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Research Article

Weight History, Smoking, Physical Activity and Breast Cancer Risk among French-Canadian Women Non-Carriers of More Frequent *BRCA1/2* Mutations

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Several lifestyle factors play a significant role in determining an individual's risk of breast cancer. Many of them could be modified to protect against the malignancy. A nested case-control study was conducted to examine the association between selected lifestyle factors and non-*BRCA*-related breast cancer risk among French-Canadian women. Some 280 women with breast cancer and who were nongene carriers of mutated *BRCA* gene were recruited as cases. Another 280 women, without any cancer and nongene carriers of mutated *BRCA* gene served as controls. A tested lifestyle questionnaire was interviewer administered to incident cases to obtain information on weight history, smoking, physical activity, and other lifestyle risk factors. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated in logistic regression models. Comparing cases to controls, breast cancer risk was higher among subjects who reached their maximum body mass index (BMI) at an older age (>50 years) (OR = 2.83; 95% CI: 2.34–2.91). A positive association was noted between breast cancer risk and weight gain of >34 lbs compared to weight gain of ≤15 lbs, since the age of 20 (OR = 1.68; 95% CI: 1.10–2.58). Weight gain of >24 lbs compared to weight gain of ≤9 lbs, since the age of 30 also resulted in the same relationship (OR = 1.96; 95% CI: 1.46–3.06). Similarly, since the age of 40, weight gain of >12 lbs compared to weight gain of ≤1 lb was associated with increased breast cancer risk (OR = 1.91; 95% CI: 1.53–2.66). Women who smoked >9 pack-years of cigarettes had a 59% higher breast cancer risk ($P = .05$). Subjects who engaged in >24.8 metabolic-equivalent-(MET-) hours per week compared to ≤10.7 MET-hours per week of moderate physical activity had a 52% ($P = .01$) decreased risk and total physical activity between 16.2 and 33.2 MET-hours per week compared to ≤16.2 MET-hours per week, resulted in a 43% ($P = .05$) lower risk of breast cancer. In conclusion, weight history did affect breast cancer risk. Moreover, smoking appeared to raise the risk, whereas moderate physical activity had a protective effect.

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1. Introduction

Breast cancer was the second main cause of all causes of death among Canadian women in 2007 [1–3]. It is now known that germline mutations in the *BRCA* breast cancer susceptibility gene increase susceptibility to breast and ovarian cancers, with an average cumulative risk for breast cancers by the age of 70 of 65% in *BRCA1*-mutation carriers and of 39% in *BRCA2* mutation carriers [4]. Several lifestyle factors may play a significant role in determining an individual's risk of breast cancer and could be modified to protect against development of malignancy. For example, obesity,

a serious public health problem that is reaching epidemic proportions in many countries, significantly contributes to the development of certain cancers, including breast cancers [5]. Although anthropometric characteristics have been evaluated as possible determinants of breast cancer risk [6, 7], studies on the association of obesity with breast cancer risk in Western women have led to contradictory results. In addition, among commonly-studied lifestyle factors, physical activity has been the focus of numerous investigations. A 3% decrease in breast cancer risk has been observed for each 1-hour increase per week in recreational physical activity during adolescence, [8]. Indeed, a recent study has concluded that there is an increased risk for development of breast cancer in the presence of obesity and low levels of physical activity [9]. Likewise, smoking plays a highly significant role in cardiovascular and respiratory disease as well as in lung cancer and could affect breast cancer risk. However, the evidence is contradictory [5], and a collaborative reanalysis of the evidence from 53 epidemiological studies worldwide found that smoking had little or no independent effect on the risk of women developing breast cancer [10]. Most studies to date have addressed the relationship between lifestyle factors and breast cancer risk among sporadic cases or gene mutation carriers. To our knowledge, this is the first study which has addressed the issue in a specific population such as French Canadians, a group with a shared, specific genetic background and relatively more common BRCA mutations. Because it is currently not known whether lifestyle influences breast cancer risk in *BRCA* nongene carriers, we undertook the present study to examine associations between selected lifestyle factors and breast cancer risk among French-Canadian women who were noncarriers of the 6 more frequent founder mutations of *BRCA1/2*.

2. Materials and Methods

2.1. Study Population. The study subjects were identified from participants in an ongoing genetic breast cancer study, which began recruitment in 2004. Breast cancer patients who attended the Breast Center of Centre Hospitalier de l'Université de Montréal (CHUM) Hotel-Dieu were invited to participate during a follow-up appointment. They were French-Canadian women (those who were born in the province of Québec and having a maternal or paternal origin from the descendants of French origins who had settled in Canada) with early-onset breast cancer. Early onset of breast cancer is as breast cancer occurring at a younger age, without metastasis and considered to be disease with a large inherited component, that is, stemming from a mutation passed on from parent to child. In this study, cases who were $\leq$50 years old at diagnosis, with non-BRCA related invasive breast cancer, were eligible for the study, while those with in situ breast cancer had to have a positive family history of breast cancer or ovarian cancer to be eligible for this study. Cases >50 years old with invasive or in situ breast cancer had to have a positive family history of breast or ovarian cancer to be eligible for this study.

The diagnosis of breast cancer was confirmed by review of pathology reports and medical records by physicians and geneticists at the Chair of Breast Cancer of the Research Center of University of Montreal (RC-CHUM).

For the current study, cases and controls were tested for founder mutations. These women also provided written consent for *BRCA* gene testing, designed to detect the presence of 6 specific mutations found more frequently in families of French-Canadian descent [11]. A DNA-based test was conducted to identify any of 6 founder mutations in *BRCA1* or *BRCA2*. These 6 mutations *(BRCA1 3875del-GTCT, BRCA1 2953delGTAinsC, BRCA1 C4446T, BRCA2 8765delAG, BRCA2 3398delAAAAG, BRCA2 6085G > T)* account for approximately 85% of all *BRCA* mutations in the French-Canadian population. If they were not carriers of these mutations, they became eligible cases for this study.

Eligible cases were identified and interviewed, in order to construct a computerized pedigree and obtain information regarding sociodemographic characteristics and breast cancer risk factors. The inclusion criteria for cases stipulated that subjects must be French-Canadian women of all ages, recruited by the research team of the Epidemiology Research Unit of RC-CHUM from 2004–2006, noncarriers of any of the 6 founder mutations mentioned above, and having primary breast cancer without metastasis. The exclusion criteria for cases were non-French-Canadian women, being too ill to answer the questionnaires and affected by cancers other than breast cancer.

Some 285 noncarriers of these mutations with breast cancer (all ages) were selected sequentially until the target sample was achieved, from the mentioned above cohort of 513 French-Canadian women diagnosed from 2004 to 2006. Of these women, 2 cases (0.7%) refused to participate after being contacted, and 3 subjects (1%) changed their address and were unreachable at the time of data collection. Therefore 280 eligible cases (98%) were interviewed.

Control subjects were women from families with breast cancer ($n = 265$), except for 15, (5.4%) who came from the same families as cases. Of these: 8 had a sister-sister relationship; 4 had an aunt-niece relationship; 2 had a mother-daughter relationship; 1 had a grandmother-granddaughter relationship (see Table 5).

The inclusion criteria for controls were as follows: French-Canadian women of all ages, recruited at RC-CHUM, subjects not carrying any of the 6 founder mutations mentioned above and free from cancer. The exclusion criteria for controls were non-French-Canadian women, being too ill to answer the questionnaires and affected by cancer.

They were matched for age group (by 10-year age intervals) to cases. A total of 300 eligible controls were identified, of whom 13 (4%) were unreachable, and 7 (2%) refused to participate after the study was explained to them. In all, 280 eligible control subjects (93%) were interviewed.

2.2. Assessment of Lifestyle Factors. To assess weight history, participants were asked about their current weight and their weight when they were 20, 30, and 40 years old. They

Table 1: Selected characteristics of the study population.

Variables	Cases ($n = 280$) (%)	Controls ($n = 280$) (%)	P value[1]
Age (years, mean ± SD)	51.9 ± 8.2	50.0 ± 9.8	.01
<30	3	4	
31–40	17	27	
41–50	45	41	
51–60	29	23	
61+	6	5	
Education attainment (years, mean ± SD)	13.4 ± 3.0	12.8 ± 3.1	.01
Marital status			
Single	12.5	11.1	
Married/Common-law	70.4	66.4	
Separated/divorced	13.9	14.6	
Widowed	3.2	7.9	.15
Parity			
Nulliparous	27.1	15.4	.01
≥1	72.9	84.6	.01
Menopausal status			
Yes	203	145	
No	77	135	.01
Oral contraceptive use			
Ever	87.9	85.0	
Never	12.1	15.0	.40
Hormone replacement therapy			
Yes	26.8	33.6	
No	73.2	66.4	.10
Smoking			
Ever	63.6	53.6	
Never	36.4	46.4	.02
Smoking (pack-years, mean ± SD)	10.3 ± 13.4	7.8 ± 12.8	.03
Age at menarche (years, mean ± SD)	12.5 ± 1.5	12.7 ± 1.6	.12
Age at menopause (years)	45.4 ± 6.9	45.3 ± 7.9	.20
Age at maximum weight (years)	46.6 ± 11.9	39.4 ± 12.5	.01
Current weight (lbs)	146.6 ± 25.3	143.1 ± 25.1	.10
Weight at the age of 20 (lbs)	116.7 ± 16.0	119.9 ± 19.7	.06
Weight at the age of 30 (lbs)	129.9 ± 21.0	127.4 ± 14.8	.18
Weight at the age of 40 (lbs)	141.8 ± 28.1	137.4 ± 29.8	.20
Maximum lifetime weight (lbs)	155.8 ± 26.4	149.9 ± 28.5	.04
Weight gain since the age of 20 (lbs)	30.0 ± 22.6	23.2 ± 21.8	.01
Weight gain since the age of 30 (lbs)	21.3 ± 20.4	15.0 ± 18.7	.01
Weight gain since the age of 40 (lbs)	12.4 ± 14.9	6.9 ± 15.2	.01
Physical activity (MET-hours/week)			
Moderate (4)	18.8 ± 13.5	21.8 ± 14.8	.01
Vigorous (7)	8.1 ± 12.0	7.1 ± 11.0	.29
Total	26.9 ± 20.0	28.9 ± 18.8	.22
Total energy intake (Kcal)	2025.6 ± 674.2	1782.1 ± 626.3	.01

[1]All P values are univariate and derived by student's t-test for continuous variables with the χ^2 test for categorical variables.
MET: metabolic equivalent.

were also asked to give their highest weight (excluding pregnancies) as well as their age at their highest weight.

To evaluate participation in sports activities or physical exercise 2 years prior to diagnosis (cases) or interview (controls), the study subjects were asked in which seasons, how often, and the average duration per session they engaged in each of the 12 most common types of leisure-time physical activities in Canada. This section of the questionnaire was

Table 2: Odd ratios and 95% confidence intervals for breast cancer risk associated with weight history.

Variables	Q1	Q2	Q3	*P* for trend
Current BMI*				
Range (kg/m^2)	≤21.1	>21.1 and ≤25.0	>25.0	
Cases/Controls	91/92	98/94	91/94	
Univariate OR (95% CI)	1.00	1.34 (0.35–1.41)	1.76 (0.91–1.78)	.08
Multivariate OR[a] (95% CI)		1.25 (0.76–1.85)	1.55 (0.77–1.89)	.09
Age at maximum BMI				
Range (years)	≤39	>39 and ≤50	>50	
Cases/Controls	58/126	108/94	114/60	
Univariate OR (95% CI)	1.00	2.50 (1.65–3.78)	2.65 (2.60–3.41)	.01
Multivariate OR[a] (95% CI)		**2.77 (1.76–4.85)**	**2.83 (2.34–2.91)**	**.01**
Weight gain since the age of 20				
Range (lbs)	≤15	>15 and ≤34	>34	
Cases/Controls	80/115	93/78	107/87	
Univariate OR (95% CI)	1.00	1.71 (1.13–2.60)	1.67 (1.18–2.64)	.01
Multivariate OR[a] (95% CI)		**1.76 (1.13–2.72)**	**1.68 (1.10–2.58)**	**.01**
Weight gain since the age of 30				
Range (lbs)	≤9	>9 and ≤24	>24	
Cases/Controls	68/117	106/84	106/79	
Univariate OR (95% CI)	1.00	2.31 (1.52–3.50)	2.17 (1.44–3.28)	.01
Multivariate OR[a] (95% CI)		**2.25 (1.75–3.49)**	**1.96 (1.46–3.06)**	**.01**
Weight gain since the age of 40				
Range (lbs)	≤1	>1 and ≤12	>12	
Cases/Controls	55/120	80/63	103/60	
Univariate OR (95% CI)	1.00	1.95 (1.16–2.74)	1.99 (1.47–2.49)	.01
Multivariate OR[a] (95% CI)		**1.82 (1.36–3.10)**	**1.91 (1.53–2.66)**	**.01**

*BMI at interview.
[a]Adjusted for age, education, physical activity, smoking, alcohol consumption and total energy intake.

developed and used over more than 10 years of studies on cancer epidemiology by the Epidemiology Research Unit, CHUM-Hôtel-Dieu. Physical activities included walking, jogging or running, gardening or yard work, housework, golf, tennis, bowling or curling, swimming or water exercise, skiing or skating, bicycling, social dancing and other strenuous exercise. They indicated their usual frequency of participation in each of the above-mentioned activities by choosing 1 of the following categories: never, less than once per month, 1–3 times per month, 1-2 times per week, 3–6 times per week or every day. The average time per episode for each of the 12 activities included less than 15, 15–30, 31–60 minutes, and more than 60 minutes. Intensity was categorized as moderate or vigorous, and classification was based on the amount of energy or effort a participant expended in performing the activity [12]. Overall, physical activity exposure was quantified in terms of metabolic equivalents (MET), representing the number of kilocalories per hour each kilogram of body weight expended in activities [12]. MET-hours per week for each activity were computed by multiplying the MET score by activity duration. Moderate physical activity was defined as MET score of 4, and for vigorous physical activity, it was defined as 7 [12]. Finally, total physical activity for each participant, as measured by weekly MET-hours, was quantified by summing overall intensity activities.

To assess smoking habits, the subjects were asked if they ever smoked, and if they were currently smoking, their age at smoking initiation, age at smoking cessation, and average cigarettes consumption per day. A pack-year index was computed by multiplying the total number of years smoked by average consumption (in packs per day) over the smoking period.

Menopausal status was classified as either premenopause, natural postmenopause, surgical post menopause, or unknown, based on self-report of menstrual history. Age at menopause was the age at last natural menstrual cycle followed by one year of amenorrhea. For stratified analyses, categories of premenopausal and postmenopausal that included both natural and surgical menopausal groups were used. Women with unknown menopausal status were excluded from the stratified analyses.

For other lifestyle factors, the study subjects completed an in person interviewer-administered core questionnaire that included information regarding age, place of residence, education, height, weight and history of weight change, reproductive history, parity, breastfeeding, age at menarche, oral contraception, hormone replacement therapy, marital

Table 3: Odd ratios and 95% confidence intervals for breast cancer risk associated with lifestyle factors, including smoking and physical activity.

Variables	Q1	Q2	Q3	*P* for trend
Smoking				
Range (pack-years)	≤0	>0 and ≤9.0	>9.0	
Cases/Controls	106/134	67/66	107/80	
Univariate OR (95% CI)	1.00	1.28 (0.84–1.96)	1.69 (1.15–2.49)	.03
Multivariate OR[a] (95% CI)		1.35 (0.86–2.09)	**1.59 (1.57–2.87)**	**.05**
Moderate physical activity				
Range (MET-hours/week)	≤10.7	>10.7 and ≤ 24.8	>24.8	
Cases/Controls	80/108	91/95	109/77	
Univariate OR (95% CI)	1.00	0.68 (0.45–1.02)	0.52 (0.35–0.79)	.01
Multivariate OR[b] (95% CI)		0.67 (0.44–1.03)	**0.48 (0.31–0.74)**	**.01**
Vigorous physical activity				
Range (MET-hours/week)	≤0.11	>0.11 and ≤7.2	>7.2	
Cases/Controls	91/94	91/92	98/94	
Univariate OR (95% CI)	1.00	1.02 (0.68–1.54)	1.08 (0.72–1.61)	.93
Multivariate OR[b] (95% CI)		1.01 (0.66–1.56)	1.05 (0.66–1.52)	.94
Total physical activity				
Range (MET-hours/week)	≤16.2	> 6.2 and ≤33.2	>33.2	
Cases/Controls	87/100	89/98	104/82	
Univariate OR (95% CI)	1.00	0.69 (0.46–1.03)	0.72 (0.48–1.08)	.14
Multivariate OR[b] (95% CI)		**0.57 (0.37–0.87)**	**0.66 (0.43–1.01)**	**.05**

[a]Adjusted for age, education, physical activity, alcohol consumption, and total energy intake.
[b]Adjusted for age, education, alcohol consumption, smoking, and total energy intake.

status, tamoxifen use and alcohol consumption. They also completed an interviewer-administered 164-items semi-quantitative food frequency questionnaire (FFQ) over the telephone, on the possible role of diet in breast cancer risk, which permitted the quantification of alcohol consumption in the etiology of breast cancer. The FFQ was developed by the National Cancer Institute of Canada.

2.3. Statistical Analysis. Descriptive statistics were compiled to characterize the study population and to examine case-control differences. Demographic features and potential risk factors between cases and controls were compared by *t*-test for continuous variables and by the chi-square (χ^2) test for categorical variables.

Conditional logistic regression analysis was used to compute the odds ratios (ORs) and associated 95% confidence intervals (95% CIs) of breast cancer for the variables of interest. Because of the limited sample size, only those variables that were confounders in this dataset and for which there was a strong biological rationale were considered. Two sets of analyses were performed. In the first model, univariate modeling was applied to identify potential confounding variables. A *P*-value less than .05 was considered to be statistically significant [13]. In the second model, multivariate analysis was applied to control for confounding factors, and these results are presented below. Variables considered as confounders were age, education, physical activity, smoking, alcohol consumption, and total energy intake. Lifestyle variables were classified according to tertile distribution, with the lowest tertile being the reference category. The control group was used to create tertile cut points. Tests for linear trend were undertaken, and dose-response trends in risk calculation were evaluated for all analyses by fitting the continuous variable into the model with Wald values [14]. Tests for linear trend were performed by replacing the indicator lifestyle variable in each multivariate model with a single variable representing the median value of the indicator variable for a given category and by using the Wald X^2 value calculated for the regression coefficient of this variable to test the null hypothesis of no linear trend component in non-BRCA related breast cancer risk across tertiles. All tests were 2-sided.

Models were run separately for both pre- and post-menopausal women and were adjusted for age. Women were considered as postmenopausal if they reported having no menstrual periods at least 1 year before data collection.

3. Results

3.1. Characteristics of Study Subjects. Selected characteristics of cases and controls are summarized in Table 1. Mean (±SD) age of the cases was 51.9±8.2 years and 50.0±9.8 years for the controls ($P = .01$). Differences in age distribution were noticeable between cases and controls with a slight excess of younger control subjects. Cases had significantly higher education levels than the controls ($P = .01$). The nulliparous rate of the cases was significantly higher than that of the controls ($P = .01$), and cases also had fewer

Table 4: Multivariable adjusted odd ratios and 95% confidence intervals for breast cancer risk in relation to BMI, weight gain, smoking, and physical activity, by menopausal status.

Variable	Premenopausal		Postmenopausal	
	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)
Current BMI (kg/m^2)*				
≤22.5	20/45	1.0[a]	64/56	1.0[a]
>22.5 and ≤26.0	30/47	1.37 (0.96–2.60)	68/50	1.65 (0.96–2.70)
>26.0	27/43	1.02 (0.52–2.07)	71/39	1.19 (0.92–2.01)
P for trend		.56		.35
Weight gain (lbs) from the age of 30 to the age of 40				
≤13	27/49	1.0[a]	65/49	1.0[a]
>13 and ≤25	25/40	1.55 (0.81–1.86)	70/51	1.95 (0.88–2.17)
>25	25/46	1.62 (1.42–1.97)	68/45	**1.98 (1.11–2.03)**
P for trend		.05		**.03**
Weight gain (lbs) from the age of 40 to the age of 50				
≤13			66/52	1.0[a]
>13 and ≤25			67/55	2.01 (0.74–2.80)
>25			70/38	**2.01 (1.45–2.91)**
P for trend				**.04**
Weight gain (lbs) from the age of 50 to the age of 60				
≤13			69/50	1.0[a]
>13 and ≤25			71/47	1.86 (0.62–1.97)
>25			63/48	**1.79 (1.21–2.33)**
P for trend				**.03**
Smoking (pack-years)				
≤0	17/41	1.0[b]	62/55	1.0[b]
>0 and ≤9	31/45	1.30 (0.76–1.86)	70/47	1.62 (0.90–1.93)
>9	29/49	1.63 (1.23–2.47)	71/43	**1.49 (1.33–2.31)**
P for trend		.05		**.04**
Moderate physical activity (MET-hours/week)				
≤10.7	25/40	1.0[c]	69/45	1.0[c]
>10.7 and ≤24.8	32/47	0.57 (0.26–1.60)	60/53	0.65 (0.96–1.71)
>24.8	20/48	0.36 (0.22–0.67)	74/47	**0.42 (0.12–0.59)**
P for trend		.02		**.03**
Vigorous physical activity (MET-hours/week)				
≤0.11	27/43	1.0[c]	68/50	1.0[c]
>0.11 and ≤7.2	26/45	0.97 (0.56–1.64)	62/47	1.05 (0.46–1.73)
>7.2	24/47	1.02 (0.71–1.57)	73/48	0.99 (0.72–1.91)
P for trend		.76		.95
Total physical activity (MET-hours/week)				
≤16.2	26/44	1.0[c]	67/49	1.0[c]
>16.2 and ≤33.2	25/46	0.70 (0.46–1.24)	70/52	0.65 (0.46–1.83)
>33.2	26/45	**0.63 (0.41–0.97)**	66/44	**0.89 (0.35–0.91)**
P for trend		**.05**		**.05**

*BMI at interview.
[a]Adjusted for age, education, physical activity, smoking, alcohol consumption, and total energy intake.
[b]Adjusted for age, education, physical activity, alcohol consumption, and total energy intake.
[c]Adjusted for age, education, alcohol consumption, smoking, and total energy intake.

children than the controls ($P = .01$). There were more postmenopausal women among the cases than the controls ($P = .01$), perhaps due to the above mentioned different age distribution among cases and controls. The cases were significantly more likely to have smoked at any time in their lives than the controls ($P = .03$). The controls were more likely to have reached their maximum lifetime weight at an earlier age (39 years) than the cases (47 years) ($P = .01$), while history of weight change indicated that the cases had significantly higher maximum lifetime weight than the

Table 5: Matched cases and controls by relationship: 15 subjects.

Age of diagnosis of breast cancer cases (index cases)	Age of controls (relatives) at interview
Relationship	
Sister-sister:	
54	74
54	58
42	45
60	50
39	48
39	49
39	51
35	41
Sub total of subjects: 8	
Aunt-niece	
50	67
39	31
50	29
42	30
Sub total of subjects: 4	
Mother-daughter	
35	50
62	44
Sub total of subjects: 2	
Grandmother-granddaughter	
62	23
Sub total of subjects: 1	
Grand total of subjects: 15	

controls (155.8 v/s 149.9) ($P = .04$). Higher weight gain since adolescence and adulthood was observed among cases than the controls ($P = .01$). Controls practiced more moderate physical activity than the cases ($P = .01$). The cases were more likely to have greater total energy intake ($P = .01$) and alcohol (ethanol) intake ($P = .03$) than the controls, whereas no difference was apparent between study groups in the use of oral contraceptives and hormone replacement therapy, age at menarche and at menopause, current weight, weight at the age of 20, 30, and 40, and vigorous and total physical activity.

3.2. Weight History. The risk of breast cancer in relation to weight history is presented in Tables 2 and 4 reporting the results stratified by menopausal status. After adjusting for age, education, physical activity, smoking, alcohol consumption, and total energy intake, breast cancer risk was increased when subjects reached their maximum body mass index (BMI) at an older age (>50 years) (OR = 2.83; 95% CI: 2.34–2.91). In addition, a positive association was noted between maximum weight gain of more than 34 lbs compared to weight gain of ≤15 lbs, since age 20 (OR = 1.68; 95% CI: 1.10–2.58). Weight gain of more than 24 lbs compared to weight gain of ≤9 lbs since the age of 30 also showed similar results (OR = 1.96; 95% CI: 1.46–3.06). Likewise, a positive association with breast cancer risk (OR = 1.91; 95% CI: 1.53–2.66) was observed for a weight gain after the age of 40 of more than 12 lbs compared to a weight gain of ≤1 lb. Weight gain of more than 25 lbs from the age of 30 to the age of 40 presented an increased risk of breast cancer in both pre- (OR = 1.62; 95% CI: 1.42–1.97) and postmenopausal women (OR = 1.98; 95% CI: 1.11–2.03). Weight gain of more than 25 lbs from the age of 40 to the age of 50 presented an increased risk of breast cancer in postmenopausal women (OR = 2.01; 95% CI: 1.45–2.91) as well as weight gain of more than 25 lbs from the age of 50 to the age of 60 showed an increased risk of breast cancer in postmenopausal women (OR = 1.79; 95% CI: 1.21–2.33). No association was apparent between breast cancer risk and current BMI, and BMI at the age of 20, 30, 40, under 49, and over 50 years. Furthermore, maximum lifetime BMI did not show any significant association with breast cancer risk (data not reported).

3.3. Lifestyle Factors

3.3.1. Smoking. The ORs and 95% CIs for breast cancer risk by smoking status for all age groups are enumerated in Table 3; these results also appear in Table 4, where they are stratified by menopausal status. After adjusting for age, education, physical activity, alcohol consumption and total energy intake, women who smoked more than 9 pack-years had a 59% greater risk of breast cancer (OR = 1.59; 95% CI: 1.57–2.87) (Table 3). A 63% higher risk of breast cancer was also noted among premenopausal women (OR = 1.63; 95% CI: 1.23–2.47), with a 49% increased risk among postmenopausal women (OR = 1.49; 95% CI: 1.33–2.31) (Table 4).

3.3.2. Physical Activity. Women who practiced >24.8 MET-hours compared to ≤10.7 MET-hours of moderate physical activity weekly had a 52% lower risk of breast cancer (OR = 0.48; 95% CI: 0.31–0.74) (Table 3). Moreover, total physical activity between 16.2 and 33.2 MET-hours per week compared to ≤16.2 MET-hours per week also showed a 43% decreased risk of breast cancer (OR = 0.57; 95% CI: 0.37–0.87), and for >33.2 MET-hours per week, there was a nonsignificantly reduced risk (OR = 0.66; 95% CI: 0.43–1.01). A protective effect of moderate physical activity of more than 24.8 MET-hours per week was observed among both premenopausal (OR = 0.36; 95% CI: 0.22–0.67) and postmenopausal women (OR = 0.42; 95% CI: 0.12–0.59). A similar outcome was noted for total physical activity of more than 33.2 MET-hours per week for both premenopausal (OR = 0.63; 95% CI: 0.41–0.97) and postmenopausal women (OR = 0.88; 95% CI: 0.35–0.91) (Table 4). However, no statistically significant association was apparent between vigorous physical activity (>7.2 MET-hours/week) and breast cancer risk, regardless of menopausal status.

4. Discussion

The present case-control study provides results on lifestyle factors and breast cancer risk among French-Canadian women who are noncarriers of the 6 most frequent *BRCA1/2* mutations in this population. To our knowledge, this is the first epidemiological investigation to assess the possible role of common lifestyle variables in the etiology of breast cancer in such a sample. Previous research on lifestyle and breast cancer risk has been mostly undertaken on either sporadic subjects or among *BRCA* mutation carriers.

Our findings concur with previous work reporting that weight gain since youth is related to increased sporadic breast cancer risk [15–19]. Our results also demonstrate that weight gain has a stronger positive association among postmenopausal than premenopausal women. A recent case-control study of changes in body weight and the risk of breast cancer in *BRCA* mutation carriers reported that among *BRCA1* mutation carriers, a weight gain of more than 10 lbs between the age of 18 and 30 was associated with a 44% greater risk of breast cancer diagnosed between the age of 30 and 40 [20]. Moreover, these results bolster those of our research group's recent case-control study of a group of French-Canadian *BRCA* carriers, indicating that weight gain from the age of 18 and 30 was positively associated with breast cancer risk [21]. On the other hand, recent prospective data from the Black Women's Health Study suggested that weight gain in this population was not linked with postmenopausal breast cancer risk providing evidence for differential results in other ethnic populations. The findings also indicated that BMI $\geq$25 at the age of 18 of relative to <20 was associated with 32% and 47% reduced risks of breast cancer among premenopausal and postmenopausal African-American women, respectively, [22]. A likely contributor to the discrepancy in findings between Black and White women with regard to current BMI, weight gain, and postmenopausal breast cancer risk is the difference in distributions of estrogen receptor (ER) and progesterone receptor (PR) status. African-American women have a considerably lower proportion of breast carcinomas that are ER^+, PR^+, or both, than White women [22].

As women age, particularly after menopause, obese women have a high level of serum estrogen as a consequence of adrostenedione conversion to estrone in adipose tissue, and also due to decreasing concentrations of sex hormone-binding globulin that elevates serum free estrogen [23, 24]. High estrogen production may promote tumor growth. Our study also found that age at attainment of maximum BMI might be an important facet of body size when assessing breast cancer risk. Understanding the importance of age as a predictor of breast cancer risk involves consideration of the influence of adipose tissue on estrogen production and circulation, particularly postmenopause. From the onset of menopause, adipose tissue becomes the primary estrogen producer, and triacylglycerol and insulin levels rise simultaneously. The combination of these events is believed to lengthen a woman's exposure to more active estrogen [25, 26]. It has also been hypothesized that the effects of obesity may be stronger among older, postmenopausal women, due to the longer period of time they are subjected to the proliferative actions of elevated circulating estrogens from adipose tissue. Indeed, a higher breast cancer risk among older postmenopausal women compared to younger women has been suggested by a pooled analysis of 7 prospective studies [27]. Therefore, one may expect that women who reach their maximum BMI later in life will be at greater risk for breast cancer.

Our study showed that more than 9 pack-years of smoking had a significant positive association with breast cancer risk among both pre- and postmenopausal women; however, this result does not support our previous report of a reduced risk of breast cancer in carriers of *BRCA* gene mutations who had smoked more than 4 pack-years [28]. The weaker breast cancer risk in these subjects may have been associated with lower levels of circulating estrogens [29]. In contrast, a recent case-control study among Polish women indicated an increased risk of invasive breast cancer with the consumption of $\geq$10 cigarettes/d among both premenopausal (OR = 2.55; 95% CI: 1.81–3.60) and postmenopausal (OR = 1.78; 95% CI: 1.33–2.37) women [30]. Likewise, another recent study [31] suggested that *BRCA* mutation carriers who smoked had 2.3-fold (95% CI: 1.6–3.5) and 2.6-fold (95% CI: 1.8–3.9), respectively, greater risk of breast cancer. Cigarette smoke contains compounds that damage DNA, and the repair of such damage may be impaired in women with germline mutations. Some genotoxic carcinogens in tobacco smoke are mammary carcinogens in rodents [32]. The enzymatic machinery required for their metabolic activation is present in human mammary epithelial cells [33], and there is evidence of carcinogen-DNA adducts in human mammary tissue [34, 35], some of which may be smoking-related.

Finally, our study found that moderate physical activity was related to a decreased risk of breast cancer regardless of menopause status. Physical activity has received much attention for its salutary effect on breast cancer risk, as it is one of the few modifiable risk factors for breast cancer. Numerous epidemiological investigations have reported a reduced risk of breast cancer with increasing levels of physical activity [36, 37]. In 2002, the International Agency for Research on Cancer (IARC) concluded that "convincing" evidence exists for an inverse association between breast cancer risk and physical activity [38]. Our finding is also consistent with most recent work in this field. For instance in a case-control study by Kamarudin et al. [39], inactive women had a 3.5-fold significantly higher breast cancer risk compared to those who exercised regularly. Data from the California Teachers Study [40] (110599 women, 2649 invasive and 593 in situ cases) also demonstrated a 20% reduction of invasive, and 31% decrease of in situ, breast cancer risk among women who exercised regularly >5 hours/week per year. The authors reported a linear diminution of risk with escalating amounts of exercise. Recently, a population-based case-control study in Massachusetts established that neither lifetime recreational nor strenuous occupational physical activity appeared to be associated with breast carcinoma risk in situ. In contrast, recreational physical activity was associated with a reduced risk of invasive breast cancer in this investigation. After adjustment for potentially confounding

factors, women averaging >6 hours per week of strenuous recreational activity over their lifetime had a 23% decrease in the risk of invasive breast cancer when compared to women reporting no recreational activity (95% CI: 0.65–0.92; $P = .05$ for trend) [41].

Several biological mechanisms have been proposed to explain the lower risk of breast cancer associated with physical activity. In adolescents and young women who are very active, vigorous exercise is accompanied by delayed menarche, irregular and anovulatory menstrual cycles, and a shortened luteal phase [42–45]. Furthermore, postmenopausal women who are physically active have lower levels of estrone and estradiol [46–48] as well as elevated sex hormone-binding globulin [49]. Higher estrogen and lower levels of sex hormone-binding globulin are associated with heightened breast cancer risk in postmenopausal women [50]. Other potential mechanisms include the prevention of weight gain, regulation of insulin sensitivity, and alterations in immune function [51–54].

Like all other case-control investigations, the present study has certain limitations. While retrospective measures may result in recall bias, such a problem is likely to be minimized since the same method served to collect information from cases and controls. Moreover, the likelihood of obtaining false information on maximum lifespan weight and age when this weight occurred can be discounted, as weight gain for a majority of women is a constant concern, and they can recall their highest weight and its timing with relatively good precision [21]. As with most case-control studies, selection and recall bias may have influenced our results.

The present work has a number of strengths. A major strength is its population-based design, which included only incident cases who had undergone genetic testing for 6 specific *BRCA* gene mutations more frequently found in French-Canadian families and who provided full information about known breast cancer risk factors. In addition, the response rate for both cases and controls was high (over 90%), suggesting that the potential for selection bias was low.

The main protective effects exerted by certain lifestyle factors identified in this paper are consistent with current recommendations by the American Cancer Society for breast cancer prevention [55, 56]. Because of the multifactorial process in breast cancer development, and the tendency for lifestyle variables to cluster, inconsistent and inconclusive data have emerged on breast cancer risk even from well-designed epidemiological research. Consequently, it is essential to continuously update knowledge on the risk factors and their impact on breast cancer. This could help women make beneficial changes in their behavior by addressing diet and physical activity patterns that could reduce their breast cancer risk. In such a context, it is interesting that recent evidence suggests that more than 50% of cancer incidence could be prevented if knowledge of risk factors was applied to changes in behavior [57]. The ultimate goal of such research is to contribute to novel prevention strategies and to decrease the number of women at risk for developing breast cancer.

In summary, we found that weight history did affect breast cancer risk. Moreover, smoking appeared to raise the risk, whereas moderate physical activity had a protective effect. Further research is warranted to confirm these associations in other study populations and hopefully in larger sample sizes.

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