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Review

A Woman's build and the Risk of Breast Cancer

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A woman's build and the risk of breast cancer seem to be related. While relative overweight, as described by the body mass index, seems to be associated with increased breast cancer risk in postmenopausal women, overweight in premenopausal women seems slightly protective. Papers from a MEDLINE search are reviewed regarding the association between build and the development of breast cancer. Different aspects of build, such as height, weight, body mass index and body shape, are discussed. The more prominent associations found through this search are a positive association between height and breast cancer risk both in pre- and postmenopausal women. Regarding body mass index, the association is negative in premenopausal women and positive in postmenopausal women. Body shape described as masculine versus feminine seems to have no impact on breast cancer risk in premenopausal women, but seems to be positively associated with breast cancer in postmenopausal women. Possible biological mechanisms responsible for the associations with breast cancer risk are discussed, including endogenous oestrogens, androgens and glucose metabolic substances. Avoiding or reducing postmenopausal overweight may modify breast cancer risk indicators in a more favourable direction. © **1998 Elsevier Science Ltd. All rights reserved.**

Key words: anthropometry, body mass index, breast cancer, prevention, risk
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INTRODUCTION

A PERSON'S BUILD seems to be associated with the risk of developing breast cancer. Build is influenced by inheritance and lifestyle factors. The latter may be modified, and, if there is a true underlying causal relationship between build and breast cancer, the risk of developing breast cancer may also be modified.

Build is not a well-defined notion. It covers simple measurements, such as height and weight, to a more advanced description of the body, including calculation of relative weight, measurements of fat distribution and estimation of total body fat. According to the different levels of measurements, different biological modes of action may be applied to elucidate the impact on the development of breast cancer.

One of the more consistent associations between build and breast cancer is the increased risk of breast cancer in relatively overweight postmenopausal women. Different hypotheses have related the risk of breast cancer development to increased exposure to female steroid hormones, particularly oestrogens [1]. According to one of these hypotheses, the increased risk of postmenopausal breast cancer due to overweight is attributed to increased aromatase activity in the adipose tissue and consequently increased levels of free oestrogens [2].

Glucose metabolism may also be involved. Overweight has been linked to increased levels of insulin and insulin resistance. Moreover, increased levels of insulin are associated with decreased levels of sex hormone binding globulin (SHBG), thus resulting in increased levels of free oestrogens [3]. Insulin-like growth factor 1, which acts as a promoter of breast cancer *in vitro*, may also play a part in this scenario [4, 5].

The distribution of adipose tissue in overweight women may also be important. Different shapes of body may be related to different risks of breast cancer, as metabolic activities change with the distribution of adipose tissue [6].

The association between body weight and the risk of breast cancer becomes even more complicated because body weight may vary throughout life. Although such data may be

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accurate, there is debate about which biological mechanisms may be responsible for the changing risk of breast cancer, and about the extent to which such mechanisms are reflected in conspicuous patterns of build. While relative postmenopausal overweight seems to increase the risk of developing breast cancer, overweight seems to be inversely associated with breast cancer risk premenopausally [7]. Thus, build has to be contemplated dynamically, and the extent of overweight must be described carefully at given ages.

This review deals with the different aspects of build and breast cancer risk in pre- and postmenopausal women. The possible biological implications associated with different types of build are discussed.

MEASUREMENT OF BUILD

Height is an easily obtainable, reliable and cheap measure of build [8]. Sitting height is also easy to measure [8], and when subtracted from height, the leg length is obtained. Sitting height or the relative sitting height (sitting height/height) may express certain growth patterns [9]. For instance, early menarche seems to be positively associated with relative sitting height [10]. Body weight is also easily obtained by standard procedures [8]. Relative weight, or degree of overweight, has been described by many formulae of the form: weight/height to the power of x, in order to obtain a measure of weight corrected for height. The body mass index ($BMI = weight/height^2$) has gained general acceptance for this purpose. In order to estimate the lean body mass and the adipose tissue component of the body, the thickness of various skinfolds has been measured [11]. Whole body impedance is a rather new measure. Body conductance is measured and this measure can be related to the lean body mass, and thus the relative percentage of body fat can be estimated [12]. The localisation of adipose tissue (body shape) can be described as central (the trunk) or peripheral (hips), alternatively as masculine or feminine. The localisation can be described from measures of the waist–hip ratio (WHR) or from the ratio between certain skinfolds [13].

LITERATURE SEARCH

The following review includes studies identified through MEDLINE (search terms: breast cancer, risk, anthropometry, body fat, body constitution, body composition, electric conductivity) for the period 1 January 1966 to 31 December 1996, and cross-references from these studies. Because of the difference in impact of build before and after the menopause, only studies stratifying for menopausal status or, alternatively, age less than or more than 50 years as an indicator of menopausal status, are included in the tables. Likewise, for all included studies it must have been possible to identify the relative risk in the published report, whether they have been calculated directly or estimated by odds ratios. Major parts of a study should not have been published within other tabulated studies. To reduce the impact of random error, studies including less than 100 cases in a menopausal stratum were excluded. This procedure has the additional advantage that the impact of publication bias is reduced.

HEIGHT

Studies on the risk of premenopausal and postmenopausal breast cancer according to body height are presented in Tables 1 and 2, respectively. In the cohort studies, increasing height was generally associated with an increased risk of both pre- and postmenopausal breast cancer. Most cohort studies used direct measurements of height and weight [14, 16, 17, 31, 33] and only two used self-reported values [15, 32]. In the case–control studies, the results were less homogeneous. Five studies described increasing body height as a significant risk factor in premenopausal [18, 28] and postmenopausal women [23, 25, 29]. The remaining studies showed non-significant and varying associations. Self-reported height was used in all but two case–control studies [28, 29].

In an international correlation study, focusing upon several risk factors, Baanders and De Waard showed that the age at first full-term pregnancy and body height together explained 80% (60 and 20%, respectively) of the total variation in breast cancer incidence in 15 European countries [35]. The general weakness in such ecological studies is that the data are estimated national means that do not necessarily refer to the cancer cases, and that confounders are not taken into account.

Vatten and associates focused on body height and breast cancer risk in different birth cohorts [36]. The increased risk due to body height was more pronounced in women who experienced their puberty during the Second World War than in women whose puberty took place before or after the war. This observation has been ascribed to a generally greater variation in diet during the war, and consequently body height. During the war, there was a general shortness of supplies, and the diet was inadequate in parts of the population, resulting in reduced body height [37].

In conclusion, the cohort data support the notion that increasing height is associated with an increasing risk of breast cancer in both pre- and postmenopausal women. Overall, the less homogeneous data from case–control studies point in the same direction.

WEIGHT

Studies on the risk of breast cancer according to body weight in premenopausal and postmenopausal women are listed in Tables 3 and 4, respectively. There is no clear tendency for premenopausal women. Only two studies showed significant results, with a reduced risk in overweight women [26, 28]. The remaining studies showed weak positive and negative associations [14, 18–21, 24, 25, 27, 29, 38–41].

The picture was more homogeneous for postmenopausal women. An increased risk according to overweight was described, which was significant in eight studies [14, 18, 21, 32, 40–42] and non-significant in nine studies [19, 25–27, 29, 31, 34, 38, 39]. Two exceptions were case–control studies based on self-reported weight that showed a non-significant decreased risk [20, 24].

Weight changes

In premenopausal women, increasing weight was associated with a reduced risk of breast cancer in several studies [15, 25, 43–46] whilst two studies showed no association [22, 47]. Most studies found increasing weight throughout adult life associated with an increased risk of postmenopausal breast cancer [15, 25, 43, 44, 47–50], whilst one study found no association [34] and one found a decreased risk [46]. One study found that weight gain after adulthood was a risk factor, and that weight gain after the age of 30 years was even more important [51]. Another study found increasing weight

from adolescence to adulthood associated with a greater risk than a more constant overweight [43].

BMI

Weight in itself is closely related to height. In order to obtain a measure that more clearly describes relative weight independent of height, BMI can be used. Studies analysing the risk of breast cancer according to BMI in pre- and postmenopausal women are listed in Tables 5 and 6, respectively.

Premenopausal women

The cohort studies showed fairly good accordance, with a significantly reduced risk according to relative overweight [14–17]. Only the study by Young and colleagues found no association [52]. A total of 24 case–control studies have been tabulated of which seven indicated a significant negative association [26–28, 47, 53, 56, 60], and one indicated a significant positive association [62]. The rest showed non-significant results indicating a negative association [18, 19, 24,

Table 1. *The association between height and the risk of premenopausal breast cancer expressed as a relative risk*

Reference	Year	Country	Number of cases	Comparison in cm	RR	95% confidence intervals
Cohort studies						
Törnberg and associates [14]	1988	Sweden	196	5 cm increase	1.1	1.0–1.3
London and associates [15]	1989	U.S.A.	658	> 168 versus < 160	1.1	0.9–1.3
Tretli [16]	1989	Norway	1000	15 cm increase	1.3	1.1–1.4
Vatten and Kvinnsland [17]	1992	Norway	164	> 167 versus < 159	1.6	1.2–2.1
Case–control studies						
Staszewski [18]	1977	Poland	300	> 170 versus < 160	2.6	Not presented*
Hislop and associates [19]	1986	Canada	316	> 170 versus < 157	0.8	0.5–1.3
Ewertz [20]	1988	Denmark	639	> 170 versus < 160	0.9	Not presented*
Parazzini and associates [21]	1990	Italy	1110	> 165 versus < 155	0.8	0.6–1.1
Lund and associates [22]	1990	Norway–Sweden	423	> 169 versus < 160	1.3	0.8–2.1
Hsieh and associates [23]	1990	International	1600	10 cm increase	1.0	0.9–1.1
Bouchardy and associates [24]	1990	France	154	> 166 versus < 156	1.3	Not presented*
Brinton and Swanson [25]	1992	U.S.A.	414	> 173 versus < 157	1.5	0.8–2.8
Taioli and associates [26]	1995	U.S.A.	196	> 168 versus < 160	0.8	0.5–1.5
Franceschi and associates [27]	1996	Italy	989	> 168 versus < 158	1.0	0.7–1.4
Swanson and associates [28]	1996	U.S.A.	1588	> 167 versus < 159	1.5	1.2–1.8
Mannisto and associates [29]	1996	Finland	132	> 169 versus < 159	1.8	0.8–4.2
Ziegler and associates [30]	1996	U.S.A.	424	> 168 versus < 150	1.9	1.0–3.6†

RR, relative risk. *Non-significant; †$P < 0.05$.

Table 2. *The association between height and the risk of postmenopausal breast cancer expressed as a relative risk*

Reference	Year	Country	Number of cases	Comparison in cm	RR	95% confidence intervals
Cohort studies						
Törnberg and associates [14]	1988	Sweden	986	5 cm increase	1.1	1.1–1.1
London and associates [15]	1989	U.S.A.	420	> 168 versus < 160	1.3	1.0–1.7
Tretli [16]	1989	Norway	7000	15 cm increase	1.4	1.3–1.5
Den Tonkelaar and associates [31]	1994	The Netherlands	260	> 166 versus < 158	1.0	0.7–1.4
Toniolo and associates [32]	1995	U.S.A.	130	> 168 versus < 158	1.7	0.9–3.3
Freni and associates [33]	1996	U.S.A.	112	> 167 versus < 156	2.0	1.0–3.8
Case–control studies						
Staszewski [18]	1977	Poland	500	> 170 versus < 160	1.2	Not presented*
Hislop and associates [19]	1986	Canada	530	> 170 versus < 157	1.3	0.9–2.0
Kolonel and associates [34]	1986	Hawaii	272	Upper quartile versus lower	1.5	Not presented*
Ewertz [20]	1988	Denmark	491	> 170 versus < 160	0.9	0.5–1.4
Parazzini and associates [21]	1990	Italy	2137	> 165 versus < 155	0.8	0.7–1.0
Hsieh and associates [23]	1990	International	3400	10 cm increase	1.1	1.0–1.2†
Bouchardy and associates [24]	1990	France	223	> 166 versus < 156	1.3	Not presented*
Brinton and Swanson [25]	1992	U.S.A.	1115	> 173 versus < 157	1.6	1.1–2.3
Taioli and associates [26]	1995	U.S.A.	421	> 168 versus < 160	0.8	0.5–1.3
Franceschi and associates [27]	1996	Italy	1580	> 168 versus < 158	0.8	0.6–1.0
Mannisto and associates [29]	1996	Finland	196	> 169 versus < 159	2.3	1.1–4.6
Ziegler and associates [30]	1996	U.S.A.	114	> 168 versus < 150	1.7	0.5–6.2

RR, relative risk. *Non-significant; †$P < 0.05$.

25, 29, 49, 59], no association [57, 58, 61], or a positive association [20, 22, 30, 43, 54, 55]. The international study by Pathak and Whittemore showed different associations in high and low risk areas, with negative and positive associations with BMI, respectively [61]. Accordingly, the only study to show a significant positive association was from Japan [62], which is a low risk area [67].

A recently published meta-analysis by Ursin and associates indicated a modest reduction of breast cancer risk in premenopausal women with increasing BMI [7]. Taking different aspects of study design into account, it appeared that this inverse association was strongest in the cohort studies, less strong in the case–control studies using community controls, and weakest in the case–control studies using hospital controls.

Control for confounders in addition to age underlined the association in the cohort studies. The heterogeneity was evident in the case–control studies. Using different quality indicators, such as short lagtime (< 6 months), the same exclusion criteria for cases and controls, and confounder

Table 3. The association between body weight and the risk of premenopausal breast cancer expressed as a relative risk

Reference	Year	Country	Number of cases	Comparison in kg	RR	95% confidence intervals
Cohort study						
Törnberg and associates [14]	1988	Sweden	196	10 kg increase	0.9	0.8–1.1
Case–control studies						
Staszewski [18]	1977	Poland	300	> 80 versus < 60	1.1	Not presented*
Brisson and associates [38]	1984	U.S.A.	104	> 75 versus < 55	1.2	0.5–2.8
Hislop and associates [19]	1986	Canada	316	> 75 versus < 54	0.6	0.4–1.2
Tao and associates [39]	1988	China	299	> 70 versus < 51	1.0	0.5–1.9
Ewertz [20]	1988	Denmark	645	> 80 versus < 60	1.1	0.6–2.0
Yuan and associates [40]	1988	China	234	> 60 versus < 50	2.1	0.8–5.3
Parazzini and associates [21]	1990	Italy	1110	> 72 versus < 54	0.7	0.5–1.0
Bouchardy and associates [24]	1990	France	154	> 66 versus < 56	0.6	Not presented*
Brinton and Swanson [25]	1992	U.S.A.	414	> 68 versus < 54	0.9	0.6–1.4
Yang and associates [41]	1993	U.S.A.	325	> 72 versus < 54	1.3	0.8–2.2
Taioli and associates [26]	1995	U.S.A.	196	> 73 versus < 57	0.4	0.2–0.7
Franceschi and associates [27]	1996	Italy	989	> 75 versus < 57	1.2	0.9–1.5
Swanson and associates [28]	1996	U.S.A.	1588	> 59 versus < 77	0.7	0.6–0.9
Mannisto and associates [29]	1996	Finland	132	> 76 versus < 55	0.8	0.4–1.8

RR, relative risk; *Non-significant.

Table 4. The association between body weight and the risk of postmenopausal breast cancer expressed as a relative risk

Reference	Year	Country	Number of cases	Comparison in kg	RR	95% confidence intervals
Cohort studies						
Törnberg and associates [14]	1988	Sweden	986	10 kg increase	1.1	1.1–1.2
Den Tonkelaar and associates [31]	1994	The Netherlands	260	> 75 versus < 62	1.3	0.9–1.8
Toniolo and associates [32]	1995	U.S.A.	130	> 73 versus < 59	2.6	1.3–5.3
Case–control studies						
Staszewski [18]	1977	Poland	500	> 80 versus < 60	1.9	Not presented*
Kelsey and associates [42]	1981	U.S.A.	284	> 57 versus < 57	1.6	1.2–2.3
Brisson and associates [38]	1984	U.S.A.	255	> 75 versus < 55	1.6	1.0–2.7
Kolonel and associates [34]	1986	Hawaii	272	Upper quartile versus lower	1.7	Not presented†
Hislop and associates [19]	1986	Canada	530	> 75 versus < 54	1.5	0.9–2.5
Tao and associates [39]	1988	China	195	> 70 versus < 51	1.9	1.0–3.8
Ewertz [20]	1988	Denmark	509	> 80 versus < 50	0.6	0.3–1.2
Yuan and associates [40]	1988	China	300	> 60 versus < 50	3.1	Not presented*
Parazzini and associates [21]	1990	Italy	2137	> 72 versus < 54	1.2	1.0–1.5
Bouchardy and associates [24]	1990	France	223	> 66 versus < 56	0.8	Not presented†
Brinton and Swanson [25]	1992	U.S.A.	1115	> 68 versus < 54	1.3	1.0–1.7
Yang and associates [41]	1993	U.S.A.	693	> 72 versus < 54	3.0	2.0–4.3
Taioli and associates [26]	1995	U.S.A.	421	> 73 versus < 57	1.1	0.7–1.6
Franceschi and associates [27]	1996	Italy	1580	> 75 versus < 57	1.2	0.9–1.5
Mannisto and associates [29]	1996	Finland	196	> 80 versus < 60	1.2	0.7–2.4

RR, relative risk. *Non-significant; †$P < 0.05$.

adjustment, the studies with the higher quality indicators showed a more positive association. Ursin and associates questioned the usefulness of these quality indicators accordingly, and referred to the fact that breast cancer cases may gain weight after diagnosis [68], which may explain some of the discrepancy.

Regarding timing, overweight in late childhood (age 8–12 years) seems to be negatively associated with the risk of breast cancer [19, 45, 57], although one study differed [69]. Overweight in the teens was uniformly associated with a reduced risk of breast cancer [15, 19, 25, 43, 45, 70], even after adjustment for age at menarche [15, 25, 43]. In adulthood, a reduced risk of breast cancer according to overweight was demonstrated [47], although most results were non-significant [19, 22, 25, 45, 47, 70]; one study, based on self-reported height and weight, showed an increased risk [46].

Postmenopausal women

The results of the cohort and case–control studies are in agreement, indicating an increased risk of breast cancer in overweight women. Only four case–control studies indicated a modest reduced risk [19, 24, 29, 66], whilst one study showed no association [25]. With one exception, these studies were based on self-reported height and weight. Only the studies of Mannisto and colleagues used direct measurements of height and weight [29]. The remaining studies showed varying degrees of increased risk in obese women, significantly [14, 16, 18, 27, 32, 43, 44, 47, 50, 54, 55, 57, 58, 61–65] and non-significantly [15, 20, 26, 30–33, 49, 53, 56, 59]. After the age of 50 years, the observed risk due to overweight seemed to increase with increasing age [15, 24].

Regarding overweight in early life, a very modest protective effect of increased childhood BMI has been observed [19, 45, 57]. Regarding teenage BMI, this tendency decreased; five studies reported a modest reduction in breast cancer risk [6, 15, 19, 25, 43], three found no association [44, 49, 70], and one found a relative risk of greater than one [45]. In adulthood, two studies reported a modest reduction [25, 45], one found no association [70], and five studies found a non-significantly increased risk of breast cancer [19, 34, 44, 46, 47].

Conclusion

In conclusion, most of the studies point in the same direction, regardless of study design or quality of data: in premenopausal women, relative overweight seems protective, and in postmenopausal women, overweight seems to be a risk factor for developing breast cancer.

Table 5. *The association between body mass index and the risk of premenopausal breast cancer expressed as a relative risk*

Reference	Year	Country	Number of cases	Comparison	RR	95% confidence intervals
Cohort studies						
Törnberg and associates [14]	1988	Sweden	196	1 unit increase	1.0	0.9–1.0†
London and associates [15]	1989	U.S.A.	658	> 29 versus < 21	0.6	0.4–0.8
Tretli [16]	1989	Norway	1000	1 unit increase	0.8	0.7–0.9
Vatten and Kvinnsland [17]	1992	Norway	164	> 27 versus < 22	0.6	0.5–0.8
Young and associates [52]	1996	U.S.A.	226	> 27 versus < 21	1.0	Not presented†
Case–control studies						
Staszewski [18]	1977	Poland	300	> 30 versus < 24	0.7	Not presented*
Paffenbarger and associates [47]	1980	U.S.A.	226	> 25 versus < 22	0.7	Not presented†
Helmrich and associates [53]	1983	U.S.A., Canada, Israel	478	> 28 versus < 21	0.5	0.4–0.7
Hislop and associates [19]	1986	Canada	316	> 27 versus < 22	0.8	0.5–1.4
Toti and associates [54]	1986	Italy	446	> 27 versus < 22	1.2	0.8–1.7
Schatzkin and associates [55]	1987	U.S.A.	224	> 30 versus < 24	1.2	0.6–1.5
Ewertz [20]	1988	Denmark	639	> 32 versus < 20	1.3	0.6–2.5
Kampert and associates [56]	1988	U.S.A.	762	> 28 versus < 20	0.6	Not presented†
Negri and associates [57]	1988	Italy	1486	> 30 versus < 20	1.0	Not presented*
Swanson and associates [58]	1989	U.S.A.	751	Upper quartile versus lower	1.0	0.7–1.3
Lund and associates [22]	1990	Norway–Sweden	420	> 23 versus < 20	1.1	0.6–1.8
Rosenberg and associates [59]	1990	Canada	270	> 26 versus < 21	0.8	0.5–1.2
Bouchardy and associates [24]	1990	France	154	> 27 versus < 23	0.4	Not presented*
Clavel and associates [60]	1991	France	381	> 30 versus < 20	0.4	Not presented†
Chu and associates [43]	1991	U.S.A.	2053	> 32 versus < 20	1.3	0.9–2.0
Harris and associates [49]	1992	U.S.A.	191	> 27 versus < 22	0.6	0.3–1.0
Pathak and Whittemore [61]	1992	International	1657	Regression coefficient	1.0	Not presented*
Brinton and Swanson [25]	1992	U.S.A.	414	> 26 versus < 20	0.7	0.4–1.0
Kato and associates [62]	1992	Japan	459	> 24 versus < 20	1.8	1.2–2.7
Taioli and associates [26]	1995	U.S.A.	196	> 27 versus < 21	0.4	0.2–0.6
Franceschi and associates [27]	1996	Italy	989	> 29 versus < 22	0.7	0.5–0.9
Swanson and associates [28]	1996	U.S.A.	1588	> 29 versus < 22	0.7	0.5–0.8
Mannisto and associates [29]	1996	Finland	132	> 28 versus < 21	0.9	0.4–1.9
Ziegler and associates [30]	1996	U.S.A.	424	> 25 versus < 18	> 1.0	Not presented*

RR, relative risk. *Non-significant; †$P < 0.05$.

BODY SHAPE

Premenopausal women

Only a few case–control studies have focused on the impact of body fat distribution and premenopausal breast cancer risk. Using WHR, two studies found no association [71, 72], while Schapira and associates, in two small studies, showed a significantly increased risk of breast cancer according to increased levels of visceral fat estimated by computed tomography scan [73] and a non-significantly increased risk due to masculine body shape, described as the ratio between suprailiac and thigh skinfolds [74].

Postmenopausal women

Body shape, described as masculine or feminine, estimated from the WHR or from the thickness of various skinfolds, was associated with an increased breast cancer risk in some studies [6, 73, 75, 76], while one study found a non-significant positive association [71]. In a study by Sellers and colleagues, the increased risk of breast cancer associated with masculine body shape was more pronounced in patients with a familial disposition to breast cancer [63].

In conclusion, there is no firm evidence regarding body shape and the risk of developing breast cancer in premenopausal women. In postmenopausal women, however, masculine body shape seems to be associated with an increased risk of developing breast cancer.

DISCUSSION

The present review indicates that build is related to the risk of breast cancer. A discussion of this relationship must take into account possible mechanistic explanations.

Height

The impact of type of data. In most cohort studies, data on height are obtained by direct measurements performed by trained personnel. These measurements give precise values, but they may date back many years before disease development. This fact may have certain implications in postmenopausal

Table 6. The association between body mass index and the risk of postmenopausal breast cancer expressed as a relative risk

Reference	Year	Country	Number of cases	Comparison	RR	95% confidence intervals
Cohort studies						
Törnberg and associates [14]	1988	Sweden	986	1 unit increase	> 1.0	1.6–1.0†
London and associates [15]	1989	U.S.A.	420	> 29 versus < 21	1.1	0.8–1.5
Tretli [16]	1989	Norway	7000	1 unit increase	1.2	1.1–1.2
Sellers and associates [63]	1992	U.S.A.	493	> 31 versus < 23	1.6	Not presented†
Tonkelaar and associates [31]	1994	The Netherlands	260	< 28 versus < 23	1.2	0.9–1.7
Toniolo and associates [32]	1995	U.S.A.	130	> 28 versus < 22	2.8	1.5–5.4
Freni and associates [33]	1996	U.S.A.	112	> 30 versus < 21	1.6	Not presented*
Young and associates [52]	1996	U.S.A.	1198	> 27 versus < 21	1.3	Not presented†
Case–control studies						
Staszewski [18]	1977	Poland	500	> 30 versus < 24	2.1	Not presented†
Paffenbarger and associates [47]	1980	U.S.A.	1038	> 25 versus < 22	1.4	Not presented†
Helmrich and associates [53]	1983	U.S.A., Canada, Israel	1185	> 28 versus < 21	1.3	1.0–1.8
Lubin and associates [44]	1985	Israel	425	< 27 versus < 19	2.4	Not presented†
Hislop and associates [19]	1986	Canada	530	> 27 versus > 22	0.9	0.6–1.3
Toti and associates [54]	1986	Italy	1107	> 27 versus < 22	1.5	1.2–2.0
Schatzkin and associates [55]	1987	U.S.A.	299	> 30 versus < 24	2.5	1.5–4.4
Ewertz [20]	1988	Denmark	489	> 32 versus < 20	1.3	0.6–2.7
Kampert and associates [56]	1988	U.S.A.	866	> 28 versus < 20	1.3	Not presented*
Negri and associates [57]	1988	Italy	2586	> 30 versus < 20	1.6	Not presented†
Swanson and associates [58]	1989	U.S.A.	1017	Upper quartile versus lower	1.3	1.0–1.7**
Rosenberg and associates [59]	1990	Canada	329	> 26 versus < 21	1.2	0.8–1.7
Bouchardy and associates [24]	1990	France	223	> 27 versus < 23	0.9	Not presented*
Graham and associates [64]	1991	U.S.A.	440	> 29 versus < 22	1.8	1.2–2.6
Chu and associates [43]	1991	U.S.A.	547	> 32 versus < 20	2.7	1.4–5.4
Pathak and Whittemore [61]	1992	International	2268	Regression coefficient	> 1.0	Not presented†
Harris and associates [49]	1992	U.S.A.	411	> 27 versus < 22	1.5	1.0–2.3
Kato and associates [62]	1992	Japan	446	> 24 versus < 20	1.6	1.1–2.4
Brinton and Swanson [25]	1992	U.S.A.	1115	> 26 versus < 20	1.0	0.7–1.3
Taioli and associates [26]	1995	U.S.A.	421	> 27 versus < 21	1.5	1.0–2.3
Franceschi and associates [27]	1996	Italy	1580	> 29 versus < 22	1.4	1.1–1.8
Thomas and associates [65]	1996	U.K.	253	> 29 versus < 22	2.0	1.2–3.2
Lipworth and associates [66]	1996	Sweden	122	Upper quartile versus lower quartile	0.6	0.3–1.4
Mannisto and associates [29]	1996	Finland	196	> 31 versus < 23	0.8	0.4–1.5
Ziegler and associates [30]	1996	U.S.A.	114	> 25 versus < 18	> 1.0	Not presented*

RR, relative risk. *Non-significant; †$P < 0.05$.

women, in whom osteoporosis may cause a decrease in height. Assuming that higher levels of oestrogens are associated with a higher risk of breast cancer, the breast cancer patients will show less reduction in height due to the oestrogenic protection against osteoporosis. Measurements in most cohort studies precede the osteoporotic height reduction and they are therefore more likely to express the maximum adult height of a woman rather than the height at disease development. This phenomenon will be more pronounced as observation time increases within a study. Thus, cohort studies are more likely to analyse the impact of maximum adulthood height and thereby growth patterns of childhood and adolescence on the development of breast cancer. In some case–control studies, data are obtained from questionnaires. While weight may be measured repeatedly throughout life, height is rarely measured. Thus, the height that a woman will state may be her height in adulthood, i.e. before osteoporotic height reduction. A study by Paganini-Hill and Ross, comparing interview data and data from medical charts, supports this notion. Their group of postmenopausal women tended to overestimate their height regardless of status as cases or controls [77]. Thus, such data tend to give the same information as the cohort studies, i.e. maximum adulthood height. In general, self-reported data may be less accurate than data obtained by trained personnel, indicating some non-differential misclassification.

In some case–control studies, measurements are performed directly after the development of breast cancer. This means that these measurements express maximum adulthood height minus possible height reduction due to osteoporosis, which in fact may tend to strengthen the association between height and the risk of breast cancer, whilst the osteoporotic height reduction is more pronounced in controls than in cases.

Associations. Body height seems to be positively associated with breast cancer risk in both pre- and postmenopausal women. A possible link between restricted diet, relatively small body height, and a decreased risk of breast cancer has been suggested by Vatten and Kvinnsland in a large Norwegian cohort [36]. Unfortunately, no confounder control, except for age, was possible, and information on the age of menarche was not available within the study. A Norwegian and a Dutch study also showed that the age at menarche increased during the 'famine' of the Second World War [78, 79]. Early menarche is an established risk factor for breast cancer, and a possible link may exist from restricted energy intake to a reduced breast cancer risk mediated via late menarche.

Height is a result of both genetics and nutrition. Nutrition during periods of growth (childhood and puberty) seems to be an especially important factor for final height [80]. Thus, height may be a proxy-variable of nutritional status during the years of growth. In a Canadian study in Quebec, diet, physical activity, and age at menarche were measured in a cohort of girls. Within this cohort, a nested case–control study demonstrated a link between increased height in childhood and early age of menarche, and to a lesser extent between high energy intake and low age at menarche [81]. However, the association between height and menarche is complex. While girls who grow quickly seem to mature early, growth in these girls stops earlier than in the girls who mature late. Age at menarche is not negatively correlated with final height—the correlation is rather null [82] or positive [83, 84]. Thus, from this point of view there is no reason to believe that the association between height and breast cancer can be explained by the taller girls having earlier menarche.

High socio-economic status is positively correlated with both body height and breast cancer risk. Nevertheless, confounding from socio-economic status is probably not prominent, as studies controlling for socio-economic status or education [24–27, 29, 33] do not show weaker associations between body height and breast cancer risk than the remaining studies. From an ideal point of view, possible confounding should be elucidated by studies stating odds ratios with and without adjustment for socio-economic status. In the absence of such studies, the comparison of studies with and without adjustment for the confounder may give a hint of possible confounding, although the representativeness of studies controlling for confounding may be questioned.

The subdivision of height into different entities may reflect different aspects of growth, i.e. sitting height or relative sitting height expressing growth of the axial skeleton. Sitting height has not often been reported in breast cancer epidemiological studies. In the NHANES study, Swanson and colleagues found that low relative sitting height was associated with late menarche, but not with the risk of breast cancer [84]. In a case–control study, Swanson and colleagues reported an association between high relative sitting height and early menarche, and between long-waisted women and a somewhat reduced risk of breast cancer [28]. Brinkley and associates reported a lower relative sitting height in breast cancer patients than in controls [85]. Thus, sitting height may reflect growth patterns that are associated with breast cancer.

In summary, increased height, which may reflect nutritional status during childhood, seems to be positively associated with the risk of breast cancer. The importance of sitting height has so far not been established.

Weight

According to the association between height and weight, we found it appropriate to evaluate the impact of weight as expressed in BMI, in order to minimise the interference of height. The quality of weight data will be discussed briefly before considering the impact of BMI. In most cohort studies, the original data, including weight data, are renewed consecutively in order to evaluate possible changes. Thus, the data should reflect the recent weight fairly well. In the case–control studies, the data on weight obtained from the participants by interview may include more random error due to self-reporting and may even induce some bias, although it is difficult to forecast the impact of such bias. It is a general notion that the very light would like to be heavier and the very heavy would like to be lighter. The size of a possible bias therefore depends on the fraction of such persons in a study and any accompanying tendency for misinformation due to status as a case or a control. In the study by Paganini-Hill and Ross, the comparison between interview data and medical charts revealed much more inaccuracy for weight than for height. Overall, there was the same degree of inaccuracy in both cases and controls, and the inaccuracy showed the same amount of under- and overestimation [77].

Another aspect of quality of weight data concerns changes due to the disease or the treatment. As breast cancer is usually diagnosed in the early stages of the disease, accompanying weight loss is rare. In contrast, adjuvant therapy may induce weight gain [86], which has to be taken into account when weight data are obtained after treatment.

Taking all these considerations into account, it is very difficult to establish a person's core weight, biologically speaking, and how such an estimate should be translated into its biological impact.

BMI

The association between BMI and the risk of breast cancer seems to be related to menopausal status. In premenopausal women, overweight is associated with a reduced risk of breast cancer, whereas overweight increases the risk of postmenopausal breast cancer development.

Theoretically, a causal relationship or a common basic cause for both breast cancer and overweight would give relative risk estimates pointing in the same direction, but with different magnitudes according to different impacts of competing risk factors [87]. Thus, a causal relation, or common basic causes, are consistent with the majority of studies, although confounding due, for example, to socio-economic and educational status, exercise or diet cannot be excluded.

Premenopausal women

From a mechanistic point of view, the decreased risk of breast cancer in overweight premenopausal women has been attributed to an increased frequency of anovulatory cycles [88]. The protective effect of overweight seems more pronounced during adolescence [45], which may fit the two-stage model of mammary carcinogenesis described by Moolgavkar and associates [89]. This model indicates a growth spurt in the mammary gland during puberty that is responsible for the final number of mammary cells vulnerable to carcinogenic transformation. Overweight during this period is associated with anovulatory cycles [90] and a limited growth spurt. The resulting reduced number of vulnerable cells in the breast should then be associated with a reduced risk of premenopausal breast cancer.

Another observation linked high-density lipoprotein cholesterol and breast cancer. In a review, Boyd and McGuire linked increased levels of high-density lipoprotein cholesterol to conditions such as living in high risk countries (northern Europe), nulliparity, high socio-economic status, and premenopausal leanness [91]. In an Italian study, Borrelli and colleagues found higher levels of high-density lipoprotein cholesterol among both pre- and postmenopausal breast cancer patients than in patients with benign breast lesions [92].

In a Swedish cohort, Törnberg and associates found an inverse association between both total cholesterol and BMI and the risk of breast cancer, and a positive association between a fraction of cholesterol (beta-lipoprotein fraction) and breast cancer risk [14].

Regarding confounding, low weight associated with high alcohol intake, which is a risk factor for breast cancer, has been discussed. London and colleagues showed, however, that intake of alcohol could not explain the inverse association between BMI and breast cancer risk, which appeared with equal strength after correction for alcohol intake [15]. Another possible confounder is socio-economic status, which is negatively correlated to body mass index and positively correlated to breast cancer risk. A protective effect of relative high body mass index should be less prominent in studies controlling for socio-economic status, a tendency which is not observed in the studies controlling for socio-economic status or education [24–27, 29, 49, 52, 55, 58] indicating that confounding from socio-economic status seems to be of minor importance.

Postmenopausal women

The major source of female steroid hormones is the ovaries, which degenerate during the menopause, after which the peripheral adipose tissue becomes the primary source. The aromatase in the adipose tissue converts androgen precursors into oestrogens [56, 93]. The increased risk of postmenopausal breast cancer in overweight women has been attributed to this conversion [2].

Another reason for increased levels of free oestrogens in overweight women is the decreased levels of SHBG [94, 95], and consequently the increased levels of free oestrogens and androgens. Furthermore, overweight is associated with increased levels of free fatty acids, which may increase the levels of free oestrogens further by displacing oestrogens from the SHBG [95]. Some studies have linked overweight with increased amounts of available androgens in breast cancer patients [96–98], but this has not been confirmed by others [99]. In a review, Bulbrook found the picture of androgens and breast cancer risk "conflicting" [100], while Bernstein and Ross, in a later review, stated that increased androgen levels increased the risk of breast cancer. They put forward the fact that the greater affinity of testosterone to SHBG increases the levels of free oestrogens by displacement from SHBG [1].

Regarding common causes of overweight and increased breast cancer risk, overweight has been linked with increased insulin levels and insulin resistance [101]. *In vitro*, insulin stimulates the proliferative activity of breast epithelium, and Bernstein has suggested that it is a promoter of breast cancer [102], but the major *in vivo* effect is probably mediated through insulin-like growth factor 1 [103]. It is suspected that high levels of insulin-like growth factor 1 increase the risk of breast cancer development [104], because insulin-like growth factor 1 stimulates breast cell proliferation *in vitro* and *in vivo* [104, 105]. Under some conditions, insulin-like growth factor 1 appears to be a more potent mitogen than oestradiol [104, 106]. Increased levels of insulin are associated with reduced levels of SHBG, and thus increased levels of available sex steroids [3]. Thus, overweight may be associated with an increased breast cancer risk through increased levels of available oestrogens, due to decreased levels of SHBG and increased levels of insulin-like growth factor 1. These considerations have attracted attention recently, and suggestions have been made for agents designed to decrease levels of insulin-like growth factor 1 [107].

Regarding confounding, Mirra and colleagues and Valoras and associates controlled for social status [108, 109], London and co-workers for age at menarche and menopause [15], London, Mirra, Valoras and co-workers for parity [15, 108, 109], Mirra and colleagues and Valoras and associates for age at first full-term pregnancy [108, 109], and London and co-workers for alcohol consumption [15]. None of these factors were important confounders. Willett and associates found no association between BMI and any type of fat intake [110]. A meta-analysis performed by Boyd and colleagues showed no association between fat intake and the risk of breast cancer in cohort studies, while relatively high fat intake was associated with a small increase of breast cancer (relative risk = 1.2) in case–control studies [111]. This discrepancy, due to study design, may be related to recall bias in

case–control studies. Giovannucci and colleagues showed that recall bias may be present in a case–control study within the Nurses' Health Study. They demonstrated a change in relative risk from 0.9 in the prospective study to 1.4 in the retrospective study [112].

Possible confounding from socio-economic status, which is negatively correlated to body mass index, appears to be of minor importance, as studies controlling for socio-economic status or education [24–27, 29, 33, 44, 49, 52, 55, 58, 64] do not show weaker associations between body mass index and breast cancer risk than the remaining studies.

Body composition may reflect physical activity. Frisch and associates, in a study of college students, found a reduced risk of predominantly postmenopausal breast cancer in the group of women who were most physically active during their college education [113]. Estimated from questionnaire data on current height and weight, this group had a significantly lower percentage of body fat. Other studies have confirmed this finding to some extent [114–118], but in the Framingham Study, exercise increased breast cancer risk [119]. The latter study used an activity index that may not discriminate between the different physical activities appropriately; strenuous physical activity was reported by only 5% of cases, versus 6% of non-cases in the cohort. In a recent review, Hoffman-Goetz and Husted summarised many possible explanations for a protective effect of physical activities, but the available studies are too small and have too many methodological problems to reach a conclusion [120]. In the study by Frisch and colleagues, overweight seemed to be associated with low physical activity [113], indicating that BMI may be a proxy-variable for physical activity.

In conclusion, it is very difficult to maintain a sharp distinction between possible confounding from diet and exercise and a common basic cause for obesity and breast cancer.

Body shape

Body shape, described as masculine or feminine, seems to have no impact on premenopausal breast cancer risk [71, 76, 95, 121]. In postmenopausal women, however, masculine body shape seems to carry a higher risk of breast cancer than feminine body shape [6, 75, 76]. Masculine body shape is related to increased plasma glucose [122], hyperinsulinaemia [122], increased insulin-like growth factor 1 [103], decreased SHBG levels [94, 123, 124], and increased androgen levels [94, 124]. The impact of these factors has been mentioned previously.

Intervention

If postmenopausal overweight is 'the villain', prevention may be possible. De Waard and colleagues have completed a feasibility study in breast cancer patients, showing that weight reduction is possible [125]. Schapira and associates showed that weight reduction induced more favourable anthropometric prognostic factors in healthy women [126]. In a study of weight reduction (mean 18 kg) in 12 overweight postmenopausal women, O'Dea and colleagues found that the levels of SHBG increased to a level even higher than in healthy non-obese controls [127]. In addition, total oestradiol was also reduced [127]. A few studies have analysed the association of weight loss with the risk of breast cancer. The results, which were not significant, indicated a small decrease in risk in two studies [25, 48] and a small increase in risk in two other studies [15, 46]. However, none of these studies could distinguish clearly between voluntary and involuntary weight loss. Ballard-Barbash and Swanson have recently claimed—based on the fact that adult weight gain has been independently and consistently found to confer an increased risk for postmenopausal breast cancer—that prevention of postmenopausal weight gain and accumulation of central body fat during adult life may reduce the risk of breast cancer [128].

Future research

It is obvious from the preceding discussion that a person's build is not a simple phenomenon that can be described by one single measure. On the contrary, build represents a refined interaction of various measures and related metabolic activities, which may be linked with certain aspects of the risk of developing breast cancer.

Future research must, therefore, describe build in detail, including measures of sitting height, distribution of adipose tissue, and the relative percentage or the absolute amount of adipose tissue in the body. These measures must be attached to biological measures such as hormone levels, composition of fatty tissue, hormone receptor status and information on menopausal status, diet and physical activity. With this information, one should be able to elucidate the intimate interaction between build and the risk of developing breast cancer in order to obtain a rational basis for possible future prevention.

Awaiting randomised trials of weight reduction in overweight peri- or postmenopausal women, or prevention of postmenopausal weight gain, we may lend an ear to Kelsey and Bernstein: "Postmenopausal obesity is probably the only established risk factor (of breast cancer) that could be affected by behaviour modifications" [129].

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