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Article

Obesity and Breast Cancer Risk in Men: A National Case-Control Study in England and Wales

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Abstract

Background: Breast cancer is rare in men, and information on its causes is very limited from studies that have generally been small. Adult obesity has been shown as a risk factor, but more detailed anthropometric relations have not been investigated. **Methods:** We conducted an interview population-based case-control study of breast cancer in men in England and Wales including 1998 cases incident during 2005-2017 at ages younger than 80 years and 1597 male controls , with questions asked about a range of anthropometric variables at several ages. All tests of statistical significance were 2-sided. **Results:** Risk of breast cancer statistically significantly increased with increasing body mass index (BMI) at ages 20 (odds ratio [OR] = 1.07, 95% confidence interval [CI] = 1.02 to 1.12 per 2-unit change in BMI), 40 (OR = 1.11, 95% CI = 1.07 to 1.16), and 60 (OR = 1.14, 95% CI = 1.09 to 1.19) years, but there was also an indication of raised risk for the lowest BMIs. Large waist circumference 5 years before interview was more strongly associated than was BMI with risk, and each showed independent associations. Associations were similar for invasive and in situ tumors separately and stronger for HER2-positive than HER2-negative tumors. Of the tumors, 99% were estrogen receptor positive. **Conclusions:** Obesity at all adult ages, particularly recent abdominal obesity, is associated with raised risk of breast cancer in men, probably because of the conversion of testosterone to estrogen by aromatase in adipose tissue. The association is particularly strong for HER2-expressing tumors.

Breast cancer is uncommon in men, about 1% of the frequency in women (1). Probably as a consequence, investigation of its etiology has been very limited. There is considerable evidence of raised risk in relation to family history (2-6), specific genetic factors (7), and Klinefelter syndrome (8), but individual studies of other factors have been relatively small and addressed a very limited range of factors (2-5,9-14).

Obesity is important in the etiology of breast cancer in women, with different effects at pre- and postmenopausal ages (15,16), different effects between estrogen receptor (ER)–positive and ER-negative tumors (17), and an independent effect of central obesity, as measured by waist size, for both pre- and postmenopausal breast cancer risk (18,19). For men, however, although there is broad evidence that obesity is associated with increased risk (2-5,9,11,14,20,21), there is virtually no other information: there have been no analyses of risks in relation to abdominal obesity or by histology or hormone receptor status, nor has cancer in situ been analyzed separately from invasive breast cancer.

In Britain, over a 12-year period, we conducted a national case-control study of breast cancer in men that is far larger and more detailed than any previously. We therefore used data from this study to analyze risk of breast cancer in men, and subdivisions of this, in relation to a range of measures of obesity.

Methods

Design, Subjects, and Data Collection

The study was of population-based case-control design. The source population for cases was all men diagnosed with primary invasive or in situ breast cancer (*International Classification of Diseases*–10 codes C50, D05 (22)) during January 1, 2005, to

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August 31, 2017, at ages younger than 80 years in England and Wales (including the Isle of Man and Channel Isles) and resident in these countries. Comprehensive notification of cases was obtained from the cancer registries for these countries plus individual notifications to us by treating clinicians. The patients were then approached by their clinician, and if they agreed to participate, a trained research nurse traveled to interview them using a structured questionnaire and took a blood sample or, if that was not practical, a saliva sample, for DNA. Information on histology and hormone receptor status of the tumors was obtained from cancer registry data and clinical and pathology sources. The questionnaire asked about demographic variables and potential causes of breast cancer in men including self-reported anthropometrics—namely, weight at ages 20, 40, and 60 years; height at age 20 years; obesity and height compared with peers at age 11 years; and waist size at age 20 years and 5 years before interview.

Response rates for population controls are now too low for such controls to provide a viable control source (23,24). We therefore used other control sources likely to give much higher response rates, from 2 sources to facilitate the identification of potential biases in case of divergent results depending on the source of controls: male nonblood relatives of the cases and husbands of women taking part in the Generations Study (25), a large cohort in the United Kingdom (see the Supplementary Methods, available online). Written consent was obtained from all subjects. The study was approved nationally by the South East Multicentre research ethics committee.

Statistical Analyses

We initially conducted analyses separately for each control group, but these showed similar results in the same direction for each, and therefore, we have presented results using the 2 control groups combined.

Analyses were by standard methods for unmatched case-control studies, using multivariable unconditional logistic regression (26) to calculate odds ratios (referred to below as relative risks) for breast cancer in relation to anthropometric risk factors with adjustment for age, socioeconomic status (Acorn score) (27), marital status, region of residence, and year of interview. Trend and interaction tests were as described in the Supplementary Methods (available online). All tests of statistical significance were 2-sided, and a P value less than .05 was considered as statistically significant. For analysis, we divided each variable into strata of equal size (except the open-ended categories at each end) and selected as the reference category, to maximize stability, the one with the largest number of subjects, adding case and control numbers. We did not use the World Health Organization categorization of body mass index (BMI) because it left too many men in a small number of categories and few men in the others; and we wanted to use the same logic of subdivision for all variables in the study and even-sized categories (other than the open-ended ones at each end), so that these categories visually corresponded to the linear trend analysis, which was analyzed per 1 category change in the table. For weight and waist size at a particular age, we excluded from analysis cases who had developed cancer by that age and controls who had reached their corresponding "index age" (see the Supplementary Methods, available online) before that age.

We also conducted, as a sensitivity analysis, further adjustment for several other factors that, although not clear confounders, are known or are possible risk factors for breast cancer in men: family history of breast cancer, chest radiotherapy, use of exogenous estrogens or testosterone, and testicular conditions. We could not adjust for Klinefelter syndrome, because we only knew of 1 control with the diagnosis, but we conducted sensitivity analyses excluding subjects with this syndrome. We also conducted sensitivity analyses excluding men whose responses were rated as less reliable by the interviewers.

Results

We identified, from cancer registries and clinicians, 3187 men diagnosed with breast cancer (2959 invasive, 204 in situ, 24 not specified) in England and Wales during January 1, 2005, to August 31, 2017, at ages younger than 80 years and resident in these countries (data not shown). Of these, 427 (13.4%) had died before we could approach them for interview (there is a considerable lag in notification of cancer registrations); 28 (0.9%) were considered by their consultant as unsuitable to approach; we could not identify the consultant for 21 (0.7%), or the consultant did not participate; 6 (0.2%) had moved abroad; and 707 (22.2%) declined to be interviewed or did not reply to the invitation. The remaining 1998 (62.7%) were interviewed and formed the study cases. By using multiple sources, we managed to obtain data on invasiveness for all cases (1838 invasive, 160 in situ); histology for 1947 (97.4%) (most commonly ductal [1706; 85.4%], lobular [50; 2.5%], and adenocarcinoma unspecified [50; 2.5%]); and estrogen receptor (ER) status for 98.0% (1802) of invasive cases but only 53.8% (86) of in situ cases because hormone receptors are often not tested clinically for such cases in the United Kingdom. For nonblood relative controls, we approached 828 men of whom 613 (74.0%) participated: 343 were brothers-in-law of the probands, 175 sons-in-law, 17 fathers-in-law, and 78 other nonblood relatives. For the Generations Study husband controls, we approached 1109 men of whom 984 (88.7%) participated. Thus, in total, there were 1597 controls.

Descriptive characteristics of cases and controls are shown in Table 1. Most cases (55.7%) were aged 50-69 years at diagnosis, but there were appreciable numbers younger, including 47 (2.4%) younger than age 40 years. The great majority of cases (94%) and controls (98%) were White.

Relative risks in relation to weight (Supplementary Table 1, available online) showed a similar pattern at each age about which we enquired (ie, 20, 40, and 60 years): risk was raised for the lowest weight group analyzed (<60 kg at age 20 years; <65 kg at age 40 years; and <70 kg at age 60 years), least for those in the next weight group, and then rose more or less consistently to greatest risk for men in the highest weight group. The linear trend in relative risk was statistically significant for weight at each age, greatest at older ages (odds ratio [OR] per 5 kg change in weight = 1.04, 95% confidence interval [CI] = 1.00 to 1.08; OR = 1.07, 95% CI = 1.04 to 1.11; and OR = 1.09, 95% CI = 1.06 to 1.13 at ages 20, 40, and 60 years, respectively; z scores = 2.20, 4.82, and 5.36 at these ages, respectively).

Adjustment for the putative confounding variables described under Methods did not alter the results materially, for this or the analyses below, and because it is uncertain whether or not the variables are confounders, these results are not presented here. Excluding respondents whose answers were rated unreliable by the interviewers (169 cases, 34 controls) also did not materially alter these results or those below, nor did exclusion of the 9 cases and 1 control known to have Klinefelter syndrome; based on cytogenetic testing of the first 901 cases and questionnaire responses from the study subjects, we identified 9 cases

Table 1. Descriptive characteristics of male breast cancer cases and controls

Characteristic	Cases No. (%)	Nonblood relative controls No. (%)	Generations husband controls No. (%)	All controls No. (%)
Year of interview				
2007-2009	447 (22.4)	229 (37.4)	214 (21.7)	443 (27.7)
2010-2014	807 (40.4)	245 (40.0)	533 (54.2)	778 (48.7)
2015-2020	744 (37.2)	139 (22.7)	237 (24.1)	376 (23.6)
Index age, y[a]				
<40	47 (2.4)	76 (12.4)	8 (0.8)	84 (5.3)
40-9	159 (8.0)	135 (22.1)	13 (1.3)	148 (9.3)
50-9	385 (19.2)	165 (26.9)	118 (12.0)	283 (17.7)
60-9	729 (36.5)	162 (26.4)	564 (57.3)	726 (45.5)
70-9	678 (33.9)	75 (12.2)	281 (28.6)	356 (22.3)
Duration between diagnosis and interview, years				
<1	509 (25.5)	—	—	—
1 to <2	999 (50.0)	—	—	—
2 to <3	389 (19.5)	—	—	—
≥3	101 (5.1)	—	—	—
Socio-economic group (Acorn)[b]				
1, highest	710 (35.5)	271 (44.2)	594 (60.4)	865 (54.2)
2	120 (6.0)	25 (4.1)	35 (3.5)	60 (3.8)
3	633 (32.2)	204 (33.3)	279 (28.4)	483 (30.2)
4	318 (15.9)	77 (12.5)	57 (5.8)	134 (8.4)
5, lowest	183 (9.2)	32 (5.2)	12 (1.2)	44 (2.7)
Uncategorized[c]	24 (1.2)	4 (0.7)	7 (0.7)	11 (0.7)
Region of residence				
North	375 (18.8)	91 (14.5)	172 (17.5)	263 (16.5)
North-West	368 (18.4)	98 (15.6)	193 (19.6)	291 (18.2)
Midlands and East (including Wales)	379 (18.9)	131 (20.9)	154 (15.7)	285 (17.8)
London and South East	465 (23.3)	159 (25.3)	270 (27.4)	429 (26.9)
South West	411 (20.6)	149 (23.7)	195 (19.8)	344 (21.6)
Marital status				
Married or cohabiting	1600 (80.1)	556 (90.7)	984 (100.0)	1540 (96.4)
Not married or cohabiting	398 (19.9)	57 (9.3)	0 (0.0)	57 (3.6)
Hormone receptor status of breast cancer				
ER positive	1860 (93.1)	—	—	—
ER negative	28 (1.4)	—	—	—
ER status not known	110 (5.5)	—	—	—
PR positive	1080 (54.1)	—	—	—
PR negative	116 (5.8)	—	—	—
PR status not known	802 (40.1)	—	—	—
HER2 positive	144 (7.2)	—	—	—
HER2 negative	1396 (69.0)	—	—	—
HER2 borderline[d]	44 (2.2)	—	—	—
HER2 status not known	414 (20.7)	—	—	—
Total	1998 (100)	613 (100)	984 (100)	1597 (100)

[a]Age at diagnosis of cases; equivalent age for controls (see Methods). ER = estrogen receptor; PR = progesterone receptor. "—" indicates not applicable.
[b]Acorn score based on postcode of residence (27).
[c]Geographic areas not covered by Acorn (Isle of Man, Channel Islands) and residence in an institution or other nonhousehold location.
[d]Included with positives for analysis.

and 1 control with Klinefelter syndrome; based on population rates (28), one would expect 1 or 2 Klinefelter subjects among the controls (data not shown).

The patterns of risk with BMI at ages 20, 40, and 60 years (Table 2) were very similar to those for weight, except that for BMI at ages 20 and 60 years, there was less evidence of a raised risk in the lowest BMI category. Trends were statistically significant at each age, greatest at older ages (OR per 2.0 change in BMI = 1.07, 95% CI = 1.02 to 1.12; OR = 1.11, 95% CI = 1.07 to 1.16; and OR = 1.14, 95% CI = 1.09 to 1.19, at ages 20, 40, and 60 years, respectively; z scores = 2.78, 5.18, and 5.63 at these ages, respectively). For body shape at age 11 years, based on a relative measure (Table 2), there were again raised risks for the lowest and highest categories but not statistically significant and with no apparent trend.

For waist circumference (Supplementary Table 2, available online), there was an increase in risk with greater circumference but little evidence of raised risk for men with the slimmest waists. The effect of greater waist size was large and highly statistically significant for waist size 5 years before interview (OR per 2-inch change in circumference = 1.16, 95% CI = 1.11 to 1.21; $P < .001$) but less marked and not statistically significant for waist size at age 20 years (OR = 1.05, 95% CI = 0.99 to 1.11; $P = .09$). To examine whether the results for reported waist size 5 years before interview might have been biased by preclinical disease or misclassified reports from breast cancer occurrence several years

Table 2. Relative risk of breast cancer in men in relation to body shape compared with peers at age 11 years and body mass index at ages 20, 40, and 60 years

Characteristic	No. of cases	No. of controls	OR (95% CI)[a]	P[b]	z score
Body shape compared with peers at age 11 years					
Much thinner	118	69	1.29 (0.92 to 1.81)	.14	
A little thinner	558	458	1.10 (0.93 to 1.29)	.29	
About the same	1035	824	1.00 (referent)		
A little fatter	232	216	1.00 (0.80 to 1.25)	.99	
Much fatter	43	30	1.29 (0.78 to 2.15)	.32	
Not known	12	0	—	—	
Trend[c]	—	—	0.95 (0.87 to 1.04)	.29	−1.05
BMI at age 20 years					
<19.0	169	130	1.06 (0.80 to 1.41)	.67	
19.0-20.9 kg/m^2	388	355	0.93 (0.76 to 1.14)	.49	
21.0-22.9 kg/m^2	527	469	1.00 (referent)	—	
23.0-24.9 kg/m^2	404	320	1.14 (0.93 to 1.40)	.22	
25.0-26.9 kg/m^2	166	128	1.19 (0.90 to 1.58)	.22	
≥27.0 kg/m^2	163	94	1.43 (1.05 to 1.94)	.02	
Not known[d]	181	101	—	—	
Trend[e]	—	—	1.07 (1.02 to 1.12)	.005	2.78
BMI at age 40 years					
<21.0 kg/m^2	153	104	1.35 (0.99 to 1.84)	.05	
21.0-22.9 kg/m^2	311	274	1.15 (0.92 to 1.44)	.23	
23.0-24.9 kg/m^2	455	452	1.00 (referent)	—	
25.0-26.9 kg/m^2	348	313	1.18 (0.95 to 1.46)	.15	
27.0-28.9 kg/m^2	255	180	1.45 (1.13 to 1.86)	.003	
≥29.0 kg/m^2	325	136	2.28 (1.76 to 2.96)	<.001	
Not known[d]	104	54	—	—	
Not yet age 40 years	47	84	—	—	
Trend[e,f]	—	—	1.11 (1.07 to 1.16)	<.001	5.18
BMI at age 60 years					
<23.0 kg/m^2	200	169	1.09 (0.81 to 1.45)	.58	
23.0-24.9 kg/m^2	293	282	1.00 (referent)		
25.0-26.9 kg/m^2	269	268	1.01 (0.78 to 1.30)	.95	
27.0-28.9 kg/m^2	211	142	1.38 (1.02 to 1.85)	.03	
29.0-30.9 kg/m^2	133	101	1.32 (0.94 to 1.84)	.10	
≥31.0 kg/m^2	238	89	2.42 (1.76 to 3.33)	<.001	
Not known[d]	63	31	—	—	
Not yet age 60 years	591	515	—	—	
Trend[e,f]	—	—	1.14 (1.09 to 1.19)	<.001	5.63

[a]Adjusted for age, socioeconomic status [Acorn score (27)], region of residence, year of interview, and marital status. BMI = body mass index; CI = confidence Interval; OR = odds ratio.
[b]2-sided *P*-value calculated using the Wald test.
[c]Linear trend excluding "Not known" category, per 1 category change in body shape.
[d]Not known: BMI at age 20 years (OR = 1.48, 95% CI = 1.10 to 1.99; P = .01), BMI at age 40 years (OR = 1.65, 95% CI = 1.13 to 2.42; P = .01), and BMI at age 60 years (OR = 1.58, 95% CI = 0.95 to 2.65; P = .08).
[e]Linear trend excluding "Not known" category, per 2.0 change in BMI (ie, per 1 category in the table).
[f]Test for curvature statistically significant for BMI at age 40 (P = .03) and 60 (P = .004) years.

earlier in cases, we conducted sensitivity analyses stratified by time from breast cancer diagnosis to interview (<1.4 years vs 1.4-4.9 years, to divide the data into 2 approximately equal sized parts; data not shown). If there were such bias, one might expect it to have less, if any, influence for men diagnosed shortly before interview (<1.4 years) than for those who were diagnosed longer ago (1.4-4.9 years) and therefore closer to the waist circumference date. Results, however, were very similar for men diagnosed more, or less, recently before interview.

Risk increased with increasing waist to height ratio non-statistically significantly at age 20 years (OR per 0.02 change in ratio = 1.04, 95% CI = 1.00 to 1.08; P = .07) and more markedly 5 years before interview (OR = 1.12, 95% CI = 1.08 to 1.15; P < .001) (Table 3).

In analyses separately for invasive and in situ tumors (Supplementary Tables 3-5, available online and data not shown), there were similar patterns of risk to those in Tables 2-3 and Supplementary Tables 1-2 (available online) for each. For invasive tumors, these results were statistically significant where the all-tumor analyses were statistically significant, but for in situ tumors, not all were significant, based on much smaller numbers. In analyses by age at diagnosis (Table 4; Supplementary Tables 6-7, available online, and data not shown), similar patterns were present, albeit less evenly based on smaller numbers, for cancers occurring at each of the age groups (younger than 50, 50-64, and 65 years and older) although generally with greatest odds ratios for cancers at the oldest ages.

When we examined the effect of BMI adjusted for waist to height ratio and vice versa (Table 5; Supplementary Table 8, available online), both adjustments diminished the effect of the primary factor somewhat, but waist to height ratio 5 years ago

Table 3. Relative risk of breast cancer in men in relation to the ratio of waist circumference at age 20 years and 5 years before interview to height at age 20 years

Characteristic	No. of cases	No. of controls	OR (95% CI)[a]	P[b]	z score
Ratio of waist circumferenceto height at age 20 years					
<0.42	277	235	1.14 (0.89 to 1.45)	.30	
0.42-0.43	272	217	1.31 (1.02 to 1.68)	.03	
0.44-0.45	373	378	1.00 (referent)		
0.46-0.47	281	261	1.07 (0.84 to 1.36)	.54	
0.48-0.49	142	101	1.31 (0.96 to 1.79)	.09	
≥0.50	182	104	1.45 (1.07 to 1.96)	.02	
Not known[c]	471	301	—	—	
Trend[d]	—	—	1.04 (1.00 to 1.08)	.07	1.74
Ratio of waist circumference 5 years ago to height at age 20 years					
<0.46	142	146	1.01 (0.73 to 1.40)	.96	
0.46-0.47	203	239	1.00 (referent)		
0.48-0.49	211	216	1.16 (0.87 to 1.54)	.32	
0.50-0.51	211	193	1.19 (0.89 to 1.59)	.25	
0.52-0.53	219	212	1.16 (0.87 to 1.54)	.32	
0.54-0.55	163	126	1.43 (1.04 to 1.98)	.03	
0.56-0.57	136	65	2.08 (1.42 to 3.03)	<.001	
≥0.58	283	103	2.47 (1.80 to 3.39)	<.001	
Not known[c]	430	297	—	—	
Trend[d]	—	—	1.12 (1.08 to 1.15)	<.001	6.96

[a]Adjusted for age, socioeconomic status [Acorn score (27)], region of residence, year of interview, and marital status. CI = confidence Interval; OR = odds ratio.
[b]2-sided *P* value calculated using the Wald test.
[c]Not known: waist to height ratio at age 20 years (OR 1.44, 95% CI = 1.09 to 1.91; *P* = .01); waist to height ratio 5 years ago (OR = 1.53, 95% CI = 1.12 to 2.11; *P* = .008).
[d]Linear trend excluding "Not known" category, per 0.02 units change in ratio (ie, per 1 category change in the Table).

remained the strongest factor and was only modestly reduced after adjustment for BMI at ages 20, 40, or 60 years (z scores = 6.37, 4.96, and 3.49, respectively), whereas waist to height ratio at age 20 years was appreciably reduced and no longer statistically significant after adjustment for BMI (z scores = 0.67, 0.39, and 0.42, respectively). BMI trends were reduced greatly after adjustment for waist to height ratio 5 years ago (z scores for BMI at ages 20, 40, and 60 years = 0.68, 2.26, and 2.42, respectively), but less changed by adjustment for this ratio at age 20 years (z scores = 2.13, 5.00, and 5.22, respectively).

With regard to ER status, only 28 (1.4%) cases were ER negative, too few to analyze separately (and there were too many ER positive to find materially different results for these than for breast cancers overall). For HER2 expression, however, there was sufficient differentiation to conduct analyses. For all of the parameters that showed statistically significant overall relations in Tables 2-3 and Supplementary Tables 1-2 (available online), the trends were statistically significant also for HER2 positive tumors and, in all instances, far stronger for HER2 positive than for HER2 negative, in several instances statistically significantly so (Table 6; Supplementary Tables 9-10, available online).

Discussion

In a much larger and more detailed study than any previously, with 1998 cases, we found risk of breast cancer in men increased with greater weight and BMI, was also raised for men with the lowest weights and BMIs, and was raised, independently and more strongly, with greater central obesity. There are limited previous data on weight or BMI, and none on central obesity, with which to compare these results.

The raised risk of breast cancer in obese men has been seen in several previous, much smaller studies ranging from 73 to 227 cases (2-5,9,11,14,20) and in a pooled analysis of many of these studies plus limited cohort data and 10% of the cases from the current study (21). We found the association greatest for breast cancer diagnosed at the oldest ages. Only the pooled analysis (21) has been previously analyzed by age, and it found a stronger association for younger age at breast cancer, comparing 2 age categories and with some heterogeneity of exposure measure between the pooled studies. The raised risk for men with the lowest BMIs has not been shown before, but because individual previous studies with BMI data have been less than 12% the size of ours, and the published pooled analysis was only able to divide their BMI data into 3 categories, this does not provide strong evidence against our result.

In women, there is a greater risk of breast cancer with greater BMI at postmenopausal ages (29,30) and the opposite at premenopausal ages (16). The raised risk in obese men may well be for the same reason believed to apply in postmenopausal women—aromatase in adipose tissue converts androgens to estrogens (this is the main source of endogenous estrogens in postmenopausal women), and therefore higher body fat levels lead to greater estrogen levels and hence greater risk of breast cancer. In men, at least half of circulating estradiol derives from aromatization of testosterone (31), and there is considerable evidence that estrogen levels are greater (32-37) and estrogen production rates greater (32) in obese than in nonobese men and that estrogen levels increase with increasing fat mass (33). Furthermore, sex hormone–binding globulin concentrations in both men and women decrease with obesity, increasing the concentrations of free, bioavailable, estradiol (37). There is borderline statistically significant evidence for greater male breast cancer risk with greater prior levels of circulating estradiol (36).

The mechanism for the rising risk of breast cancer with lower premenopausal BMI in women is unknown, although some of the suggested mechanisms (eg, polycystic ovary syndrome) could not apply in men. The lack of such an age-related

Table 4. Relative risk of breast cancer in men in relation to body shape compared with peers at age 11 years and body mass index at ages 20, 40, and 60 years by attained age

Characteristic	Attained age younger than 50 years				Attained age 50-64 years				Attained age 65 years and older			
	No. of cases	No. of controls	OR (95% CI)[a]	P[b]	No. of cases	No. of controls	OR (95% CI)[a]	P[b]	No. of cases	No. of controls	OR (95% CI)[a]	P[b]
Body shape compared with peers at age 11 years												
Much thinner	7	8	0.94 (0.30 to 2.93)	.91	45	26	1.34 (0.77 to 2.33)	.30	65	35	1.39 (0.87 to 2.24)	.17
A little thinner	71	70	1.42 (0.89 to 2.26)	.14	221	191	1.06 (0.81 to 1.38)	.68	260	197	1.03 (0.81 to 1.31)	.82
About the same	90	106	1.00 (referent)	—	344	295	1.00 (referent)	—	579	423	1.00 (referent)	—
A little fatter	35	40	1.04 (0.58 to 1.85)	.90	82	84	0.90 (0.62 to 1.30)	.56	113	92	1.07 (0.77 to 1.49)	.70
Much fatter	2	8	0.47 (0.09 to 2.36)	.36	19	10	1.30 (0.56 to 3.03)	.55	21	12	1.64 (0.76 to 3.52)	.21
Not known[c]	1	0	—	—	4	0	—	—	7	0	—	—
Trend[d]	—	—	0.84 (0.66 to 1.08)	.17	—	—	0.94 (0.81 to 1.08)	.37	—	—	0.99 (0.87 to 1.13)	.88
BMI at age 20 years												
<19.0 kg/m^2	15	13	1.34 (0.54 to 3.34)	.53	60	55	0.92 (0.59 to 1.45)	.73	92	62	1.12 (0.75 to 1.67)	.59
19.0-20.9 kg/m^2	41	47	1.51 (0.81 to 2.82)	.19	146	111	1.10 (0.78 to 1.56)	.59	193	197	0.75 (0.56 to 1.00)	.05
21.0-22.9 kg/m^2	38	61	1.00 (referent)	—	190	181	1.00 (referent)	—	291	227	1.00 (referent)	—
23.0-24.9 kg/m^2	53	59	1.41 (0.78 to 2.54)	.26	137	126	1.00 (0.71 to 1.41)	.99	206	135	1.18 (0.87 to 1.60)	.28
25.0-26.9 kg/m^2	29	20	2.71 (1.29 to 5.71)	.008	56	54	0.88 (0.56 to 1.40)	.60	79	54	1.15 (0.76 to 1.75)	.50
≥27.0 kg/m^2	17	20	1.39 (0.61 to 3.17)	.44	65	33	1.32 (0.80 to 2.19)	.28	78	41	1.45 (0.92 to 2.29)	.11
Not known[c]	13	12	—	—	61	46	—	—	104	43	—	—
Trend[e]	—	—	1.02 (0.92 to 1.14)	.71	—	—	1.03 (0.95 to 1.12)	.45	—	—	1.11 (1.03 to 1.19)	.005
BMI at 40 years												
<21.0 kg/m^2	5	3	1.94 (0.38 to 9.74)	.42	41	40	1.09 (0.64 to 1.84)	.76	105	61	1.51 (1.01 to 2.24)	.045
21.0-22.9 kg/m^2	11	15	0.96 (0.36 to 2.58)	.93	112	94	1.26 (0.86 to 1.83)	.23	182	165	1.15 (0.85 to 1.55)	.37
23.0-24.9 kg/m^2	27	38	1.00 (referent)		165	179	1.00 (referent)		253	234	1.00 (referent)	—
25.0-26.9 kg/m^2	32	32	1.65 (0.79 to 3.48)	.19	129	129	0.93 (0.65 to 1.32)	.68	181	152	1.33 (0.98 to 1.80)	.07
27.0-28.9 kg/m^2	29	29	1.77 (0.82 to 3.81)	.15	94	77	1.24 (0.83 to 1.85)	.29	124	74	1.60 (1.11 to 2.32)	.01
≥29.0 kg/m^2	43	25	2.50 (1.18 to 5.29)	.02	138	65	1.80 (1.21 to 2.67)	.003	137	46	2.76 (1.84 to 4.15)	<.001
Not known[c]	5	5	—	—	36	22	—	—	61	27	—	—
Not yet age 40 years	47	84	—	—	—	—	—	—	—	—	—	—
Trend[e]	—	—	1.10 (0.99 to 1.21)	.07	—	—	1.09 (1.02 to 1.16)	.01	—	—	1.13 (1.07 to 1.21)	<.001
BMI at age 60 years												
<23.0 kg/m^2	—	—	—	—	32	37	0.99 (0.52 to 1.87)	.97	166	132	1.10 (0.80 to 1.53)	.56
23.0-24.9 kg/m^2	—	—	—	—	61	76	1.00 (referent)		224	206	1.00 (referent)	
25.0-26.9 kg/m^2	—	—	—	—	60	88	0.85 (0.51 to 1.41)	.53	202	180	1.07 (0.79 to 1.45)	.65
27.0-28.9 kg/m^2	—	—	—	—	59	44	1.66 (0.95 to 2.90)	.08	146	98	1.25 (0.88 to 1.78)	.20
29.0-30.9 kg/m^2	—	—	—	—	30	36	1.00 (0.53 to 1.90)	.99	98	65	1.45 (0.98 to 2.15)	.07
≥31.0 kg/m^2	—	—	—	—	68	32	1.90 (1.05 to 3.41)	.03	165	57	2.62 (1.78 to 3.86)	<.001
Not known[c]	—	—	—	—	20	10	—	—	42	21	—	—
Not yet age 60 years	—	—	—	—	385	283	—	—	—	—	—	—
Trend[e]	—	—	—	—	—	—	1.12 (1.04 to 1.21)	.004	—	—	1.14 (1.08 to 1.21)[f]	<.001

[a]Adjusted for age, socioeconomic status [residential Acorn score (27)], region of residence, year of interview, and marital status. BMI = body mass index; CI = confidence interval; OR = odds ratio.

[b]2-sided P-value calculated using the Wald test.

[c]Not known: BMI at age 20 years, attained age younger than 50 (OR = 2.0, 95% CI = 0.77 to 5.20; P = .16); BMI at age 20 years, attained ages 50-64 years (OR = 1.06, 95% CI = 0.66 to 1.70; P = .82); BMI at age 20 years, attained age 65 years or older (OR = 1.74, 95% CI = 1.13 to 2.67; P = .01); BMI at age 40 years, attained age younger than 50 years (OR = 1.55, 95% CI = 0.38 to 6.37; P = .54); BMI at age 40 years, attained age 50-64 years (OR = 1.59, 95% CI = 0.86 to 2.95; P = .14); BMI at age 40 years, attained age 65 years or older (OR = 1.55, 95% CI = 0.91 to 2.65; P = .11); BMI at age 60 years, attained age younger than 50-64 (OR = 2.02, 95% CI = 0.81 to 5.02; P = .13); BMI at age 60 years, attained age 65 years or older (OR = 1.31, 95% CI = 0.70 to 2.47; P = .39).

[d]Linear trend excluding "Not known" category, per 1 category change in body shape.

[e]Linear trend excluding "Not known" category, per 2.0 Kg/m^2 change in BMI (ie, per 1 category change in the Table).

[f]Test for curvature statistically significant for BMI at age 60 years attained age 65 years and older (P = .03).

effect in men might suggest that the premenopausal effect in women may be because of female-specific, notably reproductive-related, causes rather than those that could apply in both sexes. On the other hand, the increased risk of male breast cancer for low and high BMI individuals might be a consequence of 2 simultaneous and opposite mechanisms—1 for low BMIs, as for premenopausal BMI in women, and 1 for high BMIs, as for postmenopausal women.

The associations of male breast cancer risk in our data with waist circumference and waist to height ratio were stronger than, and independent of, those with BMI but do not appear to have been examined previously. In women, abdominal (central) obesity has been shown to be associated with breast cancer risk both pre- and postmenopausally, independently of BMI (18). Abdominal visceral adipocytes are more metabolically active than other adipocytes (38). In men, free estradiol levels increase with increasing waist circumference (35,37), giving a plausible mechanism for raised breast cancer risk. We found raised breast cancer risk for 2 measures of abdominal obesity—waist circumference and waist to height ratio—strongest for the latter, which

Table 5. Relative risk of breast cancer in men in relation to body mass index at ages 20, 40, and 60 years, adjusted for the ratio of waist circumference 5 years before interview to height, and relative risk of breast cancer in men in relation to the ratio of waist circumference 5 years before interview to height, adjusted for body mass index at ages 20, 40, and 60 years

Characteristic	No. of cases	No. of controls	OR (95% CI)[a]	P[b]	z score
BMI at age 20 years, adjusted for waist to height ratio 5 years before interview					
<19.0 kg/m^2	169	130	1.12 (0.84 to 1.49)	.44	
19.0-20.9 kg/m^2	388	355	0.96 (0.77 to 1.18)	.67	
21.0-22.9 kg/m^2	527	469	1.00 (referent)	—	
23.0-24.9 kg/m^2	404	320	1.10 (0.89 to 1.36)	.37	
25.0-26.9 kg/m^2	166	128	1.05 (0.79 to 1.40)	.74	
≥27.0 kg/m^2	163	94	1.10 (0.80 to 1.51)	.57	
Not known[c]	181	101	—	—	
Trend[d]	—	—	1.01 (0.98 to 1.04)	.50	0.68
BMI at age 40 years, adjusted for waist to height ratio 5 years before interview					
<21.0 kg/m^2	153	104	1.53 (1.11 to 2.11)	.01	
21.0-22.9 kg/m^2	311	274	1.22 (0.97 to 1.53)	.10	
23.0-24.9 kg/m^2	455	452	1.00 (referent)	—	
25.0-26.9 kg/m^2	348	313	1.11 (0.89 to 1.39)	.36	
27.0-28.9 kg/m^2	253	180	1.27 (0.98 to 1.64)	.08	
≥29.0 kg/m^2	325	136	1.71 (1.28 to 2.28)	<.001	
Not known[c]	104	54	—	—	
Not yet age 40 years	47	84	—	—	
Trend[d,e]	—	—	1.03 (1.00 to 1.06)	.02	2.26
BMI at age 60 years, adjusted for waist to height ratio 5 years before interview					
<23.0 kg/m^2	200	169	1.16 (0.85 to 1.58)	.35	
23.0-24.9 kg/m^2	293	282	1.00 (referent)	—	
25.0-26.9 kg/m^2	269	268	0.96 (0.73 to 1.25)	.74	
27.0-28.9 kg/m^2	211	142	1.23 (0.90 to 1.69)	.20	
29.0-30.9 kg/m^2	133	101	1.05 (0.72 to 1.51)	.81	
≥31.0 kg/m^2	238	89	1.63 (1.10 to 2.42)	.02	
Not known[c]	63	31	—	—	
Not yet age 60 years	591	515	—	—	
Trend[d, e]	—	—	1.04 (1.01 to 1.08)	.02	2.42
Waist to height ratio 5 years before interview adjusted for BMI at age 20 years					
<0.46	142	146	1.02 (0.73 to 1.41)	.92	
0.46-0.47	203	239	1.00 (referent)	—	
0.48-0.49	211	216	1.14 (0.85 to 1.52)	.38	
0.50-0.51	211	193	1.17 (0.88 to 1.57)	.28	
0.52-0.53	219	212	1.12 (0.84 to 1.50)	.43	
0.54-0.55	163	126	1.39 (1.00 to 1.93)	.048	
0.56-0.57	136	65	2.03 (1.38 to 2.97)	<.001	
≥0.58	283	103	2.38 (1.71 to 3.31)	<.001	
Not known[c]	430	297	—	—	
Trend[f]	—	—	1.12 (1.08 to 1.15)	<.001	6.37
Waist to height ratio 5 years before interview adjusted for BMI at age 40 years					
<0.46	129	120	1.04 (0.73 to 1.47)	.82	
0.46-0.47	192	227	1.00 (referent)	—	
0.48-0.49	207	211	1.24 (0.92 to 1.66)	.16	
0.50-0.51	211	190	1.28 (0.95 to 1.73)	.11	
0.52-0.53	216	208	1.19 (0.88 to 1.61)	.26	
0.54-0.55	162	123	1.45 (1.03 to 2.05)	.03	
0.56-0.57	134	64	1.94 (1.30 to 2.90)	.001	
≥0.58	282	101	2.18 (1.52 to 3.12)	<.001	
Not known[c]	418	269	—	—	
Not yet age 40 years	47	84	—	—	
Trend[f]	—	—	1.11 (1.06 to 1.15)	<.001	0.42
Waist to height ratio 5 years before interview adjusted for BMI at age 60 years					
<0.46	67	67	0.94 (0.59 to 1.48)	.78	
0.46-0.47	133	147	1.00 (referent)	—	
0.48-0.49	126	154	0.93 (0.65 to 1.34)	.70	
0.50-0.51	146	155	0.96 (0.66 to 1.39)	.80	
0.52-0.53	167	159	1.12 (0.77 to 1.63)	.55	
0.54-0.55	130	104	1.19 (0.78 to 1.81)	.41	
0.56-0.57	109	52	1.67 (1.03 to 2.71)	.04	

(continued)

Table 5. (continued)

Characteristic	No. of cases	No. of controls	OR (95% CI)[a]	P[b]	z score
≥0.58	231	81	1.81 (1.15 to 2.86)	.01	
Not known[c]	298	163	—	—	
Not yet age 60 years	591	515	—	—	
Trend[f]	—	—	1.10 (1.04 to 1.16)	<.001	3.49

[a]Adjusted for age, socioeconomic status [Acorn score (18)], region of residence, year of interview, and marital status. BMI = body mass index; CI = confidence interval; OR = odds ratio.
[b]2-sided *P* value calculated using the Wald test.
[c]Not known: BMI at age 20 years, adjusted for waist to height ratio 5 years before interview (OR = 1.38, 95% CI = 1.02 to 1.87; P = .03); BMI at age 40 years, adjusted for waist to height ratio 5 years before interview (OR = 1.47, 95% CI = 0.99 to 2.17; P = .06); BMI at age 60 years, adjusted for waist to height ratio 5 years before interview (OR = 1.39, 95% CI = 0.82 to 2.37; P = .22); waist to height ratio 5 years before interview adjusted for BMI at age 20 years (OR = 1.45, 95% CI = 1.05 to 2.00; P = .02); waist to height ratio 5 years before interview adjusted for BMI at age 40 years (OR = 1.62, 95% CI = 1.17 to 2.25; P = .004); waist to height ratio 5 years before interview adjusted for BMI at age 60 years (OR = 1.80, 95% CI = 1.24 to 2.62; P = .002).
[d]Linear trend excluding "Not known" category, per 2.0 kg/m^2(ie, per 1 category change in the table).
[e]Test for curvature statistically significant for BMI at age 40 years (P = .03) and 60 years (P = .009) adjusted for waist to height ratio 5 years before.
[f]Linear trend excluding "Not known" category, per 0.02 units change in ratio (ie, per 1 category change in the table).

Table 6. Relative risk of breast cancer in men in relation to body mass index at ages 20, 40, and 60 years by HER2 expression status

	HER2 positive				HER2 negative				$P_{interaction}$ in trends
Characteristic	No. of cases	No. of controls	OR (95% CI)[a]	P[b]	No. of cases	No. of controls	OR (95% CI)[a]	P[b]	HER2 positive/negative[c]
BMI at age 20 years									.13
<19.0 kg/m^2	13	130	0.74 (0.36 to 1.49)	.40	118	130	1.00 (0.73 to 1.36)	.99	
19.0-20.9 kg/m^2	34	355	0.92 (0.57 to 1.51)	.75	269	355	0.86 (0.68 to 1.07)	.18	
21.0-22.9 kg/m^2	50	469	1.00 (referent)	—	388	469	1.00 (referent)	—	
23.0-24.9 kg/m^2	44	320	1.28 (0.80 to 2.05)	.31	273	320	1.07 (0.85 to 1.35)	.54	
25.0-26.9 kg/m^2	17	128	1.39 (0.74 to 2.60)	.31	111	128	1.07 (0.79 to 1.46)	.66	
≥27.0 kg/m^2	18	94	1.57 (0.82 to 2.99)	.17	113	94	1.36 (0.97 to 1.89)	.07	
Not known[d]	12	101	—	—	124	101	—	—	
Trend[e]	—	—	1.14 (1.04 to 1.25)	.006	—	—	1.07 (1.01 to 1.12)	.01	
BMI at age 40 years									.03
<21.0 kg/m^2	14	104	1.33 (0.66 to 2.69)	.43	108	104	1.36 (0.97 to 1.90)	.07	
21.0-22.9 kg/m^2	24	274	1.03 (0.59 to 1.81)	.92	237	274	1.26 (0.99 to 1.61)	.06	
23.0-24.9 kg/m^2	42	452	1.00 (referent)	—	311	452	1.00 (referent)	—	
25.0-26.9 kg/m^2	35	313	1.19 (0.71 to 2.00)	.51	235	313	1.17 (0.92 to 1.49)	.20	
27.0-28.9 kg/m^2	24	180	1.57 (0.88 to 2.82)	.13	181	180	1.53 (1.17 to 2.02)	.002	
≥29.0 kg/m^2	38	136	3.16 (1.84 to 5.44)	<.001	225	136	2.39 (1.81 to 3.16)	<.001	
Not known[d]	8	54	—	—	68	54	—	—	
Not yet age 40 years	3	84	—	—	31	84	—	—	
Trend[e]	—	—	1.20 (1.11 to 1.30)	<.001	—	—	1.11 (1.06 to 1.16)	<.001	
BMI at age 60 years									.27
<23.0 kg/m^2	22	169	1.91 (0.97 to 3.76)	.06	147	169	1.14 (0.83 to 1.56)	.41	
23.0-24.9 kg/m^2	22	282	1.00 (referent)	—	203	282	1.00 (referent)	—	
25.0-26.9 kg/m^2	23	268	1.09 (0.56 to 2.14)	.79	187	268	1.02 (0.77 to 1.35)	.90	
27.0-28.9 kg/m^2	20	142	1.73 (0.84 to 3.54)	.14	151	142	1.40 (1.01 to 1.91)	.04	
29.0-30.9 kg/m^2	12	101	1.90 (0.86 to 4.21)	.11	97	101	1.48 (1.04 to 2.12)	.03	
≥31.0 kg/m^2	28	89	4.22 (2.14 to 8.35)	<.001	178	89	2.64 (1.87 to 3.68)	<.001	
Not known[d]	2	31	—	—	46	31	—	—	
Not yet age 60 years	59	515	—	—	387	515	—	—	
Trend[e, f]	—	—	1.20 (1.09 to 1.31)	<.001	—	—	1.15 (1.09 to 1.20)	<.001	

[a]Adjusted for age, socioeconomic status [Acorn score (27)], region of residence, year of interview, and marital status. BMI = body mass index; CI = confidence interval; OR = odds ratio.
[b]2-sided *P* value calculated using the Wald test.
[c]From case-case analyses.
[d]Not known: BMI at age 20 years (HER2 positive: OR = 1.19, 95% CI = 0.57 to 2.49; P = .64); BMI at age 20 years (HER2 negative: OR = 1.38, 95% CI = 1.00 to 1.90; P = .05); BMI at age 40 years (HER2 positive: OR = 2.44, 95% CI = 1.05 to 5.68; P = .04); BMI at age 40 years (HER2 negative: OR = 1.66, 95% CI = 1.09 to 2.53; P = .02); BMI at age 60 years (HER2 positive: OR = 1.42, 95% CI = 0.31 to 6.57; P = .66); BMI at age 60 years (HER2 negative: OR = 1.73, 95% CI = 0.99 to 3.00; P = .05).
[e]Linear trend excluding "Not known" category, per 2.0 Kg/m^2 change in BMI (ie, per 1 category in the table).
[f]Test for curvature statistically significant for BMI at age 60 years for HER2 positive (P = .02) and negative (P = .005) analyses.

has been found a stronger predictor of metabolic and cardiovascular risk factors than waist circumference or BMI (39).

There have been no previous analyses of obesity and male breast cancer risk by hormone receptor or HER2 status of the cancer. Despite interviewing almost 2000 breast cancer cases, there were still too few ER negative cases in our study to analyze these separately, but we were able to conduct such analyses for HER2. These showed stronger effects for HER2-positive than for HER2-negative tumors. The equivalent analyses in women have been conducted by intrinsic subtype. The equivalent in women of HER2-negative tumors in men would combine luminal A and luminal B HER2-negative tumors, because the tumors in men were almost all ER positive. Luminal B HER2-positive tumors in women were the equivalent of HER2 positive in the males. The published analyses by intrinsic subtype in postmenopausal women, however, have not indicated any clear relation to HER2 status (40-44). In analyses adjusted for hormone receptor status, there is some evidence that HER2 overexpression in breast cancer in postmenopausal women is associated with lower BMI (45).

Testosterone levels are another potential mechanism whereby obesity, or abdominal obesity, might affect male breast cancer risk. In women, prior testosterone levels are associated with breast cancer risk (46), to a similar extent to estradiol. However, the only prospective study in men did not find an association (36), and male testosterone levels are inversely related to BMI (35,36) and more strongly inversely related to waist circumference (35,47) and waist to height ratio (48), which is not the direction of association one would expect if testosterone levels were causal of male breast cancer risk.

The estrogen to testosterone ratio has also been suggested as a potential risk factor for male breast cancer, because this ratio is raised in men with Klinefelter syndrome (49,50) who are known to be at high risk of breast cancer (8). In a prospective analysis, this ratio showed non-statistically significant evidence of a relation to subsequent breast cancer risk in men but not beyond the association for estrogens alone (36). The ratio is statistically significantly associated with male BMI and waist circumference (35). Thus, this ratio might be relevant to male breast cancer risk, but it is not clear that it adds beyond estrogen levels per se.

The effects of weight, BMI, and central obesity were similar for invasive and in situ tumors. In men, this has not been examined before, but in women, risks tend to be in the same direction for each, although possibly differing in magnitude (51).

Our study has the strengths of far larger numbers for this rare tumor than in individual previous studies, systematic national ascertainment of cases, detailed questionnaire data obtained by personal interview rather than for instance proxy data from next of kin (11), and controls not selected for illness rather than hospital-based diseased controls (13). Like almost all of the literature, however, it is of case-control design and hence potentially susceptible to the biases to which such studies are vulnerable (26). Given the lack of publicly available information on male breast cancer risk factors, it seems unlikely that recall bias would have occurred in recollection of past anthropometric variables, but it is certainly plausible that misclassification could have occurred, and indeed, this would be suggested by the steeper gradient of risk with BMI in the only cohort study (20) with measured BMI than in the present study. There is potential for survival bias in that we could not interview otherwise eligible cases who had died before we could approach them. Little is known about risk factors for survival in men with breast cancer, but the proportion who were not interviewed because of death (13.4%) is too small to explain the findings plausibly.

The control groups selected produced high response rates, which are no longer possible with population controls (23,24), but with potential for selection bias. The use of 2 control groups, with results found to be in the same direction as each other, however, minimized the possibility that the results were a consequence of such bias. Exclusion of subjects with known Klinefelter syndrome did not materially alter the results, unsurprisingly given the rarity of Klinefelter syndrome. Our anthropometric measures were self-reported, although such self-reports correlate well with measured weight and waist circumference in men (52,53), suggesting that this is not a serious limitation.

In summary, this study, the largest and most detailed to date, found risk of both invasive and in situ breast cancer in men increased with increasing BMI, probably due to greater estrogen exposure consequent on conversion of androgen to estrogens by aromatase in adipose tissue. Abdominal obesity was associated more strongly than BMI with risk, and the associations were stronger for HER2-positive than for HER2-negative tumors. There was also an association of increased risk with the lowest BMIs, which needs further investigation.

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Data Availability

The statistical output data underlying this article will be shared on reasonable request to the corresponding author. The

individual subject data underlying this article cannot be shared because of the privacy of the individuals who participated in the study.

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