REVIEW ARTICLE

Dose response relationship between breast cancer and somatotypes during childhood: a systematic review and meta-analysis

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OBJECTIVES: This study aims to evaluate the relationship between breast cancer and somatotypes during early life by meta-analysis and give the corresponding advice.
METHODS: Observational studies till April 5, 2021, which explore women with/without breast cancer who used the Stunkard Figure Rating Scale/Sørensen Somatotypes to evaluate their somatotype before 18 years of age and distant breast cancer risk were included. Using random/fixed-effect models, the pooled relative risks (RRs) and 95% confidence intervals (CIs) were estimated. Then a nonlinear dose–response meta-analysis was conducted using restricted cubic spline analysis.
RESULTS: Six articles involving 15,211 breast cancer patients from 341,905 individuals were included for performing a meta-analysis of early somatotype and breast cancer risk. The pooled results showed that the protection became stronger with the increase of somatotype until it reached 6. The restricted cubic spline model indicated a linear relationship between somatotypes and breast cancer (*P-nonlinearity* = 0.533). Subgroup analysis of menopausal status showed that increasing somatotype during childhood was increasingly protective against postmenopausal breast cancer from somatotype 3 to somatotype 6, with a 0.887-fold (RR = 0.887, 95% CI: 0.842, 0.934) to 0.759-fold (RR = 0.759, 95% CI: 0.631, 0.913) decreased risk of breast cancer (*P-nonlinearity* = 0.880), but this association was not found in the population with premenopausal breast cancer (*P-nonlinearity* = 0.757). When stratified by age, among people younger than 10 years of age, an increase in somatotype was associated with a statistically significant reduction in breast cancer risk. From somatotype 3 to somatotype 6, the risk of breast cancer was reduced by 9.7–27.7% (*P-nonlinearity* = 0.175).
CONCLUSIONS: With early-life adiposity, our data support an inverse association with breast cancer risk, especially age less than 10 years and in postmenopausal women. Since girls with overweight likely remain overweight or even develop obesity in adulthood. While adults with overweight and obese are at increased risk of breast cancer and other types of cancer and various chronic diseases. Hence, we recommend that children should maintain a normal or slightly fat somatotype throughout all periods of life.

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INTRODUCTION

Breast cancer is the world's most prevalent cancer, with more than 2.2 million cases in 2020 [1]. Nearly 1 in 12 women will develop breast cancer in their lifetime [1]. In addition, breast cancer is the leading cancer-related cause of death in women [1]. Approximately 685,000 women die of breast cancer in 2020 [2]. Breast cancer is not a transmissible or infectious disease, and no known viral or bacterial infections are associated with the development of breast cancer. Only several factors that may increase the risk of breast cancer have been found, including genetic risk factors and non-genetic risk factors, such as age (increasing age), sex (female), ethnicity (white), weight, and body fat, high stature (taller), oestrogen levels (high levels) and early menarche.

Being overweight and obesity, as potentially modifiable non-genetic risk factors for breast cancer [3], are a global public health problem, as ~40% of adults worldwide are affected by overweight or obesity [4]. Previous studies have proven that adult women with high body mass index (BMI) are associated with a significantly increased risk of breast cancer [5, 6]. What's more, some research found that the risk of breast cancer in young women is related to body size and weight gain in adolescence and early adulthood [7, 8]. However, with the rise of large cohort studies and abundant case–control studies on breast cancer risk and childhood obesity, some studies have come up with a counterintuitive association, that is, early obesity has a protective effect against breast cancer [9–11]. Moreover, early childhood obesity tends to persist into adolescence and adulthood [12]. Therefore, clarifying the relationship between obesity at a young age and the lifetime risk of breast cancer is necessary.

At present, the screening standards for overweight and obesity in children and adolescents are not uniform, but mostly use the percentile value of body mass index (BMI) level of age and gender

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for judgement. There are three main international screening standards for overweight and obesity in children and adolescents: the International Obesity Task Force (IOTF) standards (2000) [13], the American Centers for Disease Control and Prevention (CDC) standards (2000) [14], and the World Health Organization (WHO) standards (2007) [15]. However, in terms of sensitivity and specificity of overweight and obesity screening, the IOTF standard, the US CDC standard, and the WHO standard differ greatly; the age groups of children targeted by different standards also differ greatly; several criteria also differ significantly in determining overweight/obesity rates in children of different ages. Overweight and obesity evaluation criteria are an important basis for evaluating the developmental status of individual children and adolescents and for conducting cross-sectional comparisons of similar studies in different regions, so it is essential to have a global unified evaluation standard. In addition, BMI in children is strongly influenced by height [16]. There are other limitations to BMI. Women with the same BMI may have different body fat distributions and body fat levels [17]. Hence, childhood BMI performs poorly in identifying children with overweight, which can miss a large proportion of children who are really overweight. A British study [18] points out that children, who are affected by obesity may be more distributed around the waist, and their propensity to be obese is difficult to measure with BMI. Not only that, but precise BMI and percentile information from childhood are hard to find and not easily recalled.

Somatotype, which may provide an easy, uniform, and accurate assessment of obesity categories for children [8], is a comprehensive feedback of body shape. The Stunkard scale [19] shows visual numbers representing nine gender-specific body contours ranging from very thin (assigned a value of 1) to very large (assigned a value of 9). A method of anthropometric measurement that used line drawings to recall male and female body shapes and ages of children and adolescents seemed practical in the distant past. Because adults are less likely to recall their early childhood weight or height accurately, recalling somatotypes during early childhood is particularly helpful [20]. Recollections of childhood somatotypes have been proven to be plausible, even after long intervals [21].

There are currently no pooled analyses of the association of somatotype before age 18, including preschool children (2–5 years), children (6–12 years) and adolescents (13–18 years) with breast cancer risk. Studying the link between early somatotypes and breast cancer risk could improve our understanding of disease mechanisms, which have important implications for prevention and early intervention because the potential for early intervention is enormous. Therefore, we conducted a comprehensive overview and meta-analysis to clarify the impact of early obesity on breast cancer risk and explore its mechanisms.

METHODS

Eligibility and search strategy

We conducted this systematic review and meta-analysis according to the Meta-analysis of Observation Studies in Epidemiology (MOOSE) guidelines [22]. This research had been registered with the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42021247072.

We performed a systematic literature search using the electronic databases of PubMed, Embase, and Cochrane library. All English publications prior to April 5, 2021, were searched without any restriction. The following MeSH terms, words, and phrases were used in the construction of the systematic search: ("Breast Neoplasm*" OR "Breast Tumour*" OR "Breast Cancer" OR "Mammary Cancer*" OR "Breast Malignant Neoplasm*" OR "Breast Malignant Tumour*" OR "Breast Carcinoma*" OR "Human Mammary Neoplasm*" OR "Human Mammary Carcinoma*" OR "Malignant Neoplasm of Breast" OR "Malignant Tumour of Breast" OR "Cancer of Breast" OR "Cancer of the Breast") AND ("Body mass index" OR "BMI" OR "obes*" OR "Overweight" OR "Weight" OR "underweight" OR "adiposity" OR "body size*" OR "Size, Body" OR "Sizes, Body" OR "Somatotype*" OR "Body Type*" OR "Body Build*" OR "Body Shape*" OR "Mesomorph*" OR "Ectomorph*" OR "Endomorph*" OR "body fatness" AND ("child*" OR "adolescent*" OR "school child*" OR "School age" OR "teen*" OR "paediatric*" OR "kid*"). In addition, we supplemented the above process with a hand search of the bibliographies of relevant articles in the field to ensure that the collection was complete. Furthermore, if the full text of the paper is not available, we requested the paper from the author by email.

Selection and eligibility criteria

The inclusion criteria was followed: (1) research examining the relationship between somatotype/BMI and breast cancer; (2) somatotypes assessment using Stunkard Figure Rating Scale or/and Sørensen Somatotypes; (3) age less than 18 years old; (4) multivariate-adjusted effect values, with 95% confidence interval (CI), can be extracted; (5) for dose–response analysis, the number of cases and participants or person-years for each category of somatotypes/BMI were provided (or data available to calculate them). Articles that do not meet the above criteria are excluded. Besides that, for articles published in the same cohort, we only included the one with the largest sample size and the longest history, excluding the remaining same cohort articles. The two authors conducted an independent assessment.

Quality assessment

We used Newcastle–Ottawa Quality Assessment Scale (NOS) to evaluate the quality of the literature for case–control studies and cohort studies. The results were presented in Supplemental Table 1—Methodological quality. The NOS project was based on three dimensions: selection of study groups, comparability between groups, and determination of exposure or outcome of interest. Stars were assigned for studies that reported follow-ups of at least 10 years; Missed follow-ups were estimated to be less than 25%. We classified quality into 3 levels (total stars of 9): high quality, with stars between 8 and 9; moderate quality, with stars between 5 and 7; and low quality, with stars between 0 and 4 [23].

Data extraction

Two authors independently extracted data and did a quality assessment. The screening process of the studies is completed in the endnote. A pre-established checklist was created to capture relevant information independently by two reviewers. The two researchers respectively de-duplicate the selected articles, read the abstract, and then preliminarily screen the articles, carefully read the full text and screen the articles finally used for this meta-analysis according to the above inclusion and exclusion criteria. Any disagreement was resolved by discussion until consensus was reached or by consulting a third author. The following data were extracted: author, year of publication, the country where the study was performed, cohort's name, sample size, type of study, menopausal status, the effect of value, somatotype and adjustment covariables. We extracted the effect of values that reflected maximally controlled for potential confounders.

When multiple studies were published from the same cohort or data, we included the research with the longest follow-up and the largest sample size. If a study involved multiple ages, we only extracted effect sizes for the minimum age. In addition, we did not stratify by menopausal status because some studies did not specify participants' menopausal status or did not stratify analyses by menopausal status. However, we extracted premenopausal and postmenopausal effect sizes separately if relevant studies did not have pooled results [24]. To be able to evaluate whether the risk of breast cancer is modified by menopausal status, we extracted the relevant data from all articles addressing this issue.

Statistical analysis

In this study, all effect values were obtained from original studies. The conversion between OR and RR was performed using the method of Zhang et al. [25]. For somatotypes, somatotype 1 was used as the reference group. When the lowest categories of somatotype were not selected as the reference group in the studies, we changed the reference group to the lowest category and converted the corresponding RRs and 95% CIs [26]. Pooled RRs and 95% CIs were then calculated. Forest plots were presented for RRs and 95% CIs. The subgroup analysis was performed mainly on potential effect modifiers (menopausal status, age) and methodological characteristics (type of study). For subgroup analyses of age, we used 10 years of age as the basis for grouping because previous findings suggest that the inverse association between early-life BMI and breast cancer risk may begin as early as age 10 years, possibly before menarche [27].

Statistical significance was considered at P value less than 0.05, and statistical heterogeneity between studies was tested using the Cochran's Q test, and inconsistency was tested using I^2. When the heterogeneity test was statistically significant ($P < 0.10$ or $I^2 > 50\%$), the random effect model was used to calculate the overall RR; otherwise, the fixed-effect model was adopted ($P > 0.10$ and $I^2 < 50\%$).

In addition, the potential nonlinear relation between somatotypes and breast cancer was examined by a two-stage random-effects meta-analysis. Then, the somatotype was modelled with restricted cubic splines with three knots selected at the 10th, 50th, and 90th percentiles of the distribution. The Ward test was used to assess nonlinearity. The nonlinearity of the meta-analysis was assessed by testing the null hypothesis; that is, the coefficient of the second spline was equal to zero; if $P < 0.05$, a nonlinear dose response was considered; otherwise, a linear dose response was considered. The pooled RRs of each 1-unit somatotype increment were obtained using somatotype 1 as a reference.

All the analyses in this meta-analysis were performed using STATA (version 16.0; Stata Corp, College Station, TX, USA), and we considered the P value of less than 0.05 (two-sided) to be statistically significant.

RESULTS

Literature search and study characteristics

A total of 604 relevant articles were retrieved through electronic databases and manual literature searches, of which 87 full-text articles were excluded because of duplication. Then, an initial screening based on titles and abstracts was performed, and 463 articles were excluded. Therefore, the remaining 54 full-text articles were evaluated in detail, of which 6 articles were excluded because of lack of statistics on different somatotypes and breast cancer or inability to extract them; six articles were excluded because of identical cohort information; five articles were excluded because of lack of relevant information; 19 articles were excluded because of age greater than or equal to 18 years; four articles were excluded because they involved either four or five categories of BMI, and the full text of two articles was not available; thus, they were excluded. Finally, six articles [24, 28–32] were included in this meta-analysis. The flowchart of the article selection process is shown in Fig. 1.

Table 1 provides details of the included studies. The detailed data presented in the tables, when not specifically stated, are listed as summary results without distinction between premenopausal and postmenopausal and are for the youngest age shown in the article. Six articles involving 15,211 breast cancer patients from 341,905 individuals that met the eligibility criteria for meta-analysis were published between 1998 and 2020. Of these studies, two were conducted in the United States and two in Sweden. The rest are from France and Morocco. Five studies included premenopausal status, six studies included postmenopausal status, and three studies also provide the mixed menopausal status which did not distinguish menopausal status. Follow-up ranged from 10 years to 18 years, with a loss of follow-up/non-response rate of less than 20%. Among these studies, the study of Fagherazzi et al. used Sørensen Somatotypes to evaluate somatotypes, and the remaining studies used Stunkard Figure Rating Scale to evaluate somatotypes. According to the Newcastle–Ottawa Scale, all studies scored above six, indicating that all articles included were of high or moderate quality.

Pooled analysis, subgroup analysis, and dose–response analysis of somatotype and the risk of breast cancer

The relative risk (RR) of each original study reference group was recalibrated to uniformly use somatotype 1 as a reference. The risks were then calculated separately for the other somatotypes relative to the reference group. The pooled RRs were as follows: 0.941 (95% CI: 0.864, 1.025; $I^2 = 54.3$, $P\text{-heterogeneity} = 0.068$) for somatotype 2, 0.903 (95% CI: 0.869, 0.939; $I^2 = 35.6\%$, $P\text{-heterogeneity} = 0.144$) for somatotype 3, 0.892 (95% CI: 0.856, 0.928; $I^2 = 26.7\%$, $P\text{-heterogeneity} = 0.234$) for somatotype 4, 0.847 (95% CI: 0.726, 0.989; $I^2 = 79.5\%$, $P\text{-heterogeneity} = 0.001$) for somatotype 5, 0.762 (95% CI: 0.681, 0.851; $I^2 = 0$, $P\text{-heterogeneity} = 0.573$) for somatotype 6, and 0.706 (95% CI: 0.488, 1.021; $I^2 = 13.8\%$, $P\text{-heterogeneity} = 0.282$) for somatotype 7 (Fig. 2). The restricted cubic spline model in Fig. 3 indicated a linear relationship between somatotypes and breast cancer ($P\text{-nonlinearity} = 0.533$). Using somatotype 1 as the reference group, the protection became stronger with the increase of somatotype until somatotype reach 6.

When stratified by age, the summary RRs for the association between early-life somatotype and breast cancer risk were totally different. With somatotype increasing, the protective effect could only be found in groups whose age was less than 10 years old, but not in the group with age higher than or equal to 10. Among people younger than 10 years of age, an increase in somatotype was associated with a statistically significant reduction in breast cancer risk. From somatotype 3 to somatotype 6, the risk of breast cancer was reduced by 9.7–27.7% (Table 2). In a dose–response analysis of studies younger than 10 years, we found a linear trend ($P\text{-nonlinearity} = 0.175$) (Fig. 3).

The results of subgroup analysis of menopausal status showed that increasing somatotype during childhood was increasingly protective against postmenopausal breast cancer from somatotype 3 to somatotype 6, with a 0.887-fold (RR = 0.887, 95% CI: 0.842, 0.934) to 0.759-fold (RR = 0.759, 95% CI: 0.631, 0.913) decreased risk of breast cancer, but this association was not found in the population with premenopausal breast cancer. Only somatotype 3 is protective against premenopausal breast cancer (RR = 0.933, 95% CI: 0.876, 0.993) (Table 2). Dose–response analysis showed that linear trends were observed both in postmenopausal women ($P\text{-nonlinearity} = 0.880$) and premenopausal women ($P\text{-nonlinearity} = 0.757$) (Fig. 3). But the risk of developing breast cancer was associated with somatotype in premenopausal women, but not in postmenopausal women.

DISCUSSION

Our findings provide evidence supporting the long-term effect of early somatotype on breast cancer risk, with a decrease in breast cancer risk as somatotype increases during childhood (especially younger than 10 years). But the association was only seen in postmenopausal breast cancer risk, not in premenopausal breast cancer.

Byun et al. [27] published the results of an early period of adult BMI and breast cancer study in 2020, but differed from our study in that (1) the authors included subjects younger than or equal to 25 years of age and, when multiple body fat measurements (BMI or somatotypes) were provided for multiple ages in the study, only

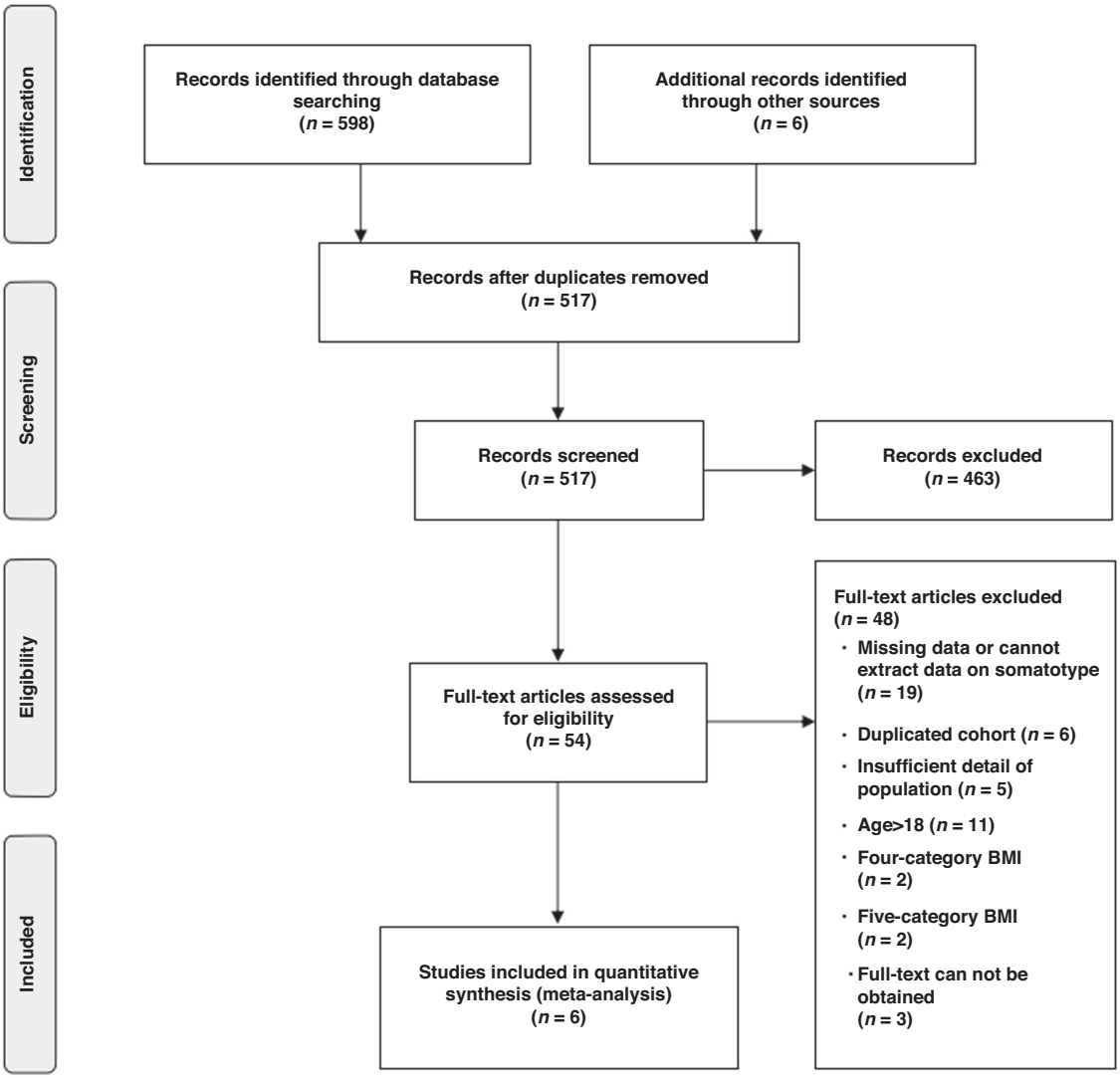

Fig. 1 The figure shows the flow of information through the different phases our meta-analysis. Flow diagram of the included studies.

the age group closest to 18 years was selected. (2) In studies using somatotypes (Stunkard or Sørensen) to assess early vital body fat, the authors inferred and estimated BMI values based on prior findings [20] and only the pictogram data for the age closest to 15 years was used. Results from pooled and subgroup analyses showed that both premenopausal and postmenopausal women were inversely associated with breast cancer risk, independent of menopausal status, different from our conclusions. In general, the study of Byun still looks at the relationship between somatotypes and breast cancer risk at age 15 and older. They do not estimate summary RRs for somatotypes at very young ages. In addition, The screening criteria for overweight and obesity in children and adolescents are mostly judged by the percentile value of body mass index (BMI) level of age and sex. There are three main international screening standards for overweight and obesity in children and adolescents: the International Obesity Working Group (IOTF) standard (2000) [13], the United States Center for Disease Control and Prevention (CDC) standard (2000) [14] and the World Health Organization (WHO) standard (2007) [15]. However, the BMI of children is strongly affected by their height [16]. Therefore, the BMI of children is not good at identifying overweight children. A British study [18] pointed out that children affected by obesity may be more distributed in the waist, and their tendency to obesity is difficult to measure with BMI. Moreover, accurate BMI and percentile information on childhood are also difficult to find and recall. Body shape can provide children with a simple, unified, and accurate assessment of obesity categories [8], which is comprehensive feedback on body shape. Because adults are unlikely to accurately recall their early weight or height, it is particularly helpful to recall body shape in early childhood [20]. The recall of childhood body shape has been proven to be reasonable, even after a long time interval [21]. Based on the above reasons, compared with BMI, the body size used in this study is more suitable for evaluating the impact of early-life obesity on breast cancer risk, and more accurate than BMI.

Weight may potentially affect breast cancer risk by altering the hormonal levels of women and metabolic factors at different times in the life course [33]. Smaller somatotypes in childhood are associated with faster pubertal development and sexual maturation [34]. Excessive pubertal growth, such as peak height growth rate, which is a measure of adolescent growth, is thought to be associated with an increased risk of breast cancer. Rapid growth during puberty may increase breast growth hormone levels and epithelial proliferation or decrease the time for DNA damage repair, thereby increasing the risk of breast cancer [35].

Adipose tissue is the site of the conversion of adrenal androgens to oestrogen. Hence, large amounts of oestrogen are produced in adipose tissue [36]. Obesity in childhood can alter

Table 1. Main characteristic of the included articles on somatotype and breast cancer.

Author, year	Study type, country	Years of follow-up	Menopausal status	Recall age	Assessment tool of somatotype	Non-response rate/lost to follow-up rate	Sample size (case)	Body size	Effect value and 95% confidence interval (CI)			Adjusted variables
									Effect value	Low	High	
Fagherazzi, 2013 [28]	Cohort (E3N -1990–2008), France	10 years for women with breast cancer and 18 years for non-breast cancer cases	Mixed menopausal, premenpausal, and postmenopausal	8 and Menarche	Sørensen's body shapes	2.1%	858	1	1			Age, level of physical activity, education, family history of breast cancer in first-degree relatives, age at menarche, parity and age at first full-term pregnancy, breastfeeding, mammography during the previous follow-up period, history of benign breast disease, BMI, use of oral progestagens alone, use of oral contraceptives, menopausal status, use of menopausal hormone therapy, age at menopause
							1189	2	0.97	0.89	1.06	
							846	3	0.94	0.85	1.03	
							680	≥4	0.83	0.75	0.92	
Baer, 2010 [31]	Cohort (NHS -1988–2004 and NHSII-1989–2005), USA	16	Mixed menopausal, premenpausal, and postmenopausal	5 and 10	Stunkard Figure Rating Scale	3%	2292	1	1			Age, time period, parity/age at first birth, family history of breast cancer, personal history of benign breast disease, height, alcohol
							2304	2	1.02	0.96	1.08	
							1376	3	0.87	0.81	0.93	
							923	4	0.8	0.74	0.87	
							498	5	0.69	0.62	0.76	
							160	6	0.71	0.61	0.84	
							29	≥7	0.61	0.42	0.88	
Magnusson, 1998 [30]	Case–control, Sweden	/	Postmenopausal	7	Stunkard Figure Rating Scale	11% for case and not mentioned for control	990	1	1.22	1.01	1.49	Age, parity, age at first birth, age at menopause and use of hormone replacement therapy
							850	2	1.28	1.05	1.56	
							515	3	1.19	0.96	1.47	
							277	4	1			
							138	5	1.02	0.76	1.38	
							35	6	0.78	0.48	1.26	
							5	≥7	0.38	0.13	1.09	
Khalis, 2020 [24]	Case–control, Morocco	/	Premenpausal	6-11	Stunkard Figure Rating Scale	3.3% for cases and 12.1% for controls	37	1	1			Age, area of residence, wealth score, number of live births, history of oral contraceptives, history of breastfeeding, age at first full-term pregnancy, physical activity and current BMI
							90	2	0.86	0.39	1.91	
							26	≥3	0.31	0.12	0.8	
			Postmenopausal				26	1	1			
							68	2	0.75	0.3	1.87	
							40	≥3	0.4	0.15	1.07	
Sangaramoorthy, 2011 [32]	Case–control, USA	/	Premenpausal	10 and 15	Stunkard Figure Rating Scale	10% for cases and 12% for controls	88	1–2	1			Age, country of birth, education, first-degree family
							90	3–4	0.76	0.48	1.2	

Table 1. continued

Author, year	Study type, country	Years of follow-up	Menopausal status	Recall age	Assessment tool of somatotype	Non-response rate/lost to follow-up rate	Sample size (case)	Body size	Effect value and 95% confidence interval (CI)			Adjusted variables
									Effect value	Low	High	
							30	≥5	0.86	0.45	1.64	history of breast cancer, prior biopsy-confirmed history of benign breast disease, number of full-term pregnancies, lifetime breastfeeding, age at first full-term pregnancy, oral contraceptive use, adult height, average alcohol consumption, and average caloric intake, and current BMI.
			Postmenopausal				99	1–2	1			
							81	3–4	0.79	0.51	1.13	
							23	≥5	0.96	0.51	1.82	
Li, 2017 [29]	Cohort (KARMA), Sweden	No mention	Mixed menopausal, premenpausal, and postmenopausal	7	Stunkard Figure Rating Scale	No mention	1573	1–2	1			Year of birth and adjusted for body mass index
							942	3–4	0.93	0.86	1.01	
							218	≥5	0.79	0.68	0.91	

BMI body mass index.

ovarian hormone production by increasing the frequency of anovulatory cycles [28]. It may cause lower levels of progesterone and estradiol [37, 38]. High progesterone levels [8] are a risk factor for malignant transformation because progesterone can increase the proliferation of breast epithelial cells. Thus, an increase in progesterone levels may increase the risk of breast cancer [30]. Postmenopausal women with obesity increased androgen-to-oestrogen conversion in adipose tissue resulting in elevated circulating oestrogen levels and low sex hormone-binding globulin (SHBG) levels, resulting in a higher proportion of bioavailable oestrogen [37, 38].

Insulin-like growth factor (IGF)-I, a mitogenic and antiapoptotic peptide, can regulate cell growth and survival, and is thought to play an important role in tumour development [39]. Several cellular effects of IGF-I favour tumour growth, including mitosis, anti-apoptosis, induction of vascular endothelial growth factor (pro-angiogenic), and increased cell migration. Furthermore, the IGF-I receptor is overexpressed in many tumour cell types, which can enhance the response to circulating IGF-I compared to equivalent healthy tissue. Circulating concentrations of IGF-I may affect the proliferation of breast epithelial cells, and are thought to have a role in breast cancer [39]. Our results showed that increased somatotype was not associated with premenopausal breast cancer risk, but significantly reduced postmenopausal breast cancer risk. We speculate that this may be due to the effect of IGF-I, because a positive relationship between circulating IGF-I concentration and risk of breast cancer was found among premenopausal since oestradiol enhances the action of IGF-I in the breast [40] but not postmenopausal women [41], this effect can attenuate the protective effect of anovulation on the risk of breast cancer in premenopausal women.

Serum IGF-I concentrations increase slowly with age in early puberty, with a further steep increase during puberty, and a decrease throughout adulthood [42]. At the same time, there was no significant correlation between BMI and serum IGF-I in prepubertal children [42]. This seems to explain why children with obesity younger than 10 years of age are more protected against breast cancer than those 10 years and older. This is because circulating IGF-I concentrations are highly correlated with growth and height during puberty. The age of ten or more (7 years onwards in girls and 9 years onwards in boys [43]) will usher in the first peak of growth—adolescence, and the concentration of circulating IGF-I will then peak. This would cut some of the protective effects of obesity. After menopause, however, the concentration of circulating IGF-I decreases with age, which attenuates the adverse effects of increased oestrogen in postmenopausal women. The risk for postmenopausal breast cancer was similar to results that did not differentiate between premenopausal and postmenopausal women, suggesting that excess body weight is associated with risk both before and after menopause [44]. However, the use of hormone replacement therapy [45] and mammographic density [46] may be additional confounding factors. This requires further research.

Although hormonal aetiology may partly explain the difference between body size and breast cancer risk, people increasingly believe that premenopausal breast cancer cases may have different aetiology from postmenopausal breast cancer cases. A recent study (Chen et al., 2016) [47] shows that obesity has different effects on the risk of breast cancer in premenopausal women and postmenopausal women, and some non-hormonal pathways may also mediate the association between obesity and breast cancer in premenopausal women. Obesity-related factors, such as inflammation, elevated insulin levels, or other factors, may play different roles in the risk of postmenopausal and premenopausal breast cancer. This may be the underlying reason for the difference in body size in the risk of postmenopausal and premenopausal breast cancer. The results of the two five-category BMIs [9, 48] were similar to those of somatotype, with

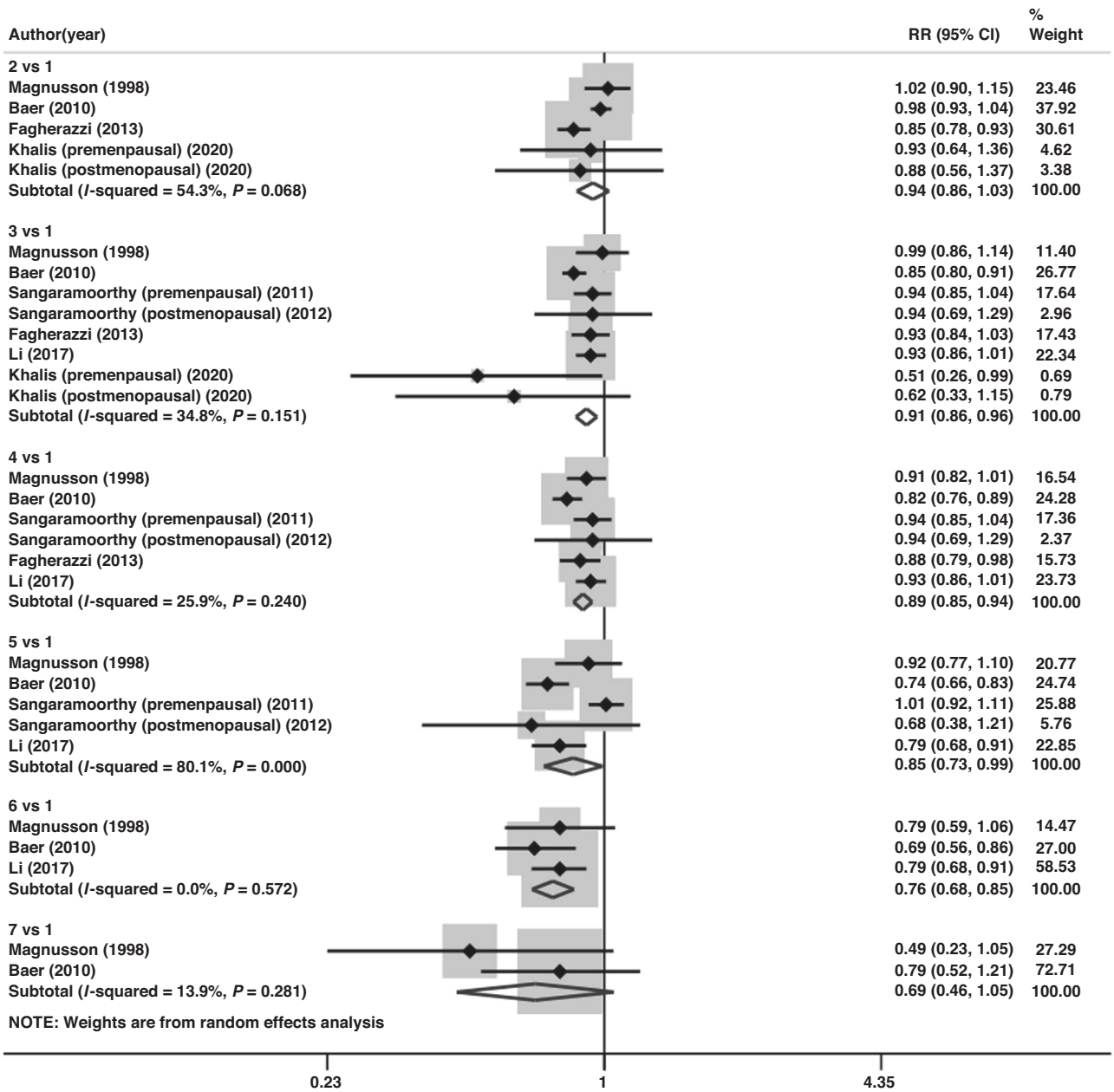

Fig. 2 Based on somatotype 1, the combined effects of other somatotypes and breast cancer were analyzed separately. The pooled analysis of somatotype and breast cancer.

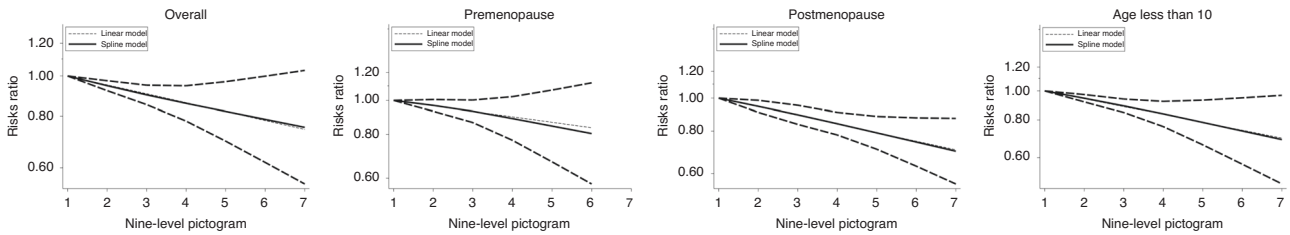

Fig. 3 The dose-effect analysis of somatotype and breast cancer was conducted on the basis of somatotype 1.

the highest category (heaviest) in the category having a protective effect on breast cancer compared to the lowest category (lightest). However, the results of a four-category BMI [49] were different from the results of somatotype, and even concluded that the higher the BMI, the higher the risk of breast cancer. This may be due to the fact that both weight and height at age 12 in the study were self-reported results, and no attempt was made to corroborate height and weight at age 12 through medical or school records, thus misrepresenting the true association. In addition, the results of another four-category BMI [50] and the

Table 2. Subgroup analysis on somatotype and breast cancer.

Comparison	Subgroups		Number of studies included*	Subgroup analysis			
				RR (95% CI)	I^2	*P*-heterogeneity	
						Within subgroup	Between subgroup
2 vs 1							
	Time of cancer occurrence	Premenopause	3	0.938 (0.857, 1.026)	23.5%	0.271	0.708
		Postmenopause	4	0.953 (0.905, 1.004)	42.8%	0.154	
	Age of somatotype evaluation	<10	5	0.941 (0.864, 1.025)	54.3%	0.068	/
3 vs 1							
	Time of cancer occurrence	Premenopause	5	0.933 (0.876, 0.993)	25.6%	0.251	0.384
		Postmenopause	6	0.887 (0.842, 0.934)	25.6%	0.242	
	Age of somatotype evaluation	<10	6	0.903 (0.839, 0.971)	50.1%	0.075	0.501
		≥10	2	0.940 (0.857, 1.031)	0	1	
4 vs 1							
	Time of cancer occurrence	Premenopause	4	0.936 (0.875, 1.002)	0	0.818	0.182
		Postmenopause	5	0.866 (0.822, 0.913)	51.4%	0.083	
	Age of somatotype evaluation	<10	4	0.880 (0.842, 0.921)	43.2%	0.153	0.261
		≥10	2	0.940 (0.857, 1.031)	0	1	
5 vs 1							
	Time of cancer occurrence	Premenopause	3	0.823 (0.620, 1.094)	85.8%	0.001	0.945
		Postmenopause	4	0.815 (0.744, 0.892)	0	0.472	
	Age of somatotype evaluation	<10	3	0.788 (0.727, 0.854)	49.1%	0.140	0.424
		≥10	2	0.999 (0.908, 1.099)	43.2%	0.185	
6 vs 1							
	Time of cancer occurrence	Premenopause	1	0.630 (0.412, 0.964)	/	/	0.431
		Postmenopause	2	0.759 (0.631, 0.913)	0	0.735	
	Age of somatotype evaluation	<10	2	0.723 (0.608, 0.860)	0	0.468	/

*Articles that differentiated by menopausal status (without pooled results that were indistinguishable) extracted premenopausal and postmenopausal data separately and counted as two studies. Therefore, the total number of included studies will be greater than 6.

results of the international classification of BMI [51] both showed that BMI was not related to somatotype. The results of childhood BMI and breast cancer risk are not uniform, and the classification is diverse and the number of studies is small. It is not possible to summarise and merge for the time being, and further exploration and research are needed in the follow-up research.

Strength and limitations

This research is the first meta-analysis study to explore somatotypes and breast cancer risk in preschool children (2–5 years), children (6–12 years), and adolescents (13–18 years).

Our study had several limitations. First is the heterogeneity as discussed above. Differences in follow-up age, and characteristics of participants, would all affect the interpretation of the conclusions. We used a stratified analysis method but maybe still under inadequate consideration of confounding factors. Second, given the paucity of relevant studies, we were unable to investigate whether oestrogen and progesterone receptor status and hormone replacement therapy affect childhood somatotypes on breast cancer risk because they are proven to have an impact in adults. In addition, each study was adjusted for different factors, and some important factors, such as regularity of menstruation, were not adjusted in many studies, which would hinder the interpretation of the underlying mechanisms. Therefore, we could not draw evidence to support an oestrogen or non-oestrogen-mediated mechanism of action. Third, although our research found with somatotype increased, the protective effect could only be found in groups whose age was less than 10 years old, but not in groups with an age higher than or equal to 10. However, due to the limited number of existing studies, we cannot analyse the interaction between age factors and the risk of premenopausal and postmenopausal breast cancer.

CONCLUSION

A dose–response relationship between breast cancer and somatotypes is observed during childhood and early adulthood. Girls who have larger somatotypes, particularly those who are affected by overweight and obesity before the age of 10, have a lower risk of breast cancer. In addition, normal somatotype has a weak protective effect against breast cancer. Girls with overweight/obesity likely remain overweight or even develop obesity in adulthood, whereas adults who are affected overweight and obese are at increased risk of breast cancer and other types of cancer and various chronic diseases. Hence, we recommend that children should not be too thin and too fat but should maintain a normal and slightly fat somatotype throughout all periods of life.

DATA AVAILABILITY

Not applicable.

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AUTHOR CONTRIBUTIONS

Each author is expected to have made substantial contributions to the work. Conceptualisation: DM and YD; methodology: DM and YD; software: YD; validation: DM; formal analysis: YD; investigation: YD, BC, XY and QX; resources: DM; data curation: DM; writing–original draft preparation: YD; writing—review and editing: DM; visualisation: YD and BC; supervision: DM; project administration: DM and YD; funding acquisition: DM. All authors have read and agreed to the published version of the manuscript. YD and DM participated in the design of this manuscript. YD, BC, XY, QX and DM participated in performing the research and statistical analysis. All authors read and approved the final manuscript.

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