Examining the etiology of early-onset breast cancer in the Canadian Partnership for Tomorrow’s Health (CanPath)

Joy Pader1 · Robert B. Basmadjian2 · Dylan E. O’Sullivan3,4 · Nicole E. Mealey4 · Yibing Ruan1 · Christine Friedenreich1,2,4 · Rachel Murphy5 · Edwin Wang6 · May Lynn Quan7 · Darren R. Brenner1,2,4,8

Received: 1 October 2020 / Accepted: 11 June 2021 / Published online: 25 June 2021
© The Author(s), under exclusive licence to Springer Nature Switzerland AG 2021

Abstract
Purpose Breast cancer incidence among younger women (under age 50) has increased over the past 25 years, yet little is known about the etiology among this age group. The objective of this study was to investigate relationships between modifiable and non-modifiable risk factors and early-onset breast cancer among three prospective Canadian cohorts.

Methods A matched case–control study was conducted using data from Alberta’s Tomorrow Project, BC Generations Project, and the Ontario Health Study. Participants diagnosed with breast cancer before age 50 were identified through provincial registries and matched to three control participants of similar age and follow-up. Conditional logistic regression was used to examine the association between factors and risk of early-onset breast cancer.

Results In total, 609 cases and 1,827 controls were included. A body mass index ≥ 30 kg/m² was associated with a lower risk of early-onset breast cancer (OR 0.65; 95% CI 0.47–0.90), while a waist circumference ≥ 88 cm was associated with an increased risk (OR 1.58; 95% CI 1.18–2.11). A reduced risk was found for women with ≥ 2 pregnancies (OR 0.76; 95% CI 0.59–0.99) and a first-degree family history of breast cancer was associated with an increased risk (OR 1.95; 95% CI 1.47–2.57).

Conclusions In this study, measures of adiposity, pregnancy history, and familial history of breast cancer are important risk factors for early-onset breast cancer. Evidence was insufficient to conclude if smoking, alcohol intake, fruit and vegetable consumption, and physical activity are meaningful risk factors. The results of this study could inform targeted primary and secondary prevention for early-onset breast cancer.

Introduction

Breast cancer is the most commonly diagnosed cancer globally among women with over two million new cases in 2018 [1]. Canada is among the top 25 countries worldwide with the highest rates of breast cancer [1]. A projected
27,400 breast cancer cases are expected to be diagnosed in Canada in 2020 [2]. Breast cancer incidence among younger women (under age 50) has increased in Canada since 2000 [3]. The Canadian Cancer Society (CCS) projected that in 2017, roughly 17% of new breast cancer cases will occur before age 50 [4]. Breast cancer diagnosed among younger women often occur outside age-restricted or high-risk screening programs, resulting in advanced stage at diagnosis and poorer survival rates [5, 6]. The diagnosis of early-onset breast cancer also presents several unique challenges, including fertility concerns and reduced quality of life due to treatment-induced premature menopause [5, 6]. While mutations in the \textit{BRCA1} and \textit{BRCA2} genes increase the risk of developing breast cancer, only a small number of breast cancers (~5 to 10%) diagnosed among young women are attributable to these mutations [7, 8], suggesting other genetic, environmental or lifestyle factors may contribute to the development of early-onset breast cancer.

Several risk factors for breast cancer have been identified, with the majority of these risk factors applying to both pre and postmenopausal breast cancer [9]. While these risk factors for old and younger breast cancer cases are similar, there is evidence of early-onset breast cancer being biologically and etiologically distinct from breast cancer diagnosed among woman of older ages and further research is required [10]. Specifically, the relationship between anthropometric factors and early-onset breast cancer risk requires clarification, with previously reported inverse associations and a conflicted evidence base [11]. For example, current evidence suggests obesity is a risk factor for postmenopausal breast cancer [12, 13], while being protective for premenopausal breast cancer [14]. Furthermore, the mechanisms explaining the underlying pathways in these associations remain unclear. However, present studies on early-onset breast cancer and associated risk factors have been limited or conflicting [10, 15, 16]. Studies have attempted to resolve previous conflicting evidence but have been impacted by smaller comparative sample sizes among younger women and varied definitions of “young women” across studies [10, 15, 16].

The objective of our study was to examine the impact of lifestyle and reproductive factors, as well as family and medical history on the risk of developing early-onset breast cancer (under the age of 50) using data from The Canadian Partnership for Tomorrow’s Health (CanPath) [17]. The CanPath cohort is a national prospective cohort study that was developed to explore the relationships between various lifestyle, genetic, and environmental factors and outcomes of disease. The national study population includes over 330,000 Canadians who were recruited between the ages of 30 and 74 years from six regional cohorts. We combined three of the six cohorts involved in CanPath: Alberta’s Tomorrow Project (ATP); British Columbia Generations Project (BCGP); and the Ontario Health Study (OHS) to investigate various risk factors for early-onset breast cancer.

\section*{Materials and methods}

\subsection*{Study population}

In this study, we pooled baseline data from 2,437 participants from the ATP, OHS and BCGP regional cohorts. ATP was initiated in 2000 and enrolled approximately 55,000 participants between the ages of 35–69 at three different time points—2001 (phase 1), 2008 (phase 2), and 2011 (phase 3). Data from phases 2 and 3 from ATP were used in this analysis since the questionnaires from those phases were harmonized with the other cohorts in CanPath. OHS has recruited over 225,000 Ontario residents in the age range of 35–74 starting in 2009, while BCGP has enrolled approximately 30,000 British Columbia residents between the ages of 30 and 74 starting in 2009.

\subsection*{Study design}

A nested matched case–control study design was used for this study. Cases and controls were selected from the same regional cohort in a 1:3 case–control ratio. Cases were defined as female participants who had an incident, primary breast cancer diagnosis under 50 years of age during the follow-up period. The incident cases were identified through data linkages done with the BC Cancer Registry, Alberta Cancer Registry and Cancer Care Ontario, respectively, using participants’ Personal Health Identification Numbers. Using an incidence density sampling approach, controls were sampled without replacement and matched to cases on follow-up (±6 months) and age (±1 year). The follow-up period for each cohort was defined from cohort initiation to the most recent linkage with their respective provincial cancer registry, which was 2008–2018 for Alberta, 2009–2017 for British Columbia, and 2009–2017 for Ontario.

\subsection*{Data Collection-Questionnaires}

Data on demographic, lifestyle, reproductive, and family and medical history factors under investigation as exposures in this study were collected through self-report questionnaires completed by participants within each cohort at baseline upon cohort entry, prior to diagnoses. The exposures were analyzed as categorical variables. Thresholds for exposure categories were defined prior to analysis and informed by previous literature. Where necessary, categories were combined to ensure sufficient case counts across categories.

The demographic exposures included marital status (married/living with a partner, divorced/separated/
widowed, single/never married); education (high school or less, some post-secondary, Bachelor’s degree or higher); and total household income (< $50,000, $50,000—$100,000, > $100,000).

The lifestyle exposures included smoking status (never smoked at least 100 cigarettes, past smoker of at least 100 cigarettes, current smoker); alcohol consumption in the previous 12 months (no, < once per week, ≥ once per week); alcohol binge drinking frequency in the previous 12 months (no, < once per week, ≥ once per week); physical activity (< 500 MET min/week, ≥ 500 MET min/week, MET = metabolic equivalency); fruit and vegetable consumption per day (0–2 servings of fruits or vegetables, 3–4 servings of fruits or vegetables, >4 servings of fruits or vegetables, >4 servings of fruits or vegetables, >4 servings of fruits and vegetables); body mass index (BMI) (underweight or normal [< 25 kg/m²], overweight [25–29.99 kg/m²], obese [≥ 30 kg/m²]); waist circumference (normal/healthy [< 88 cm], above normal/at risk [≥ 88 cm]); and waist-to-hip ratio (normal/healthy [< 0.83], above normal/at risk [≥ 0.83]).

The reproductive exposures included: age at menarche (≤ 10 years, 11–13 years, ≥ 14 years); contraceptive use and duration (never, < 10 years, 10–19 years, ≥ 20 years); total number of pregnancies (0, 1, ≥ 2); age of first pregnancy (< 20 years, 20–29 years, ≥ 30 years); and use of fertility treatments (no, yes).

The family and medical history exposures included participation in mammography screening (no, yes); family history of breast cancer and any cancer (no, yes); history of any diabetes (no, yes), including type 1, type 2, and gestational diabetes; and history of other chronic conditions (no, yes), including irritable bowel disease/syndrome, Crohn’s disease, arthritis, high blood pressure, psoriasis, ulcerative colitis, liver cirrhosis, and systemic lupus erythematosus.

Statistical analysis

Participants from each provincial cohort were pooled to generate one combined cohort. All demographic, lifestyle, reproductive, and family and medical history exposures were described using means and standard deviations (SD) for numeric variables and frequency tables with proportions for categorical variables for the combined cohort. Multivariable conditional logistic regression models were used to evaluate the association between each exposure and the development of early-onset breast cancer. For each exposure, a multivariable model was built using a priori subject matter knowledge. We performed a review of the literature to culminate information regarding demographic, anthropometric, lifestyle, reproductive, family history, and medical history risk factors for breast cancer. For every exposure variable in our study, we generated a list of variables in our data that may potentially confound the association between the exposure of interest and early-onset breast cancer. We defined a confounding variable as a variable associated with the exposure of interest and early-onset breast cancer and not on the causal pathway between exposure and early-onset breast cancer. A detailed table describing the model building procedure and reasons for the inclusion/exclusion of variables for every multivariate model used to estimate the associations of interest is provided in Supplementary File 1. We also built multivariable models using a backwards deletion approach with a p value cut-off of 0.20. Variables included in each model following backwards deletion are provided in Supplemental File 2. In lieu of missing data, we performed complete case analyses.

Results

A total of 610 cases and 1,827 controls were eligible for analysis; however, 1 case was not matched to 3 controls and was excluded as a result. Therefore, the pooled analysis included 609 cases and 1,827 controls for a total sample size of 2,436 participants across these three regional Canadian cohorts of which 14.8% (n = 360) were from Alberta, 5.7% (n = 140) from British Columbia, and 79.5% (n = 1936) from Ontario (Table 1). The mean age of all participants at baseline was 43.1 (SD = 5.1) years. The study population had a high annual average annual income (41.2% ≥ $100,000), were well-educated (44.5% had post-secondary education), and married/living with a partner (71.7%). Most of the study participants had at least one pregnancy (14.7% had one pregnancy, 63.6% had two or more), and the mean age of first pregnancy among these women was 26.1 years. In addition, these participants also reported using hormonal contraceptives (86.2%) and the mean duration of hormonal contraceptive use was 10.7 years. Only 11% of women in this study had a positive family history of breast cancer. Majority of women were absent of any diabetes (93.3%) and other chronic conditions (64.6%). Over one-third of the population was either classified as overweight (21.1%) or obese (17%) at baseline. With respect to lifestyle factors, most of study population consumed alcohol (89.6%), 17.8% were current smokers, 22.5% were past smokers, and 56.4% had never smoked. The frequency of missing data in each characteristic is also presented in Table 1.

The estimated adjusted associations between each exposure and the incidence of early-onset breast cancer in the combined cohort are presented in Table 2. There was evidence that early-onset breast cancer cases were less likely to have an average annual household income < $50,000 vs. ≥ $100,000 (OR 0.58; 95% CI 0.42–0.79), to be classified as overweight vs. underweight or normal BMI (OR 0.75; 95% CI 0.57–0.98), obese vs. underweight or normal BMI (OR 0.65; 95% CI 0.47–0.90), and to have had at
Table 1  Population characteristics of early-onset breast cancer cases and controls, Alberta’s Tomorrow Project (2008–2018), BC Generations Project (2009–2017), Ontario Health Study (2009–2017), n=2436

| Characteristics                  | Categories                          | Cases (n=609) | Controls (n=1,827) | Total (n=2,436) |
|----------------------------------|-------------------------------------|---------------|--------------------|-----------------|
| Cohort                           | Alberta                             | 90            | 270                | 360             |
|                                  | British Columbia                    | 35            | 105                | 140             |
|                                  | Ontario                             | 484           | 1,452              | 1,936           |
| Age (at time of survey)          | Mean age, (SD)                      | 43.2 (5.8)    | 43.0 (5.8)         | 43.1 (5.8)      |
| Age (at diagnosis)               | Mean age, (SD)                      | 43.7 (5.1)    | –                  | –               |
| Marital status                   | Married/living with a partner       | 426           | 1,321              | 1,747           |
|                                  | Divorced, separated, widowed        | 87            | 242                | 329             |
|                                  | Single, never married               | 75            | 237                | 312             |
|                                  | Missing                             | 21            | 27                 | 48              |
| Education                        | High school or less                 | 108           | 295                | 403             |
|                                  | Some post-secondary                 | 235           | 685                | 920             |
|                                  | Bachelor’s or higher                | 257           | 827                | 1,084           |
|                                  | Missing                             | <10           | 20                 | 29              |
| Total Household Income (SCDN)    | < $50,000                           | 76            | 345                | 421             |
|                                  | $50,000 to less than $100,000       | 177           | 518                | 695             |
|                                  | > $100,000                          | 260           | 743                | 1,003           |
|                                  | Missing                             | 96            | 221                | 317             |
| Age at menarche (years)          | Mean age, year (SD)                 | 12.7 (1.5)    | 12.8 (1.5)         | 12.7 (1.5)      |
|                                  | ≥ 14                                | 146           | 464                | 610             |
|                                  | 11–13                               | 393           | 1,160              | 1,553           |
|                                  | ≤ 10                                | 33            | 90                 | 123             |
|                                  | Missing                             | 37            | 113                | 150             |
| Ever used oral contraceptives    | No                                  | 66            | 231                | 297             |
|                                  | Yes                                 | 531           | 1,569              | 2,100           |
|                                  | Missing                             | 12            | 27                 | 39              |
| Duration of oral contraceptives  | Mean years, year (SD)               | 10.4 (6.8)    | 10.7 (7.4)         | 10.6 (7.3)      |
|                                  | Never used                          | 66            | 237                | 303             |
|                                  | Less than 10 years                  | 216           | 637                | 853             |
|                                  | 10 to 19 years                      | 182           | 526                | 708             |
|                                  | 20 or more years                    | 73            | 209                | 282             |
|                                  | Missing                             | 72            | 218                | 290             |
| No. total pregnancies            | Mean number (SD)                    | 2.1 (2.0)     | 2.3 (1.8)          | 2.2 (1.9)       |
|                                  | 0                                  | 131           | 357                | 488             |
|                                  | 1                                  | 101           | 256                | 357             |
|                                  | 2 to 3                             | 271           | 829                | 1,100           |
|                                  | ≥ 4                                | 89            | 352                | 441             |
|                                  | Missing                             | 17            | 33                 | 50              |
| Age at first pregnancy (years)   | Mean age at first pregnancy, (SD)   | 26.4 (5.9)    | 26.1 (6.1)         | 26.1 (6.1)      |
|                                  | Never                              | 131           | 357                | 488             |
|                                  | ≤ 19                               | 71            | 237                | 308             |
|                                  | 20–24                              | 103           | 355                | 458             |
|                                  | 25–29                              | 146           | 419                | 565             |
|                                  | ≥ 30                               | 136           | 408                | 544             |
|                                  | Missing                             | 22            | 51                 | 73              |
| Ever used fertility treatment    | No                                  | 546           | 1,635              | 2,181           |
|                                  | Yes                                 | 40            | 152                | 192             |
|                                  | Missing                             | 23            | 40                 | 63              |
| Ever had a mammogram             | No                                  | 134           | 827                | 961             |
Table 1 (continued)

| Characteristics                              | Categories                      | Cases  | Controls | Total  |
|----------------------------------------------|---------------------------------|--------|----------|--------|
|                                              |                                 | $(n=609)$ | $(n=1,827)$ | $(n=2,436)$ |
|                                              | Yes                             | 453    | 988      | 1,441  |
|                                              | Missing                         | 22     | 12       | 34     |
|                                              | **Family history of breast cancer** |         |          |        |
|                                              | No                              | 475    | 1,536    | 2,011  |
|                                              | Yes                             | 99     | 170      | 269    |
|                                              | Missing                         | 35     | 121      | 156    |
|                                              | **Family history of non-breast cancers** |         |          |        |
|                                              | No                              | 352    | 1,071    | 1,423  |
|                                              | Yes                             | 206    | 666      | 872    |
|                                              | Missing                         | 51     | 90       | 141    |
|                                              | **Ever smoked (100 cigarettes)** |         |          |        |
|                                              | No                              | 328    | 1,054    | 1,382  |
|                                              | Yes                             | 245    | 733      | 978    |
|                                              | Missing                         | 36     | 40       | 76     |
|                                              | **Current smoking status**      |         |          |        |
|                                              | Never smoked                    | 328    | 1,054    | 1,382  |
|                                              | Past smoker                     | 181    | 482      | 663    |
|                                              | Current smoker*                 | 63     | 248      | 311    |
|                                              | Missing                         | 37     | 43       | 80     |
|                                              | **Ever consumed alcohol**       |         |          |        |
|                                              | Yes                             | 537    | 1,684    | 2,221  |
|                                              | No                              | 37     | 108      | 145    |
|                                              | Missing                         | 35     | 35       | 70     |
|                                              | **Alcohol frequency last 12 months** |         |          |        |
|                                              | Non-drinker                     | 61     | 216      | 277    |
|                                              | Less than 1/month               | 121    | 386      | 507    |
|                                              | About once a month              | 57     | 173      | 230    |
|                                              | 2–3 times/month                 | 73     | 272      | 345    |
|                                              | Once a week                     | 66     | 225      | 291    |
|                                              | 2–3 times/week                  | 113    | 273      | 386    |
|                                              | 4 or more a week                | 83     | 232      | 315    |
|                                              | Missing                         | 35     | 50       | 85     |
|                                              | **Alcohol binge drinking frequency in the last 12 months** |         |          |        |
|                                              | Non-drinker                     | 229    | 682      | 911    |
|                                              | 1–5 times/year                  | 166    | 529      | 695    |
|                                              | 6–11 times/year                 | 40     | 101      | 141    |
|                                              | About once a month              | 27     | 95       | 122    |
|                                              | 2–3 times/month                 | 23     | 71       | 94     |
|                                              | Once a week                     | 17     | 71       | 88     |
|                                              | 2–3 times/week                  | 22     | 44       | 66     |
|                                              | 4–5 times/week                  | < 10   | < 10     | 10     |
|                                              | 6–7 times/week                  | < 10   | < 10     | < 10   |
|                                              | Missing                         | 78     | 216      | 294    |
|                                              | **Physical activity**            |         |          |        |
|                                              | Mean physical activity, MET min/week (SD) | 2,309.5 (2,511.9) | 2,425 (2,723.9) | 2,397 (2,673.2) |
|                                              | < 500 MET min/week              | 137    | 395      | 532    |
|                                              | ≥ 500 MET min/week              | 391    | 1,228    | 1,619  |
|                                              | Missing                         | 81     | 204      | 285    |
|                                              | **Fruit and vegetable consumption per day** |         |          |        |
|                                              | 0–2 servings of fruit and/or vegetables | 222    | 653      | 875    |
|                                              | 3–4 servings of fruit and/or vegetables | 249    | 822      | 1,071  |
|                                              | ≥ 4 servings of either fruit or vegetables | 73     | 243      | 316    |
|                                              | ≥ 4 servings of fruit and vegetables | 21     | 41       | 62     |
|                                              | Missing                         | 44     | 68       | 112    |
|                                              | **Body mass index (BMI)**        |         |          |        |
|                                              | Mean BMI                        | 26.0 (5.6) | 26.9 (6.6) | 26.7 (6.3) |
|                                              | Underweight or normal           | 235    | 679      | 914    |
|                                              | Overweight                      | 121    | 393      | 514    |
least two pregnancies vs. no pregnancies (OR 0.76; 95% CI 0.59–0.99). There was suggestive evidence that cases were less likely to be current smokers vs. never having smoked at least 100 cigarettes (OR 0.75; 95% CI 0.54–1.05), although this estimate did not achieve statistical significance. Early-onset breast cancer cases were more likely to have a waist circumference of ≥ 88 cm vs. < 88 cm (OR 1.58; 95% CI 1.18–2.11), waist-to-hip ratio of ≥ 0.83 vs. < 0.83 (OR 1.41; 95% CI 1.06–1.86), highest education of high school degree or less vs. bachelor’s degree or more (OR 1.39; 95% CI 1.03–1.87), and a family history of breast cancer vs. no family history (OR 1.95; 95% CI 1.47–2.57). There was suggestive evidence that cases were more likely to be divorced, separated, or widowed vs. married/living with a partner (OR 1.34; 95% CI 0.98–1.81), although this estimate did not achieve statistical significance. Supplemental File 3 contains a table comparing measures of association based on multivariable models built with a priori subject matter knowledge versus the backwards deletion approach, which show similar findings between the two approaches.

Table 1 (continued)

| Characteristics Categories | Cases (n = 609) | Controls (n = 1,827) | Total (n = 2,436) |
|---------------------------|----------------|---------------------|------------------|
| Obese                     | 90             | 324                 | 414              |
| Missing                   | 163            | 431                 | 594              |
| Waist circumference (cm)  |                |                     |                  |
| Mean waist circumference (SD) | 88.0 (13.9)   | 86.6 (14.4)         | 87 (14.3)        |
| Normal, healthy (<88.0 cm) | 166            | 593                 | 759              |
| Above normal, at risk (≥88.0 cm) | 160          | 446                 | 606              |
| Missing                   | 283            | 788                 | 1,071            |
| Waist-to-hip ratio        |                |                     |                  |
| Mean waist-to-hip ratio (SD) | 0.86 (0.1)    | 0.85 (0.1)          | 0.86 (0.1)       |
| Normal, healthy (<0.83)   | 101            | 375                 | 476              |
| Above normal, at risk (≥0.83) | 213          | 614                 | 827              |
| Missing                   | 295            | 838                 | 1,133            |
| History of any diabetes (includes type 1 and gestational) | | | |
| No                        | 556            | 1,718               | 2,274            |
| Yes                       | 25             | 78                  | 103              |
| Missing                   | 28             | 31                  | 59               |
| History of other chronic conditions | | | |
| No                        | 382            | 1,192               | 1,574            |
| Yes                       | 214            | 631                 | 845              |
| Missing                   | 13             | < 10                | 17               |

SD standard deviation, METs metabolic equivalent tasks (defined as the caloric need per kilogram of body weight per hour of activity divided by the caloric need per kilogram of body weight per hour at rest)
*Includes occasional and daily smokers as current smokers

Discussion

To our knowledge, this pooled analysis is the first to investigate the etiology of early-onset breast cancer in a large Canadian population. For breast cancer under 50 years, we observed risk decreases of 25%, 35%, 42% and 24% in overweight BMI, obese BMI, low income, and multiple pregnancy categories, respectively. Conversely, risk increases of 58%, 41%, 39%, and 95% were observed for larger waist circumference, larger waist-to-hip ratio, lower educational attainment, and a positive family history of breast cancer categories, respectively.

It is well established that weight gain and obesity increase breast risk in postmenopausal women [13]. Consistent positive associations have been reported between BMI, waist circumference, and waist-to-hip ratio and the risk of breast cancer among postmenopausal women [18, 19] but results are inconsistent for younger women. Our study suggests that an overweight and obese BMI are associated with lower early-onset breast cancer risk. Similar results were seen in a pooled analysis of 19 prospective studies including women under 55 years of age [11]. Our results also suggest that high waist circumference and waist-to-hip ratio are predictors of breast cancer in younger women, independent of BMI, consistent with other prospective studies adjusting for BMI in premenopausal women [19–23]. The opposing effect of BMI and waist circumference on breast cancer risk in young women seen in our study and elsewhere requires further clarification. Possible differences in these associations could be related to differential roles of overall adiposity, captured by BMI, and central adiposity, captured by waist circumference, on metabolism and their contribution to breast cancer development among younger women. Both overall and central adiposity are associated with more anovulatory cycles and
Table 2  Adjusted associations between each exposure and early-onset breast cancer in the CanPath combined cohort

| Characteristics | Categories                              | Cases   | Controls  | OR (95% CI)             | p value   |
|-----------------|-----------------------------------------|---------|-----------|-------------------------|-----------|
| **BMI**         | Underweight/normal                      | 235     | 679       | 1.00                    | –         |
|                 | Overweight                              | 121     | 393       | 0.75 (0.57–0.98)        | 0.037     |
|                 | Obese                                   | 90      | 324       | 0.65 (0.47–0.90)        | 0.009     |
| **Waist circumference** | <88 cm                                | 166     | 593       | 1.00                    | –         |
|                 | ≥88 cm                                  | 160     | 446       | 1.58 (1.18–2.11)        | 0.002     |
| **Waist-to-hip ratio** | <0.83                                  | 101     | 375       | 1.00                    | –         |
|                 | ≥0.83                                   | 213     | 614       | 1.41 (1.06–1.86)        | 0.016     |
| **Alcohol frequency in past 12 months** | Non-drinker                            | 61      | 216       | 1.00                    | –         |
|                 | Less than 1/week                        | 251     | 831       | 1.06 (0.76–1.46)        | 0.744     |
|                 | 1/week or more                          | 262     | 730       | 1.20 (0.86–1.68)        | 0.279     |
| **Alcohol binge drinking frequency in past 12 months** | Non-drinker                            | 229     | 682       | 1.00                    | –         |
|                 | Less than 1/week                        | 233     | 725       | 0.90 (0.72–1.12)        | 0.342     |
|                 | 1/week or more                          | 69      | 204       | 1.00 (0.72–1.40)        | 0.989     |
| **Smoking status** | Never smoker                           | 328     | 1,054     | 1.00                    | –         |
|                 | Past smoker                             | 181     | 482       | 1.18 (0.94–1.48)        | 0.162     |
|                 | Current smoker                          | 63      | 248       | 0.75 (0.54–1.05)        | 0.092     |
| **Marital status** | Married/living with a partner           | 426     | 1,321     | 1.00                    | –         |
|                 | Divorced, separated, widowed            | 87      | 242       | 1.34 (0.98–1.81)        | 0.061     |
|                 | Single, never married                   | 75      | 237       | 1.10 (0.78–1.56)        | 0.574     |
| **Income**      | < $50,000                               | 76      | 345       | 0.58 (0.42–0.79)        | <0.001    |
|                 | ≥ $50,000 < $100,000                    | 177     | 518       | 0.94 (0.74–1.19)        | 0.608     |
|                 | ≥ $100,000                              | 260     | 743       | 1.00                    | –         |
| **Highest education** | High school or less                    | 108     | 295       | 1.39 (1.03–1.87)        | 0.034     |
|                 | Some post-secondary                     | 235     | 685       | 1.19 (0.95–1.49)        | 0.127     |
|                 | Bachelor’s degree                       | 257     | 827       | 1.00                    | –         |
| **Age at menarche (years)** | ≥ 14                                   | 146     | 464       | 1.00                    | –         |
|                 | 11–13                                   | 393     | 1,160     | 1.08 (0.87–1.35)        | 0.481     |
|                 | ≤ 10                                    | 33      | 90        | 1.17 (0.75–1.82)        | 0.499     |
| **Total number of pregnancies** | Never                                  | 131     | 357       | 1.00                    | –         |
|                 | 1                                       | 101     | 256       | 1.05 (0.76–1.45)        | 0.783     |
|                 | 2 or more                               | 360     | 1,181     | 0.76 (0.59–0.99)        | 0.039     |
| **Age of first pregnancy (years)** | Never                                  | 131     | 357       | 1.00                    | –         |
|                 | ≤ 19                                    | 71      | 237       | 0.77 (0.53–1.12)        | 0.175     |
|                 | 20–29                                   | 249     | 774       | 0.81 (0.61–1.08)        | 0.151     |
|                 | ≥ 30                                    | 136     | 408       | 0.89 (0.65–1.23)        | 0.491     |
| **Duration of oral contraceptives (years)** | Never used                             | 66      | 237       | 1.00                    | –         |
|                 | < 10                                    | 216     | 637       | 1.26 (0.91–1.75)        | 0.171     |
|                 | 10–19                                   | 182     | 526       | 1.24 (0.86–1.75)        | 0.209     |
|                 | ≥ 20                                    | 73      | 209       | 1.20 (0.81–1.78)        | 0.370     |
| **Use of fertility treatment** | No                                      | 546     | 1,635     | 1.00                    | –         |
|                 | Yes                                     | 40      | 152       | 0.77 (0.53–1.12)        | 0.168     |
| **Physical activity** | < 500 MET min/week                     | 137     | 395       | 1.14 (0.89–1.46)        | 0.311     |
|                 | ≥ 500 MET min/week                      | 391     | 1,228     | 1.00                    | –         |
| **Fruit and vegetable servings per day** | ≤ 2 servings of fruit or veg           | 222     | 653       | 1.00                    | –         |
|                 | 3 to 4 servings of fruit or veg         | 249     | 822       | 0.84 (0.67–1.06)        | 0.136     |
|                 | > 4 servings of fruit or veg            | 73      | 243       | 0.84 (0.61–1.16)        | 0.297     |
|                 | > 4 servings of fruit and veg           | 21      | 41        | 1.50 (0.85–2.64)        | 0.165     |
| **Family history of breast cancer** | No                                      | 475     | 1,536     | 1.00                    | –         |
|                 | Yes                                     | 99      | 170       | 1.95 (1.47–2.57)        | <0.0001   |
lower estradiol levels in premenopausal women [24], which would be expected to reduce breast cancer risk. However, central adiposity is also an independent predictor of both hyperinsulinemia and levels of insulin-like growth factor 1 (IGF-1), which have been previously found to be related to premenopausal breast cancer risk [18, 25]. These findings suggest that chronic inflammation and metabolic abnormalities induced by central adiposity are mechanistically important for higher breast cancer risk in young women, independent of sex hormones, which may explain the observed increase in risk for high waist circumference and waist-to-hip ratio in our study. These findings may also suggest that, in the absence of central obesity and its metabolic abnormalities, lower sex hormones are protective against breast cancer development in younger women, which could explain why young women with higher BMI are observed to
be at lower breast cancer risk. Another possible explanation for the opposing effect of BMI and waist circumference on breast cancer risk in young women is estrogen/progesterone (ER/PR) tumor status. High BMI has been observed to be protective in ER/PR+ cancers but not in ER/PR- cancers, and higher waist circumference has been observed to increase risk of ER/PR- cancers but not ER/PR+ cancers [13]. The distribution of ER/PR+ and ER/PR- tumors in young women in this study may account for these opposing effects. Unfortunately, we did not have access to the tumor characteristic data to confirm whether the effect of BMI and waist circumference depended on receptor status or subtype.

A positive family history is an important risk factor for breast cancer and the strength of association increases as age of diagnosis decreases. In a pooled analysis of data from 52 epidemiological studies, including 58,209 women with breast cancer and 101,986 controls, the risk of breast cancer was two times greater in women under 50 years of age with at least one affected first-degree relative, whereas a 1.5-fold increase in risk was observed in women older than 50 years [26]. We observed an approximate two-fold risk increase in women under age 50 years with a family history of breast cancer and 101,986 controls, the risk of breast cancer was two times greater in women under 50 years of age, whereas a 1.5-fold increase in risk was observed in women older than 50 years [26].

The only reproductive risk factor that was statistically significant in this study was gravidity, in which a 24% reduction in breast cancer risk was observed for women with multiple pregnancies compared to nulliparous women. Recently, a 27% reduction in breast cancer risk was observed in a meta-analysis of 13 studies in women under the age 50 with multiple pregnancies compared to nulliparous women [34]. However, the age at first full term pregnancy influences the association between gravidity and early-onset breast cancer risk, which was not statistically significant in our models.

In large prospective studies, it has been shown that women whose first full term pregnancy is in their twenties remained at an increased risk of breast cancer well into their fifties relative to nulliparous women [35–37]. Conversely, women whose first full term pregnancy is in their twenties were at an increased risk that peaks five years postpartum then declines to null 10–15 years postpartum and becomes protective around 20 years postpartum [35, 37]. Several etiologic studies explored the underlying biological processes of this association. Russo et al. found that parous postmenopausal women without breast cancer had unique gene expression patterns including differential expression of apoptosis-related genes and others related to cell cycle and cell signaling, suggesting that pregnancy may induce a signature that provides long-term protection from developing breast cancer [38]. Another study showed that parity downregulates Wnt and Notch signaling, and suppresses progenitor cells, suggesting that this pathway could be a potential mechanism explaining the long-term protective effect of pregnancy [39]. The transient increase in the risk of breast cancer after giving birth is thought to be due to the mitogenic effect of high estrogen levels during pregnancy [40]. While our result indicates a protective effect from multiple pregnancies, no recommendations regarding risk reduction can be made given that the decision to have children is highly personal.

Most of the current evidence has found that higher socioeconomic status is linked to increased risk of breast cancer, specifically among high income countries in North America and Europe [41–46]. This association is mainly seen among postmenopausal breast cancer cases [42, 47]. Our study found evidence that the odds of early-onset breast cancer were significantly lower for women with lower average annual household income. This finding is consistent with several studies that found women with higher household incomes had an increased risk of breast cancer compared to women in lower income households [48, 49]. In contrast, our study found evidence of low education (high school degree or less) associated with increased risk of early-onset breast cancer. The majority of the findings on breast cancer and education suggest that higher education is associated with increased breast cancer risk in Western or high-income countries [46, 50, 51]. Correlations of higher education and breast cancer incidence in these studies were
explained by factors such as age at first pregnancy, oral contraceptive (OC) use and hormone replacement therapy use. However, results from a Dutch study found respondents with low education had an increased risk of all cancers including breast cancer among women [52]. The study suggested that factors such as alcohol consumption, obesity and poor diet may explain, in part, the association between breast cancer and low education [52–55]. Another possibility for our findings of low education and increased breast cancer risk may be related to chronic inflammation and the biomarker C-reactive protein (CRP), a protein produced by the liver in response to systemic inflammation [56, 57]. Several studies found elevated CRP levels among populations with lower education compared to higher levels of education attainment [56, 58, 59]. Relatedly, multiple systematic reviews have found chronic inflammation and CRP to be associated with increased breast cancer risk [56, 58, 60, 61]. Our study provides additional evidence on the potential life-course pathways of the impacts of socioeconomic status and early-onset breast cancer.

Strengths and Limitations

Our study has numerous strengths worth highlighting. We pooled data from a national prospective study from three regional cohorts that were each linked to provincial cancer registries. Each cohort collected detailed health and lifestyle questionnaire data at baseline prior to a breast cancer diagnosis, ensuring that each risk factor temporally preceded the onset of disease. In addition, the prospective nature of the data ensured that the results of this study were not subject to recall or selection bias.

There are several limitations of this pooled analysis that must be acknowledged. First, data from the health and lifestyle data are from self-reported study participant questionnaires. While the questionnaires were deemed reliable and valid [62], data from self-reported questionnaires are inherently subject to response biases such as social desirability bias. Secondly, we only had data from one time point and assumed that these data represented average exposure during young adulthood. While differential misclassification of exposure by case status is unlikely since questionnaires were answered prior to the development of breast cancer, non-differential misclassification of exposures is likely. For binary exposures this would have biased effect estimates toward the null and either toward or away from the null for exposures with three or more categories. The sample size was also insufficient to explore whether or not the association between gravidity and breast cancer risk was modified by age of first pregnancy. There were also concerns regarding missing data for several exposures, particularly BMI, waist circumference, and waist-to-hip ratio. Although missingness in exposures was unlikely related to case status and therefore would not bias our estimates, exclusion of participants with incomplete exposure resulted in losses of precision and power. Finally, we did not include race/ethnicity data for participants and could not assess whether the associations between the various exposures and early-onset breast cancer differed by racial group.

Conclusion

Our study provides further insight on sociodemographic, lifestyle, and reproductive factors associated with the risk of breast cancer under 50 years in a large Canadian prospective cohort, which may have important implications for etiology and screening. We provide evidence consistent with other epidemiologic studies that central adiposity increases breast cancer risk in women under 50 years. Lifestyle behaviors, such as a healthy diet and physical activity that reduce central adiposity may be feasible primary prevention strategies to reduce breast cancer risk, in addition to other chronic diseases in younger women. We also provide further evidence that women under 50 years with a positive family history of breast cancer should speak with their primary care provider about options for breast cancer screening, which is in accordance to screening guidelines to high-risk women set by the Canadian Cancer Society and Canadian Task Force on Preventive Health Care. Future research is still needed to explore whether or not risk factors for breast cancer under age 50 differ by molecular subtype (luminal A, luminal B, HER2 enriched, and triple-negative breast cancer). Detailed analyses are also needed to assess differences in risk factors by race and socioeconomic status, since our study only had data on income and education, but not occupation and other measures of social inequality. Etiologic research, such as exome-sequencing studies, is warranted to explore the mutational impact of lifestyle behaviors on the genome and yield discoveries regarding the underlying biological processes of breast cancer development in younger women. Such studies may provide mechanistic insights on the opposing effect of high BMI and waist circumference on breast cancer risk, as well as how pregnancy may lead to a transient increase in risk, followed by a long-term protective effect.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10552-021-01460-y.

Acknowledgments We would like to thank and acknowledge the Alberta Cancer Registry, Alberta’s Tomorrow Project, BC Generations Project, Ontario Health Study, and Cancer Care Ontario. Alberta’s Tomorrow Project is only possible because of the commitment of its research participants, its staff and its funders: Alberta Health, Alberta Cancer Foundation, Canadian Partnership Against Cancer and Health Canada, and substantial in kind funding from Alberta Health Services. Cancer registry data was obtained through linkage with Surveillance & Reporting, Cancer Research & Analytics, Cancer Care Alberta. The views
expressed herein represent the views of the author(s) and not of the data sources or any of its funders. The views expressed herein represent the views of the author(s) and not of the data sources or any of its funders.

**Author contributions**  DRB: Conception and design. DRB, RBB, DEO and JP: Development of methodology. DRB, CMF, RM, EW, MLQ, and JP: Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.). JP, RBB, DEO and DRB: Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis). JP, RBB, DEO and DRB: Writing, review, and/or revision of the manuscript. JP, RBB: Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases). DRB: Study supervision.

**Funding** Dr. Darren R. Brenner is supported by the Armstrong Investigatorship in Molecular Epidemiology from the Cumming School of Medicine at the University of Calgary and a Canadian Institutes of Health Research Grant (#397332). Dylan O’Sullivan was supported by an Ontario Graduate Scholarship and a Chen-Aronson Fellowship in Causes of Cancer.

**Data availability** The data that support the findings of this study are available from Alberta’s Tomorrow Project, BC Generations Project, Ontario Health Study, and Cancer Care Ontario but restrictions apply to the availability of these data, which were used under license for the Ontario Health Study, and Cancer Care Ontario but restrictions apply to the availability of these data, which were used under license for the study. The data that support the findings of this study are available from Alberta’s Tomorrow Project, BC Generations Project, Ontario Health Study, and Cancer Care Ontario but restrictions apply to the availability of these data. Since data are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of Alberta’s Tomorrow Project, BC Generations Project, Ontario Health Study, and Cancer Care Ontario.

**Declarations**

**Conflict of interest** The authors declare no potential conflict of interest.

**References**

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jamal A (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Cancer J Clin 68:394–424
2. Brenner DR, Weir HK, Demers AA et al (2020) Projected estimates of cancer in Canada in 2020. Can Med Assoc J 192:E199
3. Heer E, Ruan Y, Mealey N, Quan ML, Brenner DR (2020) The incidence of breast cancer in Canada 1971–2015: trends in screening-eligible and young-onset age groups. Can J Public Health 111:787–793
4. Canadian Cancer Society’s Advisory Committee on Cancer Statistics (2017) Canadian cancer statistics 2017. Canadian Cancer Society, Toronto
5. Assi HA, Khoury KE, Dhouk H, Khalil LE, Mouhieddine TH, El Saghir NS (2013) Epidemiology and prognosis of breast cancer in young women. J Thorac Dis 5(Suppl 1):S2–S8
6. Brenner DR, Brockton NT, Kotsopoulos J et al (2016) Breast cancer survival among young women: a review of the role of modifiable lifestyle factors. Cancer Causes Control 27:459–472
7. Malone KE, Daling JR, Neal C et al (2000) Frequency of BRCA1/BRCA2 mutations in a population-based sample of young breast carcinoma cases. Cancer 88:1393–1402
8. Peto J, Collins N, Barfoot R et al (1999) Prevalence of BRCA1 and BRCA2 gene mutations in patients with early-onset breast cancer. J Natl Cancer Inst 91:943–949
9. Butt Z, Haider SF, Arif S et al (2012) Breast cancer risk factors: a comparison between pre-menopausal and post-menopausal women. J Pak Med Assoc 62:120–124
10. Chollet-Hinton L, Anders CK, Tse C-K et al (2016) Breast cancer biologic and etiologic heterogeneity by young age and menopausal status in the Carolina Breast Cancer Study: a case-control study. Breast Cancer Res 18:79
11. The Premenopausal Breast Cancer Collaborative G (2018) Association of body mass index and age with subsequent breast cancer risk in premenopausal women. JAMA Oncol 4:e181771
12. Kabat GC, Kim MY, Lee JS et al (2017) Metabolic obesity phenotypes and risk of breast cancer in premenopausal women. Cancer Epidemiol Biomark Prev 26:1730–1735
13. Picon-Ruiz M, Morata-Tarifa C, Valle-Goffin JJ, Friedman ER, Slingerland JM (2017) Obesity and adverse breast cancer risk and outcome: mechanistic insights and strategies for intervention. Cancer J Clin 67:378–397
14. Rose DP, Vona-Davis L (2010) Interaction between menopausal status and obesity in affecting breast cancer risk. Maturitas 66:33–38
15. Althuis MD, Brogan DD, Coates RJ et al (2003) Breast cancers among very young premenopausal women (United States). Cancer Causes Control 14:151–160
16. Tavani A, Gallus S, La Vecchia C et al (1999) Risk factors for breast cancer in women under 40 years. Eur J Cancer 35:1361–1367
17. Dummer TJ, Awadalla P, Boileau C et al (2018) The Canadian Partnership for Tomorrow Project: a pan-Canadian platform for research on chronic disease prevention. Can Med Assoc J 190:E710
18. Amadou A, Hainaut P, Romieu I (2013) Role of obesity in the risk of breast cancer: lessons from anthropometry. J Oncol 2013:906495
19. White AJ, Nichols HB, Bradshaw PT, Sandler DP (2015) Overall and central adiposity and breast cancer risk in the sister study. Cancer 121:3700–3708
20. Huang Z, Willett WC, Colditz GA et al (1999) Waist circumference, waist: hip ratio, and risk of breast cancer in the nurses’ health study. Am J Epidemiol 150:1316–1323
21. Lahmann PH, Hoffmann K, Allen N et al (2004) Body size and breast cancer risk: findings from the European prospective investigation into cancer and nutrition (EPIC). Int J Cancer 111:762–771
22. Harris HR, Willett WC, Terry KL, Michels KB (2010) Body fat distribution and risk of premenopausal breast cancer in the Nurses’ Health Study II. J Natl Cancer Inst 103:273–278
23. Fagherazzi G, Chabbert-Buffet N, Fabre A et al (2012) Hip circumference associated with the risk of premenopausal breast cancer. Int J Cancer 111:762–771
24. Slingerland JM (2017) Obesity and adverse breast cancer risk in premenopausal women. JAMA Oncol 4:e181771
25. Andrew GR, Michelle H, Anthony H (2006) Insulin-like growth factor (IGF)-I, IGF binding protein-3, and breast cancer risk: eight years on. Endocrine-Relat Cancer Endocr Relat Cancer 13:273–278
26. Collaborative Group on Hormonal Factors in Breast Cancer (2001) Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58 209 women with breast cancer and 101 986 women without the disease. The Lancet 358:1389–1399
27. Anders CK, Johnson R, Litton J, Phillips M, Bleyer A (2009) Breast cancer before age 40 years. Semin Oncol 36:237–249
28. Petö J, Mack TM (2000) High constant incidence in twins and other relatives of women with breast cancer. Nat Genet 26:411–414
29. Ginsburg OM, Akbari MR, Aziz Z et al (2009) The prevalence of germ-line TP53 mutations in women diagnosed with breast cancer before age 30. Fam Cancer 8:563
30. Canadian Cancer Society (2020) Getting screened for breast cancer
31. Canadian Task Force on Preventive Health Care (2020) Breast cancer tools and resources
32. NCCN Clinical Practise Guidelines In Oncology (2019) Breast Cancer Screening and Diagnosis. Nation Comprehensive Cancer Network
33. Klarenbach S, Sims-Jones N, Lewin G et al (2018) Recommendations on screening for breast cancer in women aged 40–74 years who are not at increased risk for breast cancer. Can Med Assoc J 190:E1441
34. Nelson HD, Zakher B, Cantor A et al (2012) Risk factors for breast cancer for women aged 40 to 49 years: a systematic review and meta-analysis. Ann Intern Med 156:635–648
35. Albrektsen G, Heuch I, Hansen S, Kvåle G (2005) Breast cancer risk by age at birth, time since birth and time intervals between births: exploring interaction effects. Br J Cancer 92:167–175
36. Liu Q, Wu J, Lambe M, Hsieh S-F, Ekbom A, Hsieh C-C (2002) Transient increase in breast cancer risk after giving birth: postpartum period with the highest risk (Sweden). Cancer Causes Control 13:299–305
37. Nichols HB, Schoemaker MJ, Cai J et al (2018) Breast cancer risk after recent childbirth. Ann Intern Med 170:22–30
38. Russo J, Balogh GA, Russo IH (2008) Full-term pregnancy induces a specific genomic signature in the human breast. Cancer Epidemiol Biomark Prev 17:51–66
39. Meier-Abt F, Milani E, Roloff T et al (2013) Parity induces differentiation and reduces Wnt/Notch signaling ratio and proliferation potential of basal stem/progenitor cells isolated from mouse mammary epithelium. Breast Cancer Res 15:R36
40. Lyons TR, Schedin PF, Borges VF (2009) Pregnancy and breast cancer: when they collide. J Mammary Gland Biol Neoplasia 14:87–98
41. Akinremiyo TF, Pisu M, Waterbor JW, Altekruse SF (2015) Socioeconomic status and incidence of breast cancer by hormone receptor subtype. Springerplus 4:508
42. Heck KE, Pamuk ER (1997) Explaining the relation between education and postmenopausal breast cancer. Am J Epidemiol 145:366–372
43. Robert SA, Strombom I, Trentham-Dietz A et al (2004) Socioeconomic risk factors for breast cancer: distinguishing individual- and community-level effects. Epidemiology 15:442–450
44. Tweed EJ, Allardice GM, McLoone P, Morrison DS (2018) Socioeconomic inequalities in the incidence of four common cancers: a population-based registry study. Public Health 154:1–10
45. Akinremiyo TF, Demb J, Izano MA et al (2018) The association of early life socioeconomic position on breast cancer incidence and mortality: a systematic review. Int J Public Health 63:787–797
46. Lundqvist A, Andersson E, Ahlberg I, Nilbert M, Gerdhham U (2016) Socioeconomic inequalities in breast cancer incidence and mortality in Europe—a systematic review and meta-analysis. Eur J Pub Health 26:804–813
47. Gadeyne S, Deboosere P, Vandenheede H, Neels K (2012) Does birth history account for educational differences in breast cancer mortality? A comparison of premenopausal and postmenopausal women in Belgium. Int J Cancer 131:2878–2885
48. Lehrer S, Green S, Rosenzweig KE (2016) Affluence and Breast Cancer. Breast J 22:564–567
49. Borugian MJ, Spinelli JJ, Abanto Z, Xu CL, Wilkins R (2011) Breast cancer incidence and neighbourhood income. Health Rep 22:7–13
50. Goldberg M, Calderon-Margalit R, Paltiel O et al (2015) Socioeconomic disparities in breast cancer incidence and survival among parous women: findings from a population-based cohort, 1964–2008. BMC Cancer 15:921
51. Menvielle G, Kunst AE, van Gils CH et al (2010) The contribution of risk factors to the higher incidence of invasive and in situ breast cancers in women with higher levels of education in the European prospective investigation into cancer and nutrition. Am J Epidemiol 173:26–37
52. de Kok IMCM, van Lenthe FJ, Avendano M, Louwman M, Coebergh J-WW, Mackenbach JP (2008) Childhood social class and cancer incidence: results of the globe study. Soc Sci Med 66:1131–1139
53. Gerber B, Müller H, Reimer T, Krause A, Friese K (2003) Nutrition and lifestyle factors on the risk of developing breast cancer. Breast Cancer Res Treat 79:265–276
54. Möller H, Törnæs H (1997) Alcohol drinking, social class and cancer. IARC Sci Publ 138:251–263
55. Potter JD (1997) Diet and cancer: possible explanations for the higher risk of cancer in the poor. IARC Sci Publ 138:265–283
56. Berger E, Castagné R, Chadeau-Hyam M et al (2019) Multi-cohort study identifies social determinants of systemic inflammation over the life course. Nat Commun 10:773
57. Pepys MB, Baltz ML (1983) Acute phase proteins with special reference to C-reactive protein and related proteins (pentaxins) and serum amyloid A protein. Adv Immunol 34:141–212
58. Mcdade TW, Lindau ST, Wrobleswki K (2011) Predictors of C-reactive protein in the national social life, health, and aging project. J Gerontol B Psychol Sci Soc Sci 66:129–136
59. Kershaw KN, Mezuk B, Abdou CM, Rafferty JA, Jackson JS (2010) Socioeconomic position, health behaviors, and C-reactive protein: a moderated-mediation analysis. Health Psychol 29:307–316
60. Gao L, Liu S, Zhang S et al (2015) C-reactive protein and risk of breast cancer: a systematic review and meta-analysis. Sci Rep 5:10508
61. Asegaonkar SB, Asegaonkar BN, Takalkar UV, Advani S, Thorat AP (2015) C-reactive protein and breast cancer: new insights from old molecule. Int J Breast Cancer 2015:145647
62. Robson PJ, Solbak NM, Haig TR et al (2016) Design, methods and demographics from phase I of Alberta’s Tomorrow Project cohort: a prospective cohort profile. CMAJ Open 4:E515–E527

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.