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Breast cancer risk and the interaction between adolescent body size and weight gain in later life: A case-control study

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ABSTRACT

Background: While the breast cancer risk associated with increasing adult BMI in postmenopausal women can be explained by increases in concentrations of endogenous estrogens the biologic mechanisms behind the inverse association between adolescent BMI and breast cancer risk are still a subject of controversial debate.
Methods: We investigated the association of breast cancer with body size and changes in body size across life time estimated by age-specific BMI Z scores and changes in BMI Z scores from teenage years to middle age in an age-matched population-based case-control study of 2994 Australian women. Logistic regression adjusted for the matching factor age and further potential confounders was used.
Results: Adolescent body leanness in postmenopausal women and excess adult weight gain in all study participants were associated with an increased breast cancer risk with an odds ratio [95% confidence interval] of 1.29 [1.08,1.54] and 1.31 [1.09,1.59], respectively. Interaction analyses restricted to postmenopausal women revealed an increased risk of breast cancer in those who were lean during adolescence and gained excess weight during adulthood (odds ratio [95% confidence interval]: 1.52 [1.19,1.95]) but not in women who were lean during adolescence and did not gain excess weight during adulthood (1.20 [0.97,1.48]) and not in women who were not lean during adolescence and but gained excess weight during adulthood (1.10 [0.95,1.27]) compared to postmenopausal women who were neither lean during adolescence nor gained excess weight.
Conclusion: In postmenopausal women adolescent leanness was only associated with increased breast cancer risk when excess weight was gained during adulthood.

1. Introduction

Breast cancer is the most common cancer in women and second most common cancer overall worldwide, with nearly 1.7 million new cases diagnosed in 2012 [1]. Evidence for the role of obesity and adult weight gain in the carcinogenesis of breast cancer has been strengthened by many large cohort studies with over 50,000 or even 100,000 participants, where associations of BMI and especially adult weight gain with incident cases of breast cancer were observed [2–7]. Adult weight gain has been suggested to be a better metric than BMI, which is the most widely used metric of adiposity in adults, because weight gain captures the dynamic pattern of weight trajectory throughout adult life [5].

An inverse association of childhood and adolescent body size with breast cancer risk adjusted for other breast cancer risk factors has been reported previously based on data from the Nurses' Health Study [8–10] and the French E3N cohort study [11]. In these studies body size at a younger age was recalled using body shape figure rating scales. Case-control studies, such as the Women's Circle of Health Study, observed decreased postmenopausal breast cancer risk among white women who were heavier at menarche, after excluding hormone replacement therapy users [12]. The Carolina Breast Cancer Study observed decreased cancer risk with heavier childhood relative weight among premenopausal white women but not among black women and postmenopausal white women [13]. In these studies recalled body size at a younger age was assessed by comparative weight, where perceived weight in comparison to peers was reported. So far, there are only a few

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studies investigating the association of breast cancer risk with bothchildhood and adult weight. While all of these studies observed an inverse association of breast cancer risk with childhood or adolescent body size, contradictory results concerning the association with adult weight and weight gain were reported [10,12,13].

We investigated the association of breast cancer with both teenage and adult BMI Z scores and weight gain during lifetime calculated from recalled weight values as continuous variables. Therefore the same metric was used across lifetime and dose-response relationships were investigated using continuous variables. In comparison to previous studies, data on recalled weight values were collected in addition to recalled comparative weight assessment.

2. Methods

2.1. Study population

The Breast Cancer Environment and Employment Study (BCEES) is a population-based case–control study, which has been described in detail previously [14,15]. Briefly, eligible cases were women aged 18–80 years and diagnosed with breast cancer (ICD-10 C50) between 1 May 2009 and 31 January 2011 and reported to the Western Australian Cancer Registry before 31 July 2011. Among the 2089 eligible cases, 1205 (58%) consented to participate. Age-matched controls were randomly selected from the electoral roll of Western Australia between May 2009 and July 2011. Voting is compulsory in Australia, and the electoral roll is considered an almost complete list of Australian citizens. Of the 4358 eligible frequency age-matched controls 1789 (41%) consented to participate. Compared with participants, those who did not consent to participate were older, while those who did not respond were younger [14].

The study was approved by the Human Research Ethics Committee of The University of Western Australia and the Western Australian Department of Health. Informed consent was obtained from all participants.

2.2. Exposure variables

Participants completed a questionnaire containing questions on their current height ("How tall are you?") and weight ("How much do you weigh now?"), their weight in their early teenage years ("How much did you weigh in your early teenage years (around the age of your first period)?"), and in their early thirties ("How much did you weigh when you were in your early 30s?", and their maximal weight ("What is the most you have ever weighed? (not including pregnancy")). Women were also asked about their comparative weight as a teenager ("When you were a teenager, what do you think you weighed compared with other girls of the same age and height?") and at age 30 years ("When you were in you early 30s, how did your weight compare with women the same age and height?"). Five responses were available, 'a lot less', 'a little less', 'about the same', 'a little more' and 'a lot more'.

We investigated five exposure variables characterizing body size and weight gain during life time: Z score of BMI in teenage years (Z_{teens}), Z score of BMI in early thirties years of age (Z_{30s}), Z score of maximal BMI during life time (Z_{max}), difference between Z scores of BMI in early thirties and in teenage years ($\Delta Z_{30s\text{-}teens}$), difference between Z scores of maximum BMI during life time and of BMI in early thirties ($\Delta Z_{max\text{-}30s}$). BMI at different ages was calculated as weight (kg) at different ages divided by squared height (m^2). To determine BMI in teenage years and in early thirties, we assumed that current height could be used as an estimate of height at those ages. We further assumed that the maximum BMI occurred after age 30.

Age-specific BMI Z scores were calculated based on the WHO reference using the LMS method, where a normal distribution after Box-Cox power transformation is assumed [16,17]. The median WHO reference for BMI in adulthood was taken as 22.5 kg/m^2 and in teenage years as 18.8 kg/m^2 at 13 years obtained from WHO growth reference [18].

2.3. Statistical analysis

To estimate odds ratios (OR) and 95% confidence intervals (CI) unconditional logistic regression with the matching factor age in 5-year groups included in all models was used [19] and the following variables were considered as potential confounders based on prior knowledge from scientific literature [2–15]: age at menarche (in years), body height, family history of breast cancer, number of children, age at first birth, breastfeeding, ever use of hormone contraception, education, country of birth, alcohol consumption and smoking status. Menopausal status and use of hormone replacement therapy were determined before cancer diagnosis for cases using the questions about age when the woman started to use hormone replacement therapy (HRT), age when menopause started and age at cancer diagnosis. Menopausal status and use of hormone replacement therapy for controls were assessed at current age minus one year since the study was conducted on average one year after the diagnosis of breast cancer.

For most of the variables the number of subjects with missing data was less than 5% of the total but for weight in teenage years and in early thirties the percentage was 31% and 12%, respectively (Table 1). To replace missing values, multiple imputation using the Markov chain Monte Carlo (MCMC) method creating five imputations was conducted. Missing BMI values in teenage years and early thirties, where comparative weight values were available, were replaced by a random sample (without replacement) of available BMI values stratified by comparative weight categories. Sensitivity analyses using the complete records for BMI values were conducted for comparison since different results have been reported previously for datasets using complete records and imputed data [20].

To investigate the dose-response association between the continuous confounding and exposure variables and the outcome (case/control status), and to check for the linearity assumption of the logistic regression model, we used restricted cubic spline (RCS) regression [21]. Knots were set at 5th, 25th, 75th, 95th percentiles and reference values were set at the median [22]. Dose-response relationships were inspected and are shown in Fig. 3 for exposure variables where the test for the non-linear association [21] was significant. Variables showing a non-linear association were included in the conditional logistic regression model in categorized form using quartiles as cutoffs. Because of the u-shaped association of the confounding variable 'age at first child' it was recoded together with the variable 'parity' into categories 'no parity', 'age at first child <22 years', 'age at first child >27 years' with 'age at first child between 22 and 27′ as the reference. Interactions between the exposures of interest and effect modification by menopausal status and HRT-use were analyzed as recommended by Knol and VanderWeele [23,24].

Data were analysed using the SAS software package (Version 9.4 and Enterprise Guide 6.1, SAS Institute, Cary, NC). Covariates were described by median and interquartile range or by frequency. Two-sided p-values of 0.05 or 95% confidence intervals of odds ratio excluding 1 were considered significant.

3. Results

Based upon age at the time of the interview nearly 57% of the controls and of the cases were overweight or obese (Table 1).