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EPIDEMIOLOGY

# Physical activity and the risk of breast cancer in BRCA1/2 mutation carriers

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**Abstract** BRCA1/2 mutation carriers have a high lifetime risk of developing breast cancer. Differences in penetrance indicate that this risk may be influenced by lifestyle factors. Because physical activity is one of the few modifiable risk factors, it may provide a target to add to breast cancer prevention in this high-risk population. We examined the association between self-reported lifetime sports activity and breast cancer risk in a nationwide retrospective cohort study, including 725 carriers, of whom 218 had been diagnosed with breast cancer within 10 years prior to questionnaire completion. We found a nonsignificantly decreased risk for ever engaging in sports activity (HR = 0.84, 95%CI = 0.57–1.24). Among women who had participated in sports, a medium versus low level of intensity and duration (i.e., between 11.0 and 22.7 mean MET hours/week averaged over a lifetime) reduced the risk of breast cancer (HR = 0.59, 95%CI = 0.36–0.95); no dose–response trend was observed. For mean hours/week of sports activity, a nonsignificant trend was observed ($HR_{low\ versus\ never} = 0.93$, 95%CI = 0.60–1.43; $HR_{medium\ versus\ never} = 0.81$, 95%CI = 0.51–1.29; $HR_{high\ versus\ never} = 0.78$, 95%CI = 0.48–1.29; $p_{trend\ overall} = 0.272$; $p_{trend\ active\ women} = 0.487$). For number of years of sports activity no significant associations were found. Among women active in sports before age

The Netherlands Collaborative Group on Hereditary Breast Cancer (HEBON) is given in Appendix.

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30, mean MET hours/week showed the strongest inverse association of all activity measures ($HR_{medium\ versus\ low} = 0.60$, 95%CI = 0.38–0.96; $HR_{high\ versus\ low} = 0.58$, 95%CI = 0.35–0.94; $p_{trend} = 0.053$). Engaging in sports activity after age 30 was also inversely associated with breast cancer risk (HR = 0.63, 95%CI = 0.44–0.91). Our results indicate that sports activity may reduce the risk of breast cancer in BRCA1/2 mutation carriers.

**Keywords** Physical activity · Breast cancer · BRCA1/2 · HEBON · Epidemiology

## Introduction

The lifetime risk estimates for breast cancer in BRCA1/2 mutation carriers vary from 30 to 80% [1–7]. Differences in penetrance between generations, together with differences in age at onset and phenotypic expression between and within BRCA1/2 families, indicate that the risk of breast cancer may also be influenced by modifying genes and by environmental and lifestyle factors (with changing prevalence over time) [8]. It is well established that increased levels of physical activity decrease the risk of breast cancer in the general population by approximately 20–40% [9–13]. The association is most pronounced for postmenopausal women, although several recent large prospective cohort studies concluded that increased physical activity may decrease the risk for premenopausal breast cancer as well [14–16]. Because physical activity is one of the few modifiable risk factors, it may provide a target to add to breast cancer prevention in this high-risk population.

Only two small studies investigated physical activity and breast cancer risk in BRCA1/2 carriers [6, 17]. In a case–case study ($N = 104$) [6], teenage sports activity (yes vs. no) was associated with a 10-year delay in breast cancer onset (univariate analyses). An unmatched case–control study ($N = 137$) [17] investigated recent leisure-time physical activity and breast cancer risk and observed no apparent association. To our knowledge, this is the first large study specifically examining physical activity and breast cancer risk in BRCA1/2 mutation carriers.

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## Materials and methods

### Study population

The present study is part of an ongoing nationwide study [HEreditary Breast and Ovarian cancer study, the Netherlands (HEBON study)] among members of BRCA1/2 families in the Netherlands. The general design includes a retrospective cohort [because the BRCA1/2 DNA test is available only fairly recently (1995)] with a prospective follow-up. BRCA1/2 families were identified through ten centers [nine Clinical Genetic Centers (CGCs)/Family Cancer Clinics and the Foundation for the Detection of Hereditary Tumours (STOET)]. The study was approved by the medical ethics committees of all participating centers. Female family members were eligible if they (a) carried a BRCA1 or BRCA2 mutation; (b) were alive and had no personal history of breast and/or ovarian cancer on January 1, 1960, or born after 1960; and (c) were at age 18 or older at study entry. A self-administered risk factor questionnaire was mailed to eligible individuals by their clinical geneticist in the period of January 1999 to August 2007. To reduce potential survival bias, a close relative was asked to complete a shorter version of the standard questionnaire (proxy questionnaire) for eligible individuals who had died. Informed consent was obtained from each individual (or their proxy). Information on cancer history and prophylactic surgeries was either self-reported for the period not covered by the registries (<1989) and/or collected through the Netherlands Pathology Database (PALGA) [18] and the Netherlands Cancer Registry (NCR) until August 2007. Ninety-five percent of breast cancers diagnosed after 1988 were confirmed by PALGA/NCR. Information on deaths was retrieved through municipal registries.

The initial cohort consisted of 1,120 BRCA1/2 mutation carriers (response 80%; among proxies 76%). For 26% of eligible deceased carriers ($n = 299$), we could not find a proxy. We excluded seven carriers of whom the age at end of follow-up was missing ($n = 7$), and for reliability reasons we also excluded carriers of whom at least 50% of physical activity information was missing [$n = 87$, of which 53 (62%) were proxy questionnaires]. This resulted in an entire cohort of 1,026 carriers, of whom 468 had been diagnosed with breast cancer.

### Analytic cohort

Physical activity is related to overall survival [19, 20] and breast cancer-related survival [21–23]. Consequently, in this study population of women at high risk of cancer death, prevalent cases that were relatively active may have been overrepresented in our entire cohort, leading to bias toward unity (assuming physical activity reduces breast cancer

risk). Therefore, to reduce potential survival bias, we restricted the analysis to person-years within 10 years prior to questionnaire completion [24–26]. In total, 218 cases were diagnosed with breast cancer within the 10-year period. The cohort included 20 obligate carriers (not tested themselves but considered as carrier because they had at least one proven carrier among their children, while inheritance was not paternal). Five percent ($n = 37$) of the questionnaires in the analytic cohort was completed by proxies.

### Assessment of sports activity

For each sport practiced over a lifetime, we collected information on type of sport, number of hours spent per week, and ages at which it was practiced. Women were instructed to report only sports activities that were performed for at least 6 months for 1 h per week. The detailed information allowed us to analyze the data time-varying. To investigate the intensity of activity, we assigned a metabolic equivalent (MET) value to each reported activity according to the compendium by Ainsworth et al. [27, 28].

### Statistical analysis

The adjusted hazard ratios (HRs) as estimates of relative risk and 95% confidence intervals (95%CI) were obtained using a time-varying, multivariable Cox proportional hazards model with age (in years) as time scale. Follow-up started at 10 years prior to questionnaire completion and ended at date of first breast cancer diagnosis, date of bilateral prophylactic mastectomy, date of linkage with PALGA/NCR, date of completing the questionnaire if no informed consent for linkage was given, or date of death, whichever occurred first. All analyses were adjusted for age at the start of follow-up, intrinsically stratified for birth cohort (<1943, 1943–1954, 1955–1963, >1963) and gene (BRCA1 and BRCA2) and clustered on family to correct for potential within-family correlations in risk factors. Additionally, all analyses were weighted according to the weighted cohort approach to correct for potential testing bias [29].

We investigated average lifetime sports activity, sports activity before and after age 30 (cutoff was based on power issues), and recent sports activity in different time windows (1, 2, 5, and 10 years). We analyzed three measures of sports activity for all active years: mean hours per week, mean MET hours/week, and number of active years. Number of active years counts any sport activity. Sports activity was categorized into four groups: a nonactive group and three physically active groups (tertiles) based on the (average) activity level at end of follow-up in breast cancer cases in order to maximize power. The nonactive women were considered as the reference group. To disentangle independent effects of the three measures of sports activity, we examined the association with breast cancer risk among women active in sports with women in the lowest tertile as the reference group. In this way we could simultaneously include mean MET hours/week or mean hours per week with number of active years in the model. Only exposure information in the period at risk (before the end of follow-up) was considered.

For the multivariate models, forward stepwise confounder selection, in which the effect of adding one confounder at a time was evaluated, was based on a more than 10% change in (at least one of) the $\beta$-estimates of the main exposure variables: ever/never lifetime sports activity, mean MET hours/week, and number of active years. Confounders (categorized based on the distribution in the entire cohort at the end of follow-up) were menopausal status, use of oral contraceptives, use of hormonal replacement therapy (HRT), body mass index (BMI) at age 18, age-specific BMI, parity, and alcohol consumption. For lifetime sports activity, the multivariate models were also adjusted for occupational activity (mean MET hours/week), which was based on the hours per week spent on the longest held occupation, the period it was practiced, and its intensity (sedentary, standing, or vigorous). Age at menarche, age at first full term pregnancy, breast-feeding, educational level, smoking, and family history did not change the $\beta$-estimates by more than 10% and were omitted from our final model. No violation of the proportional hazards assumption by any of the variables was observed.

All analyses were also performed for premenopausal women separately, using the same age at censoring as before or age at menopause, whichever occurred first. Two-sided p-values $\leq 0.05$ were considered statistically significant. All analyses were performed using STATA/SE 10.0 (StataCorp LP).

## Results

The characteristics of the study population are summarized in Table 1. The mean age at end of follow-up was 44.5 ± 13.3 years, and there was no difference between cases and noncases ($p = 0.277$). The mean age at questionnaire completion was 45.5 ± 12.7 years (cases were older than noncases: 48.1 ± 10.6 versus 44.4 ± 13.3 years, $p < 0.001$; proxy data excluded). Seventy-nine percent of women had ever participated in sports activity (69 and 85% among women were born before and after 1955, respectively). In active periods, the median MET hours/week of sports activity in active periods throughout life was 17.0 [which equals, for example, about 2.5 h of tennis (MET = 7.0) per week]. The median number of hours of sports activity per week was 2.7, and the median number of active years was 16.

**Table 1** Characteristics of the study population ($N = 725$)

| Characteristic | Cohort ($n = 725$) | | Cases ($n = 218$) | |
|---|---|---|---|---|
| | No.[a] | (%) | No.[a] | (%) |
| Gene | | | | |
| BRCA1 | 558 | (77) | 170 | (78) |
| BRCA2 | 167 | (23) | 48 | (22) |
| Carrier type | | | | |
| Proven | 705 | (98) | 213 | (98) |
| Obligate | 20 | (3) | 6 | (2) |
| Proxy data | | | | |
| No | 688 | (95) | 203 | (93) |
| Yes | 37 | (5) | 15 | (7) |
| Birth cohort | | | | |
| <1943 | 101 | (14) | 31 | (14) |
| 1943–1954 | 165 | (23) | 67 | (31) |
| 1955–1963 | 199 | (27) | 66 | (30) |
| >1963 | 260 | (36) | 54 | (25) |
| Age at end of follow-up | | | | |
| <35 years | 180 | (25) | 51 | (23) |
| 35–41 years | 159 | (22) | 47 | (22) |
| 42–50 years | 180 | (25) | 61 | (28) |
| >50 years | 206 | (28) | 60 | (28) |
| Age at menarche | | | | |
| ≤12 years | 232 | (33) | 77 | (36) |
| 13 years | 183 | (26) | 51 | (24) |
| ≥14 years | 291 | (41) | 84 | (40) |
| Parity | | | | |
| Nulliparous | 185 | (26) | 47 | (22) |
| Parous | 540 | (74) | 171 | (78) |
| Number of children | | | | |
| 1–2 children | 365 | (68) | 128 | (75) |
| >2 children | 175 | (32) | 43 | (25) |
| Age at first full term pregnancy | | | | |
| <24 years | 143 | (27) | 55 | (32) |
| 24–28 years | 185 | (34) | 53 | (31) |
| ≥28 years | 212 | (39) | 63 | (37) |
| Breast-feeding | | | | |
| Never | 137 | (25) | 46 | (27) |
| Ever | 402 | (75) | 125 | (73) |
| Age-specific BMI (kg/m$^2$) | | | | |
| <22 | 227 | (32) | 71 | (33) |
| 22–25 | 239 | (33) | 68 | (32) |
| ≥25 | 251 | (36) | 76 | (35) |
| BMI at age 18 (kg/m$^2$) | | | | |
| <19.6 | 244 | (34) | 72 | (33) |
| 19.6–21.8 | 237 | (33) | 74 | (34) |
| ≥21.8 | 244 | (34) | 72 | (33) |
| Oral contraceptive use | | | | |
| Never | 92 | (13) | 23 | (11) |
| Ever | 631 | (87) | 194 | (89) |
| Menopausal status | | | | |
| Premenopausal | 417 | (58) | 155 | (71) |
| Postmenopausal | 308 | (42) | 63 | (29) |
| Type of menopause | | | | |
| Natural | 138 | (45) | 49 | (78) |
| Surgical, prophylactic | 138 | (45) | 13 | (21) |
| Surgical, ovarian cancer | 26 | (8) | 1 | (1) |
| Unknown | 6 | (2) | 0 | (0) |
| HRT use | | | | |
| Never | 211 | (69) | 46 | (73) |
| Ever | 93 | (31) | 27 | (27) |
| Alcohol consumption | | | | |
| Never | 290 | (40) | 92 | (43) |
| Ever | 433 | (60) | 124 | (57) |
| Smoking | | | | |
| Never | 336 | (46) | 100 | (46) |
| Ever | 389 | (54) | 118 | (54) |
| Educational level | | | | |
| Low | 281 | (39) | 90 | (42) |
| Medium | 241 | (34) | 62 | (29) |
| High | 197 | (27) | 63 | (29) |
| Family history | | | | |
| No | 301 | (43) | 80 | (37) |
| Yes | 405 | (57) | 135 | (63) |

[a] Numbers do not always add up to 100% due to missing values; Number of children, Age at first full term pregnancy and Breast-feeding apply to parous women only (100%); Type of menopause and HRT use apply to postmenopausal women only (100%)

The estimated hazard ratios for the association between average lifetime sports activity and the risk of breast cancer are presented in Table 2. We observed a nonsignificant risk reduction for ever engaging in lifetime sports activity (HR = 0.84, 95%CI = 0.57–1.24). Overall, a medium level of intensity and duration (mean MET hours/week averaged over a lifetime) of sports activity was associated with a risk reduction (HR = 0.64, 95%CI = 0.38–1.06) when compared to never sports activity. A medium level was defined as between 11.0 and 22.7 MET hours/week, which equals, e.g., 1.6 to 3.2 h of tennis. Among active women, a medium level of intensity and duration of sports (corrected for number of active years) was associated with a risk reduction (HR = 0.59, 95%CI = 0.36–0.95) when compared to a low level while for a high level the risk was not significantly decreased (HR = 0.77, 95%CI = 0.64–1.27). For mean hours of sports activity per week (corrected for number of active years), a nonsignificant trend was

**Table 2** Lifetime sports activity and the risk of breast cancer ($N = 725$)

| | Person-years | Cases | Multivariate | |
|---|---|---|---|---|
| | | | HR (95% CI)[a] | HR (95% CI)[b] |
| Lifetime sports activity | | | | |
| Never | 1,199 | 46 | 1.00 | – |
| Ever | 4,726 | 172 | 0.84 (0.57–1.24) | |
| Mean MET hours/week | | | | |
| Low (<11.0) | 1,255 | 54 | 1.06 (0.70–1.59) | 1.00 |
| Medium (11.0–22.7) | 1,788 | 52 | 0.64 (0.38–1.06) | 0.59 (0.36–0.95) |
| High (≥22.7) | 1,683 | 66 | 0.83 (0.50–1.37) | 0.77 (0.48–1.24) |
| $p_{trend}$ | | | 0.286 | 0.494 |
| Mean hours/week | | | | |
| Low (<2.0) | 1,280 | 53 | 0.93 (0.60–1.43) | 1.00 |
| Medium (2.0–3.3) | 1,732 | 53 | 0.81 (0.51–1.29) | 0.88 (0.56–1.39) |
| High (≥3.3) | 1,714 | 66 | 0.78 (0.48–1.29) | 0.85 (0.54–1.34) |
| $p_{trend}$ | | | 0.272 | 0.487 |
| Number of active years | | | | |
| <9 years | 821 | 36 | 0.80 (0.49–1.31) | 1.00 |
| 9–19 years | 1,607 | 59 | 0.89 (0.55–1.43) | 1.21 (0.72–2.03) |
| ≥19 | 2,298 | 77 | 0.83 (0.52–1.30) | 1.11 (0.67–1.85) |
| $p_{trend}$ | | | 0.468 | 0.820 |

Missing values (<4%) were coded as an additional level to include as many participants as possible for the adjustment factors. Test for trend were conducted on the medians of the categories of sports activity

*HR* Hazard ratio, *CI* confidence interval

[a] A weighted time-varying Cox proportional hazards model, stratified for genes (BRCA1 and BRCA2) and birth cohort (<1943, 1943–1954, 1955–1963, >1963), and clustered on family (404 clusters) with never sports activity as the reference category. The models are adjusted for use of oral contraceptives (never/ever), parity (nulliparous, 1–2 children, >2 children), menopausal status (premenopausal, natural menopause, surgical prophylactic, surgical ovarian cancer; time-varying), HRT use (never/ever), age-specific BMI (<22, 22–25, ≥25 kg/m$^2$; time-varying), BMI at age 18 (<19.6, 19.6–21.8, ≥21.8 kg/m$^2$), alcohol consumption (never/ever), and occupational activity (mean MET hours/week)

[b] As model [a]with the lowest sports activity category as the reference category and adjusted for activity (yes/no). The models for mean MET hours/week and mean hours/week were additionally adjusted for number of active years, and the models for number of active years were additionally adjusted for mean MET hours/week

observed ($HR_{low\ versus\ never} = 0.93$, 95%CI = 0.60–1.43; $HR_{medium\ versus\ never} = 0.81$, 95%CI = 0.51–1.29; $HR_{high\ versus\ never} = 0.78$, 95%CI = 0.48–1.29; $p_{trend\ overall} = 0.272$; $p_{trend\ active\ women} = 0.487$). For number of active years of sports activity no significant associations were found.

Ever versus never having participated in sports activity before age 30 was not associated with breast cancer risk (Table 3). However, among women active in sports before age 30, we observed stronger risk reductions for increasing levels of sports activity. The inverse association was most clear for mean MET hours/week ($HR_{medium\ versus\ low} = 0.60$, 95%CI = 0.38–0.96; $HR_{high\ versus\ low} = 0.58$, 95%CI = 0.35–0.94, $p_{trend} = 0.053$). For sports activity after age 30, we found that any activity was associated with a risk reduction of breast cancer (HR = 0.63, 95%CI = 0.44–0.91). No dose–response trends were observed for any of the aspects of sports activity after age 30. Additional adjustment for sports activity in the other periods did not materially affect the results (data not shown).

For recent sports activity (Table 4), the associations were less strong but similar to those found for sports activity after age 30 (Table 3). Furthermore, no differences between the different time windows were observed.

Effect modification by age-specific BMI (<23.8 and ≥23.8 kg/m$^2$) was investigated by stratified (unweighted) analysis (data not shown). When compared to the unweighted results (data not shown), the inverse associations were somewhat more pronounced for relatively lean women but the differences were small. The largest discrepancy was observed for sports participation after age 30: the HRs were 0.58 (95%CI = 0.38–0.88) and 0.75 (95%CI = 0.49–1.15) in lean and heavy women, respectively.

The analyses restricted to premenopausal carriers and BRCA1 carriers yielded essentially the same results (data not shown).

**Table 3** Sports activity before and after age 30 and the risk of breast cancer ($N = 725$)[a]

| Period | Activity | Person-years | Cases | Multivariate | |
|---|---|---|---|---|---|
| | | | | HR (95% CI)[b] | HR (95% CI)[c] |
| Before age 30 | Sports activity | | | | |
| | Never | 1,692 | 62 | 1.00 | – |
| | Ever | 4,233 | 156 | 1.01 (0.69–1.49) | |
| | Mean MET hours/week | | | | |
| | Low (<10.6) | 1,111 | 51 | 1.43 (0.94–2.17) | 1.00 |
| | Medium (10.6–21.7) | 1,434 | 45 | 0.83 (0.52–1.33) | 0.60 (0.38–0.96) |
| | High (≥21.7) | 1,688 | 60 | 0.77 (0.46–1.28) | 0.58 (0.35–0.94) |
| | $p_{trend}$ | | | 0.113 | 0.053 |
| | Mean hours/week | | | | |
| | Low (<2.0) | 1,128 | 49 | 1.32 (0.85–2.06) | 1.00 |
| | Medium (2.0–3.3) | 1,481 | 49 | 0.91 (0.58–1.42) | 0.70 (0.43–1.14) |
| | High (≥3.3) | 1,624 | 58 | 0.81 (0.48–1.36) | 0.65 (0.40–1.07) |
| | $p_{trend}$ | | | 0.223 | 0.128 |
| | Number of active years | | | | |
| | <7 years | 721 | 36 | 1.24 (0.76–2.04) | 1.00 |
| | 7–14 years | 1,537 | 56 | 1.13 (0.70–1.81) | 0.95 (0.56–1.63) |
| | ≥14 | 1,975 | 64 | 0.76 (0.48–1.20) | 0.68 (0.40–1.16) |
| | $p_{trend}$ | | | 0.195 | 0.109 |
| After age 30 | Sports activity | | | | |
| | Never | 2,619 | 112 | 1.00 | – |
| | Ever | 3,306 | 106 | 0.63 (0.44–0.91) | |
| | Mean MET hours/week | | | | |
| | Low (<11.0) | 1,176 | 31 | 0.55 (0.34–0.90) | 1.00 |
| | Medium (11.0–21.0) | 1,080 | 35 | 0.70 (0.44–1.14) | 1.27 (0.73–2.24) |
| | High (≥21.0) | 1,050 | 40 | 0.68 (0.43–1.09) | 1.24 (0.70–2.19) |
| | $p_{trend}$ | | | 0.157 | 0.509 |
| | Mean hours/week | | | | |
| | Low (<2.0) | 1,180 | 30 | 0.53 (0.32–0.86) | 1.00 |
| | Medium (2.0–3.0) | 829 | 30 | 0.80 (0.47–1.36) | 1.53 (0.83–2.83) |
| | High (≥3.0) | 1,297 | 46 | 0.66 (0.42–1.04) | 1.25 (0.71–2.20) |
| | $p_{trend}$ | | | 0.135 | 0.574 |
| | Number of active years | | | | |
| | <5 year | 938 | 30 | 0.52 (0.32–0.85) | 1.00 |
| | 5–11 years | 951 | 37 | 0.78 (0.48–1.26) | 1.29 (0.61–2.71) |
| | ≥11 | 1,417 | 39 | 0.64 (0.39–1.03) | 1.03 (0.61–1.73) |
| | $p_{trend}$ | | | 0.119 | 0.990 |

Missing values (<4%) were coded as an additional level to include as many participants as possible for the adjustment factors. Test for trend were conducted on the medians of the categories of sports activity

[a] For these analyses we excluded women who were censored/diagnosed before the age of 30 ($n = 91$; 29 cases)

*HR* Hazard ratio, *CI* confidence interval

[b] A weighted time-varying Cox proportional hazards model, stratified for genes (BRCA1 and BRCA2) and birth cohort (<1943, 1943–1954, 1955–1963, >1963), and clustered on family (387 clusters) with never sports activity as the reference category. The models are adjusted for use of oral contraceptives (never/ever), parity (nulliparous, 1–2 children, >2 children), menopausal status (premenopausal, natural menopause, surgical prophylactic, surgical ovarian cancer; time-varying), HRT use (never/ever), age-specific BMI (<22, 22–25, ≥25 kg/m$^2$; time-varying), BMI at age 18 (<19.6, 19.6–21.8, ≥21.8 kg/m$^2$), and alcohol consumption (never/ever)

[c] As model [b]with the lowest sports activity category as the reference category and adjusted for activity (yes/no). The models for mean MET hours/week and mean hours/week were additionally adjusted for number of active years, and the models for number of active years were additionally adjusted for mean MET hours/week

**Table 4** Recent sports activity and the risk of breast cancer in different time windows ($N = 725$)

| | Time window[a] | | | |
|---|---|---|---|---|
| | Multivariate[b] | | | |
| | HR (95% CI) 1 year[a] | HR (95% CI) 2 years[a] | HR (95% CI) 5 years[a] | HR (95% CI) 10 years[a] |
| Recent sports activity | | | | |
| No | 1.00 | 1.00 | 1.00 | 1.00 |
| Yes | 0.78 (0.55–1.09) | 0.76 (0.55–1.07) | 0.79 (0.57–1.09) | 0.77 (0.55–1.08) |
| Mean MET hours/week | | | | |
| Low (<10.0) | 0.64 (0.37–1.12) | 0.64 (0.38–1.07) | 0.64 (0.42–0.98) | 0.73 (0.49–1.09) |
| Medium (10.0–21.0) | 0.80 (0.50–1.28) | 0.74 (0.46–1.20) | 0.91 (0.56–1.50) | 0.70 (0.41–1.20) |
| High (≥21.0) | 0.88 (0.55–1.41) | 0.93 (0.58–1.49) | 0.92 (0.57–1.50) | 0.95 (0.59–1.54) |
| Mean hours/week | | | | |
| Low (<2.0) | 0.48 (0.26–0.87) | 0.49 (0.29–0.85) | 0.70 (0.47–1.03) | 0.70 (0.48–1.03) |
| Medium (2.0) | 0.90 (0.55–1.47) | 0.89 (0.52–1.50) | 0.71 (0.34–1.49) | 0.55 (0.16–1.94) |
| High (≥3.0) | 0.90 (0.58–1.40) | 0.94 (0.61–1.44) | 0.99 (0.63–1.55) | 0.83 (0.53–1.30) |
| Percent active years[c] | | | | |
| ≤50% | – | 0.43 (0.15–1.25) | 0.59 (0.31–1.12) | 0.63 (0.41–0.97) |
| >50% | 0.78 (0.55–1.09) | 0.80 (0.57–1.13) | 0.83 (0.59–1.17) | 0.84 (0.58–1.22) |

Missing values (<4%) were coded as an additional level to include as many participants as possible for the adjustment factors

*HR* Hazard ratio, *CI* confidence interval

[a] Age-specific mean sports activity (time-varying) in 1, 2, 5, and 10 year time windows. Example for the 5-year time-window: mean MET hours/week at age 35 is (Σ(MET hours/week at ages 35, 34, 33, 32, and 31))/5

[b] A weighted time-varying Cox proportional hazards model, stratified for genes (BRCA1 and BRCA2) and birth cohort (<1943, 1943–1954, 1955–1963, >1963), and clustered on family (404 clusters) with never sports activity as the reference category. The models are adjusted for use of oral contraceptives (never/ever), parity (nulliparous, 1–2 children, >2 children), menopausal status (premenopausal, natural menopause, surgical prophylactic, surgical ovarian cancer; time-varying), HRT use (never/ever), age-specific BMI (<22, 22–25, ≥25 kg/m$^2$; time-varying), BMI at age 18 (<19.6, 19.6–21.8,≥ 21.8 kg/m$^2$), and alcohol consumption (never/ever)

[c] The percentage of active years within the time window under investigation (e.g., for time window 1, ≤50 and >50% equals no and yes sports activity in that period, respectively; for time window 2, ≤50 and >50% equals 1 and 2 years of sports activity, respectively)

## Discussion

The results of this first large study specifically investigating physical activity and breast cancer risk in BRCA1/2 mutation carriers indicate that sports activity may reduce the risk of breast cancer in BRCA1/2 mutation carriers. Among women who had ever participated in sports activity, a medium versus low level of intensity and duration (mean MET hours/week in the active period) reduced the risk of breast cancer (HR = 0.64) but a higher activity level was not associated with a stronger risk reduction. Mean hours of sporting per week was associated with a nonsignificant risk reduction, while number of years engaged in sports activity did not appear to be associated with breast cancer risk. Among women who had participated in sports before age 30, trends for lower breast cancer risk with increasing mean MET hours/week, hours/week, or number of active years were observed. For sports activity after age 30, being active was associated with lower breast cancer risk (HR = 0.63) but no dose–response trends were found.

One of the two studies [6, 17] on physical activity and breast cancer risk in BRCA1/2 mutation carriers found an association and the other did not. The literature on physical activity and breast cancer risk in the general population [9] indicates a risk reduction of 25–30%, independent of BMI, with a dose–response effect (for each additional hour of activity per week the risk decreased by 6%). Stronger decreases in risk were reported for, among others, recreational activity, lifetime or later life activity, vigorous activity, among postmenopausal women, women with normal BMI, and those with hormone receptor-negative tumors [13]. The results of our study among BRCA1/2 mutation carriers are generally in line with the literature on the general population.

Sports activity may inversely be related to other measured and unmeasured physical activity dimensions. We also collected, although less extensively, information on occupational, household, and walking/cycling activity. We adjusted lifetime sports activity analyses for occupational activity (mean MET hours/week in active period), but none

of the aspects of occupational activity showed any significant associations with breast cancer risk (data not shown). In the Netherlands, walking and cycling is an important source of daily physical activity, e.g., grocery shopping by foot and going to school or work by bicycle. Because the total amount of walking/cycling is composed of many varying small amounts, walking/cycling is hard to report over a lifetime, although it certainly contributes to a higher background level of physical activity compared to studies in other countries. Because it was not feasible to collect lifetime information on walking/cycling and household activities, we assessed these activities for the year prior to questionnaire completion only, to be able to investigate the association with all aspects of physical activity in future prospective studies. We did not find a difference in the amount of time spent on walking/cycling or household activities in the year prior to the questionnaire completion between women who did and did not participate in sports activity (data not shown). This suggests that the other physical activity dimensions have not affected our risk estimates.

For lifetime sports activity, reduced risks were found for mean MET hours/week and hours/week and were less clear for number of active years. It was difficult to investigate the true separate effects of mean MET hours/week and hours/week (and to a lesser extent number of active years), because these were highly correlated (Pearson's $r = 0.86$, $p < 0.001$, $\chi^2$ $p < 0.001$) and the number of women with only vigorous sports activity was too small for a separate analysis. Our age-specific and recent sports activity analyses indicate that engaging in sports activity throughout life is important, because the observed associations were not limited to recent activity.

Despite the predominantly negative estrogen receptor status of BRCA1 breast cancers [30, 31], BRCA-related breast cancer is a hormone-sensitive tumor. This is reflected by, for example, the reduced risk of breast cancer in carriers who underwent prophylactic (salpingo-)oophorectomy [32]. Also, in vitro studies indicate that estrogens may play a role in BRCA1-related carcinogenesis [33]. In the general population, proposed mechanisms for a protective effect from physical activity are decreased lifetime exposure to estrogens and decreased percent of visceral body fat [34–36]. Furthermore, in the general population, the association between physical activity and breast cancer risk is most pronounced for postmenopausal and weaker for premenopausal breast cancer [9]. However, the evidence that physical activity may protect against premenopausal breast cancer is increasing [14–16]. Our study, which had most power for premenopausal breast cancer (71% of cases), adds to this evidence; the analysis restricted to the premenopausal period gave essentially the same results (data not shown) as for pre- and postmenopausal women together. An analysis restricted to postmenopausal women lacked power ($N = 308$; 63 cases). It is hypothesized that the risk reduction could be stronger after menopause because physical activity influences both endogenous hormone exposure and obesity, which has an independent association with breast cancer risk [37, 38]. Whether this difference also exists for BRCA1/2 mutation carriers is not yet known. The confounding effects of BMI at age 18 and age-specific BMI (time-varying) in the present study were small but enough to include them as covariates. We found no clear effect modification by BMI.

Several strong and weak points of our study should be considered in the interpretation of these results. Strengths of our study include, among others, the detailed information on lifetime sports activity, the medical confirmation of nearly all breast cancer diagnoses, the weighted cohort approach [29], the adjustment for age-varying BMI, and the high response rate suggesting that selection bias due to nonresponse is not likely in our study. However, the retrospective character of our cohort and the type of study population, consisting of carriers tested in the clinical setting, may have caused some biases in our results.

Even though we already reduced potential survival bias by restricting the analysis to person-years within 10 years prior to questionnaire completion, some survival bias may have affected our results, i.e., because relatively inactive BRCA1/2 carriers with early-onset breast cancer and a poor prognosis may not have survived 10 years to participate in our study. Comparison of the HRs for ever lifetime sports activity and the risk of breast cancer between the entire cohort (HR = 1.21, 95%CI = 0.94–1.57; data not shown) and the analytic cohort (HR = 0.84, 95%CI = 0.57–1.24), indeed suggested that survival bias might be present in our entire cohort. Hence, we cannot exclude the possibility of some survival bias in our results based on the analytic cohort. However, we were able to include information on deceased carriers through proxies. Unfortunately, a large proportion of proxy questionnaires had to be excluded because of incomplete physical activity information, resulting in the use of only 12% ($n = 37/299$) of the data of eligible proxies. An incident or a stricter analytic cohort (i.e., 5-year) analysis was not possible because the number of cases was too small ($n = 14$ incident cases).

Although our questionnaire was based on a validated questionnaire [39], measuring lifetime physical activity is difficult and, therefore, all studies suffer to a greater or lesser extent from (nondifferential) misclassification bias. Nondifferential misclassification may have resulted in some bias toward unity. Differential misclassification (recall bias) as an explanation for the risk reductions observed would imply that case subjects underreported their sports activities more frequently than noncases. This does not seem likely, because as shown in the Nurses' Health Study [40], cases tended to

underreport their activity less than controls. Furthermore, clinically tested unaffected BRCA1/2 carriers may be considered to be as health conscious as affected carriers.

We observed a significant risk reduction for ever participating in sports activity after age 30 while for sports activity before age 30, we only observed risk reductions among active women. Additionally, we found nonsignificantly increased risks for the lowest categories of all three measures of sports activity when compared to no sports activity before age 30. Recall of physical activity in the distant past may be more difficult than recalling recent activities [41]. Cases might be more motivated to report relatively short periods of sport activity in the distant past (or at relatively young ages) than noncases while for recent activity, quality of recall may be more equal for cases and noncases. Also, changes in physical activity after breast cancer diagnosis may to some extent have affected reported prediagnostic physical activity.

In conclusion, our results indicate that sports activity may reduce the risk of breast cancer in BRCA1/2 mutation carriers. However, more research is needed focusing on prospective follow-up of our cohort and similar cohorts in other countries before a definitive conclusion can be drawn and specific recommendations can be made.

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## Appendix

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