCA2* mutation. Further data of the ongoing LIBRE 2 study are necessary to confirm these findings in a larger cohort of 600 mutation carriers.

Keywords BRCA1 · BRCA2 · Physical activity · Lifestyle · Smoking · Cancer prevalence

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Background

Breast cancer is the most common cancer among women especially in developed countries, with an estimated 1.7 million new cases diagnosed worldwide each year [1]. Incidence rates vary nearly fourfold among different regions of the world [1], which obviously reflects differences in reproductive and lifestyle risk factors such as obesity, inactivity, and hypercaloric nutrition [2]. Therefore, these factors warrant special scientific interest. Numerous prospective studies have demonstrated that physical activity, the dietary pattern, and body weight, but also the social environments have a significant impact on the incidence of sporadic breast cancer, coping, and prognosis [2]. To what extent lifestyle factors can even intervene in the well-being of patients with genetic predisposition such as BRCA1 or BRCA2 mutation has hardly been studied.

Familial susceptibility to breast cancer accounts for approximately 25% of all breast cancer cases, 30% of which is attributed to the cancer susceptibility genes BRCA1 and BRCA2 [3]. These germline mutations are transmitted as an autosomal dominant form with incomplete penetrance. BRCA1 and BRCA2 are tumor suppressor genes that encode proteins that act in common pathways of genome protection and play important roles at different stages in DNA damage response and DNA repair [3]. Mutations in these genes confer a high risk of breast as well as ovarian cancer. The average cumulative cancer risk by the age of 70 has been estimated to be 80 and 55%, respectively, for BRCA1 mutation carriers and 60 and 16.5%, respectively, for BRCA2 mutation carriers [4]. Ovarian carcinoma occurs at a younger age in BRCA1 mutation carriers than in BRCA2 mutation carriers or the general population [5].

Current literature implies that the risk of developing cancer in gene carriers may be influenced through genetic factors (polymorphisms), as well as exogenous factors such as reproductive factors, lifestyle, and physical activity during adolescence [6–9]. The lifetime cancer risk ranges from 30 to 80% [6–9]. It also raises the question whether disease progression is influenced by the socioeconomic background. Lifestyle modulating factors such as smoking, alcohol consumption, eating habits, and physical activity are unevenly distributed among socioeconomic classes, and an influence on breast cancer risk is suspected [10–12].

So far, there are only few prospective studies examining the influence of the socioeconomic background, as well as modulating risk factors in women with BRCA 1 and 2 mutations. Overall, the importance of hereditary breast and ovarian cancer has been growing, since recent studies assume an increasing penetrance of inherited BRCA1 mutations as generations proceed [6, 13, 14]. Antoniou et al. postulate an increase of breast cancer penetrance at the range of 24–67% for female carrier of a *BRCA1* mutation, born after 1940.

Similar results were observed in an Icelandic cohort. The penetrance of the mutation has quadrupled in female *BRCA*1 mutation carriers born before versus after 1920, namely 18.6% (95% CI 11.0–29.5%) up to a value of 71.9% (95% CI 45.9–100%) ($p < 0.001$) [15]. A possible explanation for the increased penetrance may be a change of reproductive behavior [16], lifestyle, and social environment over the years.

The scientific analysis of the social composition, as well as the detection of a possible interaction of personal risk factors, lifestyle, and environmental determinants has achieved a unique degree of importance to prevent mutation carriers from developing cancer. Focusing on health consciousness and socioeconomic background, we aimed to analyze these factors in our study on a BRCA1 and 2 positive cohorts [17] and accentuate the differences to the age-adapted female German population.

Subjects and methods

Study cohort and patient recruitment

The BRCA 1 and BRCA 2 female mutation carriers described in this analysis were participants of the lifestyle intervention study LIBRE-1. A multicentre, interdisciplinary, prospective, open study design was used with two arms, randomizing participants into a control and an intervention group with a ratio of 1:1. LIBRE-1 aimed to analyze the feasibility of a lifestyle intervention for non-diseased and diseased BRCA mutation carriers in the form of a supervised physical training program and nutrition education focusing on the Mediterranean dietary pattern [17]. A large consecutive efficacy study including 600 mutation carriers is planned in the scope of the LIBRE 2 study [18].

The study was conducted at three study centers of the German Consortium of Hereditary Breast and Ovarian Cancer (GC-HBOC, http://www.konsortium-familiaerer-brustkrebs.de), Cologne, Kiel, and Munich. From February to July 2014, 68 patients with a pathogenic BRCA gene mutation were recruited for the clinical study. Inclusion criteria were a documented pathogenic BRCA 1 or BRCA 2 germline mutation, age over 18, and written informed consent. Exclusion criteria were an above-average physical fitness at the baseline visit with a ventilatory threshold VT1 in spiroergometry (VO_{2max}) > 150% of the general population at the baseline visit and different factors that interfere with a successful intervention: metastatic tumor disease, life expectancy < 3 years, limiting cardiovascular and lung diseases (instable coronary heart disease, heart failure NYHA stage IV, chronic obstructive pulmonary disease (COPD) GOLD IV, maximal resting blood pressure at rest > 160/100 mmHg), significant orthopaedic

problems, serious diseases, not allowing a participation in group interventions (e.g., psychiatric or internal ailment), a Carnovsky-Index < 60% [19], an exercise capacity < 50 W, food allergies not allowing consumption of a Mediterranean dietary pattern, a vegan diet, BMI < 15 kg/m^2, current pregnancy, insufficient knowledge of the German language, unwillingness to cooperate, and current participation in other lifestyle intervention trials.

The patients were recruited from the GC-HBOC register, from interdisciplinary genetic counseling units at the hospitals and via advertising campaigns in print media, on the Internet and at patient information events. Eligible patients received an information package, consisting of patient information, the written consent form, and the study flyer.

Approval, registration, and funding

The local Ethical Committees of the Universities of Munich, Kiel, and Cologne approved the study protocol [17], and written informed consent was obtained from all participants before entry into the study. The study has been registered at the German study register for clinical studies DRKS https://drks-neu.uniklinik-freiburg.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00005736), at the study register of the National Institutes of Health (clinicaltrials.gov Identifier: NCT02087592) and at the WHO (http://apps.who.int/trialsearch/Trial.aspx?TrialID=NCT02087592) and has been funded by the German Cancer Aid as a focus project for primary prevention (funding code 110013).

Within this clinical analysis, the impact of lifestyle risk factors and socioeconomic status was evaluated for our study cohort of non-cancer and cancer diseased BRCA mutation carriers, and a comparison was made to the age-adapted female German reference group according to the recent publication of the German Federal Statistical Office.

Assessment of the clinical baseline data

We conducted a baseline survey at the first study visit. Two interview forms were used to record the patient's medical history, disease status, and risk factors for carcinogenesis such as hormone replacement, reproduction, and behavioral factors of her lifestyle (clinical baseline questionnaire "KBAS"). Furthermore, the familial and social background, the grade of education, and the participant's income were encompassed (sociodemographic questionnaire "SOZ").

To record the smoking behavior, we asked the participating mutation carriers if they had ever smoked (yes/no), age of smoking begin, and the quantity and duration of the cigarette consumption, and if they were currently smoking. In addition, the participants were interviewed about their activity patterns in everyday life. Therefore, we assessed the time which they spent with bike riding, walking, gardening, fitness, and housework in winter and summer months on a daily base. Moreover, within the baseline questionnaire, study participants were requested to compare their individual activity pattern to age peers (clearly less active/slightly less active/the same level of activity/clearly more active than other women at the age of 10–19, 20–29, 30–39, 40–49, 50–59, and 60–69). Furthermore, alcohol consumption habits were investigated including the participants' age when she started to consume alcoholic beverages, the quantity, and alcoholic content that is consumed on a regular base (glasses of wine, aperitif, beer, and spirituous beverages/rarely or never/1 per month to < 1 per week/1–5 per week/6–10 per week/10–15 per week/> 15 per week). These data were converted into grams ethanol per day (g/day).

Besides that the mutation carriers were interviewed about their graduation degree and their income, divided into own salary and household income, to assess their socioeconomic level.

Statistical analysis

We used the electronic study management software "Open-Clinica" for the documentation of study visits. The statistical analysis was carried out after the database finalization at 07/01/2016. The statistical analysis was carried out using IBM SPSS 23. The planned number of patients for this feasibility analysis was 60. As the study was well accepted and the demand for participation was high, the recruited number of patients was 68.

Our analysis was of a descriptive nature, comparing the two groups diseased and healthy mutation carriers with one another. Where the parameters being analyzed were binary items, we applied a Chi-square test, and for metric parameters, we applied a t test for independent samples. As we view this work as hypothesis generating for the larger LIBRE 2 study, we decided not to apply a correction on the level of statistical significance, which was 0.05.

Results

Clinical data records were available for all subjects ($n = 68$) at study enrollment. Of the 68 participants, 8 were enrolled in Cologne, 23 in Kiel, and 37 in Munich. Thirty five of the participating women were randomized to the control group, and 33 to the intervention group.

Baseline data

Clinical data: age, prophylactic surgery, mutation, and cancer status

At study entry, the baseline median age of the study subjects was 41.5 years ranging from 24 to 72. 61.8% ($n = 42$) of the

patients showed a mutation in the BRCA1 gene, whereas 38.2% (n = 26) were carriers of a BRCA 2 mutation. Forty-six (67.6%) participants had previously developed cancer including three cases of ovarian cancer and 43 cases of breast cancer. As far as surgical interventions are concerned, 31 women (45.6%) had already undergone an adnexectomy mostly in terms of prophylactic bilateral salpingo-oophorectomy (PBSO), whereas 21 women (30.9%) had received a mastectomy, among them 7 cases with unilateral and 14 cases with bilateral mastectomy.

Lifestyle factors: smoking, BMI, physical activity, and alcohol consumption

At the time of study enrollment, eight participants were current smokers, 24 non-smokers, and 36 were former smokers. Sixty seven indicated intermittent alcohol consumption, of mostly wine or beer. Considering spirituous beverages, excessive drinking behavior was not reported.

Emphasizing physical constitution, clinical examination revealed a median BMI of 23.2 kg/m^2 determined within a range of 18 and 45 kg/m^2 in our study population of mutation carriers.

With reference to the statements about physical activity, 51% of the participating mutation carriers spent 1–3 h on physical training per week, whereas 21% showed an even higher level of activity consisting of 3–5 h/week. Ten percent of the mutation carriers stated a maximum of more than 5 h of physical training per week. Sixteen percent admitted to not doing any sports, and 2% did not provide information about their physical activity.

Evaluating the activity pattern in childhood and adolescence, defined as the time period between the age of 10–19, in our study, 55.1% of the mutation carriers stated to have participated in more than 3 h of sports per week, in contrast to 13% that admitted a lower level of physical activity during childhood and adolescence consisting of 2 h and 1 h/week, respectively, for another 13%. However, another 18.8% performed less than 1 h of physical exercise per week.

Socioeconomic factors: income and education

At study entry, 42 out of 68 provided information about their socioeconomic background. The mean net income was stated to be €3700 at the time of study enrollment.

Referring to educational level, 47% of the mutation carriers had a very high level of education, 13% a high level, and 40% indicated to have a low level of education.

Baseline data compared to the German population (Table 1)

BMI

Clinical examination revealed a median BMI of 23.2 kg/m^2 in our study population of mutation carriers. In this regard, the mean BMI in this study was well below the average of the female German peer group according to the latest release of the German Federal Ministry of Health 2013, which is specified in 25.7 kg/m^2 comprising women at the age of 41 ± 10 years (24.9 kg/m^2 in women at the age of 30–35, 25.4 kg/m^2 in women at the age 35–40, 25.7 kg/m^2 in women at the age 40–45, 25.9 kg/m^2 in women at the age 45–50, and BMI 26.7 kg/m^2 in women at the age 55–60).

Physical activity

Comparing our results of physical activity to the average German activity level, clear differences could be noticed as well. According to the Robert Koch Institute 2013, in

Table 1 Comparison of the study group with the German population

Parameter	LIBRE study group	Reference value	Cohort	Source
Physical activity (h/week)			40–49-year-old German females	Robert Koch Institute 2013
< 2.5	51%	83%		
> 2.5	49%	17%		
BMI (kg/m^2)	23.2	25.7	40–45-year-old German females	German Federal Ministry of Health
Present smoking (%)	11.8%	28.4%	40–49-year-old German females	German Federal Ministry of Statistics 2014
Netto household income (€)	€3700 (mean)	€3147 (mean)	German population	German Federal Ministry of Statistics 2014
Education level			German population	German Federal Ministry of Statistics 2015
Very high	47%	29.5%		
High	13%	29.4%		
Low	40%	32.9%		
Risk drinking (> 10 g/day)	1.5%	22.1%	German female population	Robert Koch Institute 2014

the age-adapted German reference group, the proportion of women who do not at all or rarely exercise was stated to be 47%, a percentage of 25% performed 1–3 h physical training per week, 21% showed a training level of 3–5 h/week, and only 5% exercise more than 5 h/week.

Smoking and alcohol consumption

In the scope of our analysis, the rate of active smokers in our collective (11.8%) was stated below the average of the German reference group of current smokers (28.4% in 2014) as published by the German Federal Statistical Office.

In terms of alcohol consumption, only one participant indicated a risky alcohol consumption of more than 10 g/day. According to the Robert Koch Institute, the proportion of women with an alcohol consumption of more than 10 g/day was 23.12% in an age-adapted control group of German women 2014. However, as far as moderate alcohol consumption is concerned, 31% of our study participants stated to have a moderate alcohol consumption compared to a share of 52.3% of age-correlated German women [20].

Socioeconomic background

A total of 24 indicated to have more than the national average net income at their disposal, which is specified at €3147 or above per month. In addition, analysis showed no significant difference concerning the educational level in our study group compared to the German reference group, stating 47.0 vs. 29.5% of very high educational level, 13.0 vs. 29.4% of high educational level, and 40.0 vs. 32.9% of low educational level, respectively.

Comparison of cancer diseased and non-cancer diseased mutation carriers

As far as health consciousness and priorities in lifestyle intervention are concerned, some differences could be noticed between diseased and non-diseased mutation carriers. Cancer diseased mutation carriers seemed to have a lower BMI than non-diseased study participants, although this was not statistically significant ($p = 0.079$) (Tables 2, 4). However, analyzing the motivation for physical activity, women without cancer in medical history revealed significantly higher levels of physical training per week compared to women that had already received a diagnosis of breast cancer (Tables 2, 4).

In the scope of physical activity, an additional analysis was then made examining the activity pattern in childhood and adolescence, in our study defined as the time period between the age of 10–19.

Accordingly, there is an indication for an important association between physical activity and cancer risk reduction by being more active than average during childhood and adolescence ($p = 0.019*$) (Tables 2, 4, Fig. 1).

Overall data illustrated a higher cancer prevalence in the study collective of present and former smokers ($p < 0.001$) compared to non-smokers. An association was not demonstrably attributable to the period of smoking time or age at smoking initiation (Tables 2, 3, 4).

In the context of analyzing the correlation of alcohol consumption and increase of cancer risk, this did not show statistical significance (Tables 2, 3, 4, Fig. 2).
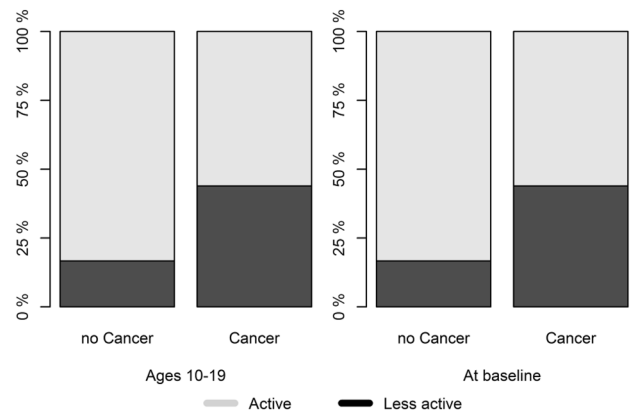

Fig. 1 Age-related physical activity of women diagnosed with cancer compared to women without cancer

Table 2 Comparison of diseased and non-diseased carriers at baseline

Parameter	Diseased mutation carriers $n = 46$	Non-diseased carriers $n = 22$	*p* value
Physical activity (h/week) at baseline	8	15	**0.046**
BMI (kg/m^2)	24 (mean)	28 (mean)	0.079
BMI at study time (kg/m^2)	22.5 ± 5 (mean)	25 ± −8 (mean)	0.079
BMI at age of 20	20.5 ± 3	22.5 ± 5	0.273
Ever smoked	$n = 35$	$n = 10$	**0.023**
Income (€)	4157 (mean)	3296 (mean)	0.189

Bold value indicates statistical significant

Furthermore, we examined the socioeconomic background considering discrepancies in the collective of our study participants. According to our data, diseased mutation carriers seemed to have lower households' incomes, but higher own incomes compared to healthy mutation carriers. Emphasizing the educational level, no difference could be demonstrated.

Table 3 Smoking behavior and alcohol consumption

	Diseased mutation carriers ($n = 46$)	Non-diseased mutation carriers ($n = 22$)	*p* value
Present smoker	6	2	0.535
Former smoker	27	9	1.000
Non-smoker	12	12	–
Age of smoking begin	16 ± 4	16 ± 4	0.666
Number of years smoked	12.5 ± 6	8 ± 9	0.527
Alcohol consumption			
Ever consumed alcohol	45	22	1.000
Consumption of more than 1 cl glass/day at the age of 20	8	6	0.356
Age at which regular alcohol consumption began	18.1	17.7	0.780

Correlation is significant at the 0.05 level (twotailed)

Discussion

Numerous studies demonstrate a noticeably increasing disease rate among BRCA mutation carriers. According to an Icelandic publication, a cumulative incidence of breast cancer (before the age of 70) between 1920 and 2000 among BRCA2 mutation carriers showed a fourfold increase (18.6 vs. 71.9%) [15]. A similar escalation of risk occurred in the general population, showing that the cumulative incidence for sporadic breast cancer has increased from 1.8 to 7.5% over the last 80 years [15]. Overall, a clear increase of penetrance within the context of a BRCA mutation can be noted, whereby, besides genetic variants, this might be contingent on a change in reproductive behavior, as well as lifestyle factors.

However, possible modifying lifestyle risk factors have mainly been examined in retrospective case–control studies in mutation carriers, whereby the results were mostly distorted by bias in the clinical setting as well as survival.

Table 4 Association between breast cancer and lifestyle

	Breast cancer	*n*	Mean (SD)	*p* value
Number of years smoked	No	11	12.4 (8.8)	0.808
	Yes	33	12.9 (6.0)	
Started smoking prior to breast cancer	No	0		**< 0.001**
	Yes	30		
More than a 1 cl glass of alcohol per day at 20	No	7		0.222
	Yes	7		
BMI at age of 20	No	24	22.5 (3.9)	0.419
	Yes	44	21.7 (3.5)	
More active than average before 20	No	17		**0.016**
	Yes	21		
HRT ever taken	No	4		0.185
	Yes	3		
Use of hormonal contraception—years	No	22		0.394
	Yes	42		
Age at menarche	No	23	12.9 (1.0)	0.095
	Yes	43	13.4 (1.5)	
ABITUR achieved	No	13		0.613
	Yes	20		
Academic (i.e., university level)	No	13		0.451
	Yes	19		

Bold value indicates statistical significant

ABITUR qualification at the end of high or secondary school (ca. 18 years of age), *HRT* hormone replacement therapy

Fig. 2 Influence of household income (left) and own net income (right) on cancer prevalence
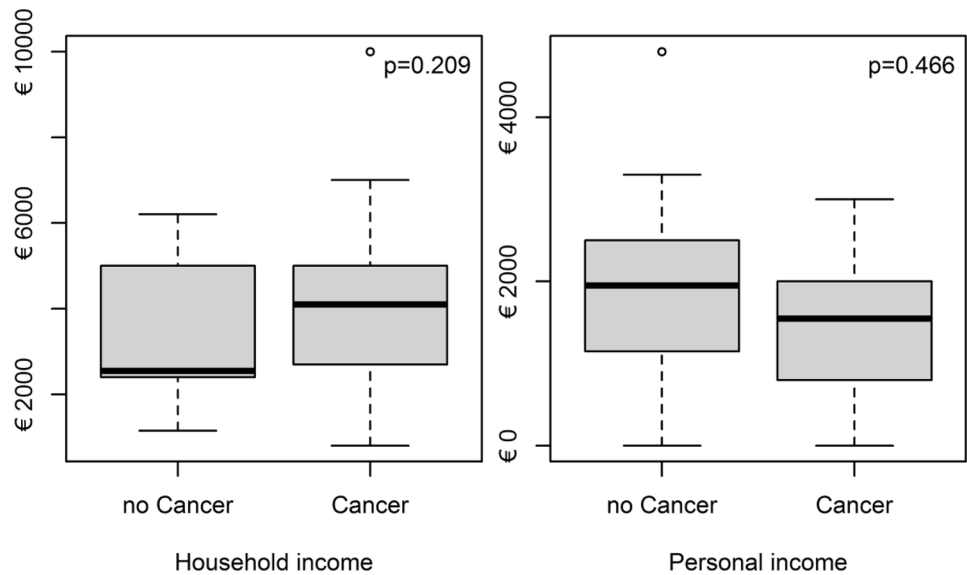
A validation of these findings through independent prospective studies has rarely taken place so far. The previous analyses yielded evidence of a presumable increase in risk through overweight, smoking, as well as lack of physical activity in the high-risk group of BRCA mutation carriers [9, 21]. Nonetheless, the limitations of these studies are small sample sizes, meaning that large prospective studies are necessary to validate these assumptions in the group of genetically predisposed women. The LIBRE-1 study aimed to illustrate, in terms of a prospective, randomized feasibility study (*n* = 68), that a lifestyle intervention in the high-risk group of BRCA mutation carriers is possible. If this can be undertaken successfully, a validation of the modified lifestyle factors can be carried out with a large collective in the scope of LIBRE-2 with the aim of developing programs to reduce cancer incidence in BRCA mutation carriers.

Along with surveillance for BRCA mutation carriers, there is still a need for evidence-based recommendations regarding lifestyle choices besides the rather radical options of prophylactic surgery. Particularly, among women who are not opting to undergo prophylactic surgery or who are delaying surgery, we are in need of these alternative options to improve the physicians' counseling [9].

Smoking

According to current data, smoking can be defined as a risk factor for the development of sporadic breast cancer [22]. Smoking during adolescence up until the first pregnancy is considered particularly risky due to the increased susceptibility to chemical carcinogens of the, at this point, still incompletely differentiated mammary gland [23, 24].

To what extent smoking can also have an effect as a modulating factor in the scope of a strong genetic predisposition such as a BRCA mutation has been examined in few studies this far, and the existing data are inconsistent.

In 2009, Ginsburg et al. reported that there was no increase in the risk of breast cancer associated with current smoking in BRCA1 or BRCA2 carriers, based on their study of 2536 cases of breast cancer among women with a BRCA mutation [25]. Nevertheless, they noted that there seemed to be a possibility of an increased risk of breast cancer among BRCA1 carriers associated with past smoking [25]. Concluding it can be assumed that there are different effects of carcinogens in BRCA mutation carriers, depending on the timing of exposure [25].

Within our collective, 45% of the subjects stated that they had smoked in the past, at the beginning of the study 11.6% still smoked. Analyzing the data with respect to a smoking related increase in cancer prevalence, a statistically significant higher occurrence of cancer diseases could be determined in the collective of the BRCA positive smokers. However, an association between the intensity as well as the accumulated time period of nicotine consumption could not be found. This means that even in this small cohort, alone the habit of smoking can be considered as a significant risk factor for the high-risk collective of BRCA mutation carriers in developing carcinoma. Nonetheless, additional studies with a larger number of cases and an adjustment for other factors are necessary and already planned in the framework of the LIBRE 2 study.

In the scope of our analysis, we also noticed that a majority of the mutation carriers in our study collective already seem to display health-oriented efforts prior to the start of the study. They had already attempted to stop smoking by the time of the start of the study. The rate of active smokers in our collective (11.8%) was below the average of the

German reference groups of current smokers (28.4% in 2014) as published by the German Federal Statistical Office.

Body weight

In the scope of large cohort studies, obesity as well as weight gain during adulthood are consistently associated with an increased risk, particularly for postmenopausal, sporadic breast cancer [26]. Weight gain of more than 20 kg during adulthood doubles the risk of developing sporadic breast cancer [26]. In the framework of the Women's Health Study, which examined more than 34,000 women, a 25–40% risk reduction could be demonstrated for postmenopausal breast cancer through a weight reduction of at least 5% [26–29]. In the context of a meta-analysis, Suzuki et al. compared the highest versus the reference categories of relative body weight, showing that the risk for hormone receptor positive tumors was 20% lower among premenopausal and 82% higher among postmenopausal women [30]. To explain these contrary effects of BMI and obesity on breast cancer risk by menopausal status, for the most part, researchers have assumed that risk is moderated through an alteration in the source and levels of endogenous sex hormones, specifically estrogen as well as progesterone [9, 31]. Despite this, epidemiological evidence indicated an increased risk of triple-negative breast cancer with obesity, especially for premenopausal breast cancer [32].

Referring to *BRCA* mutation carriers, there are also data, which provide important evidence that the maintenance of a BMI within the recommended limits may even reduce the incidence of high-risk BRCA-associated breast cancer [9].

Kotsopoulos et al. conducted a large study including 2146 BRCA mutation carriers as matched pairs [BRCA1 ($n = 797$ pairs), BRCA2 ($n = 276$ pairs)] [33]. Within this trial, a loss of at least 10 lb (4.5 kg) in the period between 18 and 30 years was associated with a decreased risk of breast cancer between the age of 30 and 49, whereas weight gain during the same interval did not influence the overall risk [33]. Nevertheless, large prospective studies are needed to evaluate the influence of body weight and weight gain or loss in BRCA mutation carriers.

Now focusing on our collective, the participants showed an average BMI of 23.2 kg/m^2 at the start of the study. In this regard, the mean BMI in our study was well below the average of the female German reference group according to the latest release of the German Federal Ministry of Health (2013).

According to subgroup analysis women already diagnosed with breast cancer tended to show a lower BMI than women without diagnosis of cancer. This could possibly mean that women who suffer from cancer may try to reduce possible risk factors yielding in a reduction of body weight (Table 2). Conversely, other hypotheses contend a possible risk reduction for premenopausal breast cancer by overweight, accentuating the mostly premenopausal age at the time of cancer diagnosis when carrying a BRCA mutation. To clarify this question, we will need more data, which we expect within the framework of LIBRE 2.

Physical activity

Numerous studies proved a risk-reducing effect of physical activity, particularly during adolescence, on the development of pre- and postmenopausal breast cancer, a risk reduction that was even present in patients with a familial predisposition, although less pronounced [34]. Potential protective effects are suspected in the reduction of the endogenous concentration of sex hormones, insulin resistance, as well as chronic inflammatory processes [34]. In addition, actual studies suggested that factors, which increase the physiologic expression of the normal copy of the BRCA1 or BRCA2 gene and thereby normalize protein levels, contribute to stem cell homeostasis, and/or affect hormone levels, and, therefore, might mitigate the effects of an inherited BRCA mutation [9]. In an in vivo study (Wang et al. 2009, an increase in BRCA1 mRNA expression could be demonstrated with increasing levels of physical activity [9]. Within this study, Wang et al. mentioned that physical activity, particularly during childhood, may be linked to a reduced risk of developing breast cancer in BRCA1 mutation carriers [9].

In our study group, 55.1% of the participants indicated that they had partaken in physical activity over average during their adolescence (ages 10–19) resulting in statistically significant fewer cancer diseases in a grouped analysis (Table 2, 4, Fig. 1). This finding commensurates Wang's hypothesis in 2009.

Moreover, analysis of the physical activity level of women who had already had a diagnosis of breast cancer revealed a significantly lower performance per week compared to women without breast cancer (Table 2, Fig. 1).

As described previously, our collective had already depicted impressive physical activity at the start of the study, 51% of the subjects indicated that they exercised one to 3 h/week, 21% even indicated a weekly activity level of 3–5 h.

Comparing this activity level to the average German activity level, clear differences were to be noticed, where the proportion of women who were not doing any/rare sports was stated to be 47%. In this average German collective, a percentage of 25% performed 1–3 h physical training per week, 21% showed a training level of 3–5 h/week, and only 5% exercised training of more than 5 h/week (Table 1).

Alcohol consumption

As already pointed out, risky and moderate alcohol consumption of our LIBRE-1 collective was far below the

average of German women in 2014. In our analysis, we could not detect an alcohol-related change in breast cancer prevalence, which may be due to the small number of cases or the uniform levels of alcohol consumption in our population.

Socioeconomic background

In our analysis, there were no statistically significant findings regarding the influence of socioeconomic environment to cancer prevalence in BRCA mutation carriers. This will be further analyzed in the larger LIBRE-2 cohort [18].

In summary, the majority of the mutation carriers in our study seemed to be a rather health-oriented collective already before the start of the study. Lifestyle risk factors such as smoking and overweight were less prevalent than in peers. Physical activity was favored.

It seems that within our lifestyle intervention study, the mutation carriers at high risk for developing cancer disease might already have taken action to reduce cancer risks by a comparatively high level of health awareness. This might represent a selection bias of those, who consent to study participation. Digianni et al. [35] evaluated complementary and alternative medicine (including vitamins, special diets, herbal remedies, exercise, meditation/yoga, and acupuncture) by high-risk women before and 1 year following the confirmation of their BRCA1/2 genetic test results [9]. Women who are tested positive for a high-risk BRCA mutation frequently adopt new complementary and alternative medicine (CAM) use in the first year after learning about their genetic status considering these as part of their cancer preventive regimen [35].

This study likewise illustrates that after women receive a positive test result, they will modify their health practices and initiate supportive drugs for cancer prevention [9].

In particular, especially women diagnosed with cancer disease before, but also women who are aware of their high genetic cancer risks, show an outstanding interest in their health, resulting in a participation in physical training as well as awareness of nutrition and, therefore, body weight. This might also be their major motivation to participate in our lifestyle intervention trial (LIBRE-1). In this context, we must wait to see to what extent a significant improvement of the risk profile can be achieved through a lifestyle intervention conducted in our study, compared to an equally health-oriented control group. It can be assumed that so far two key events in BRCA mutation carriers sensitize them to lifestyle changes. The first is after they have been informed of the mutation and the second when they have been diagnosed with cancer. This information should be implemented in prevention programs for BRCA mutation carriers.

Despite careful attention to the methodology, there were a number of limitations that should be considered. This underlying analysis is a retrospective evaluation of clinical baseline characteristics of *BRCA* mutation carriers that were enrolled in the LIBRE-1 study. On one hand, the selected sample (only women who decided to participate in the lifestyle intervention program were included) results in a group of overall high degree of motivation and less overall variability of motivation. On the other hand, the sample size is very low; a more representative sample size is planned in the LIBRE-2 study. Therefore, our current analysis must be considered as hypothesis generating emphasizing the limitations of the study.

Compliance with ethical standards

Conflict of interest There is no conflict of interest.

Ethical approval All procedures performed in the LIBRE Study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This chapter does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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