Epidemiologic Reviews
Vol. 36, 2014
DOI: 10.1093/epirev/mxt010

Body Mass Index and Breast Cancer Risk According to Postmenopausal Estrogen-Progestin Use and Hormone Receptor Status

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Accepted for publication September 10, 2013.

To assess the joint relationships among body mass index, menopausal status, and breast cancer according to breast cancer subtype and estrogen-progestin medication use, we conducted a meta-analysis of 89 epidemiologic reports published in English during 1980–2012 identified through a systematic search of bibliographic databases. Pooled analysis yielded a summary risk ratio of 0.78 (95% confidence interval (CI): 0.67, 0.92) for hormone receptor–positive premenopausal breast cancer associated with obesity (body mass index (weight (kg)/height $(m)^2$) ≥30 compared with <25). Obesity was associated with a summary risk ratio of 1.39 (95% CI: 1.14, 1.70) for receptor-positive postmenopausal breast cancer. For receptor-negative breast cancer, the summary risk ratios of 1.06 (95% CI: 0.70, 1.60) and 0.98 (95% CI: 0.78, 1.22) associated with obesity were null for both premenopausal and postmenopausal women, respectively. Elevated postmenopausal breast cancer risk ratios associated with obesity were limited to women who never took estrogen-progestin therapy, with risk ratios of 1.42 (95% CI: 1.30, 1.55) among never users and 1.18 (95% CI: 0.98, 1.42) among users; too few studies were available to examine this relationship according to receptor subtype. Future research is needed to confirm whether obesity is unrelated to receptor-negative breast cancer in populations of postmenopausal women with low prevalence of hormone medication use.

body mass index; breast neoplasms; estrogen receptors; meta-analysis as topic; postmenopausal hormone replacement therapy; progesterone receptors

Abbreviations: CI, confidence interval; ER, estrogen receptor; MeSH, Medical Subject Headings; PR, progesterone receptor; RR, risk ratio.

INTRODUCTION

Obesity has dramatically increased in prevalence since the early 1980s, as documented in risk factor surveillance studies (1, 2), and the consequences of this epidemic in terms of health-care expenditures and future expected mortality are staggering (3). In particular, 65 million more obese adults are projected in the United States by the year 2030, among whom over 500,000 additional cases of cancer are expected to be diagnosed (3). The greater medical costs associated with obesity demand approximately 9% of all medical spending (4). The results of numerous studies—as summarized in both systematic reviews (5) and meta-analyses (6, 7)—have accumulated to strongly suggest that obesity represented by body mass index increases the relative risk of postmenopausal breast cancer. The World Cancer Research Fund determined that evidence is convincing that so-called body fatness increases the relative risk of postmenopausal breast cancer (5). In 1 meta-analysis of 34 cohort studies including over 2.5 million women, Renehan et al. (7) reported that each 5 kg/m^2 increase in body mass index was associated with a 12% (95% confidence interval (CI): 8, 16) increased relative risk of postmenopausal breast cancer, whereas each 5 kg/m^2 increase in body mass index was associated with an 8% (95% CI: 3, 12) decreased relative risk of premenopausal breast cancer. The World Cancer Research Fund determined that the strength of the evidence suggests that the inverse association between body fatness and premenopausal breast cancer is probable (5).

Several epidemiologic studies conclude that obesity may be more strongly associated with estrogen receptor–positive postmenopausal breast cancer (6, 8–10). However, a recent publication showed that obesity was similarly related to both estrogen receptor (ER)–positive (hazard ratio = 1.35,

95% CI: 1.20, 1.51) and triple-negative (hazard ratio = 1.37, 95% CI: 0.98, 1.93) disease in a combined analysis of data from the Women's Health Initiative observational cohort and randomized trial (11).

The relationship between obesity and postmenopausal breast cancer may be modified by use of postmenopausal hormone therapy. One of the first studies to demonstrate potential heterogeneity in the association between obesity and postmenopausal breast cancer according to hormone use was published by the Nurses' Health Study in 1997 (12). In this prospective study, body mass index and adult weight gain were associated with 60% to 2-fold increased relative risks, respectively, of postmenopausal breast cancer among women who had never used hormones, whereas the relationships were attenuated among users of hormones. Although numerous studies over the past 2 decades have examined the interaction between hormone use and obesity in relation to postmenopausal breast cancer, many reports combined estrogen-alone therapy with estrogen-progestin hormone preparations in the statistical analysis (12–18). More recently, heterogeneity in the relationship between obesity and breast cancer according to type of hormone therapy has been reported, with mixed results (19, 20). Consideration of the influence of estrogen-alone hormone therapy separately from estrogen-progestin use is motivated by results from the Women's Health Initiative that showed an increased risk of postmenopausal breast cancer for estrogen-progestin (21) but not estrogen-alone (22) therapy.

Given the high prevalence of obesity, we aimed to conduct a meta-analysis of the association between body mass index and breast cancer depending on menopausal status and hormone receptor subtype. To the extent possible, relationships were investigated according to race and ethnicity. We were particularly interested in evaluating the association between obesity and postmenopausal breast cancer according to use of estrogen-progestin hormone therapy, because this association has received inadequate systematic evaluation, published studies appear to include inconsistent results, and prevalence of use of hormone medications has changed dramatically over the past decade.

METHODS

Search strategy and selection criteria

We conducted a systematic review of the literature starting with a review of the National Cancer Institute's Physician's Data Query Breast Cancer Summary of Evidence to identify key studies of the relationship between body mass index and postmenopausal hormone therapy with breast cancer incidence. After reviewing the articles referenced in the Physician's Data Query, we performed a search by topic combining Medical Subject Headings (MeSH) and non-MeSH keyword terms using PubMed (1980–2012). "Breast neoplasms" was combined with "risk factors" and permutations, variations, and abbreviations of the relevant MeSH keywords including "BMI" OR "obesity" OR "overweight" OR "Quetelet" and also "HRT" OR "hormone replacement therapy" OR "PMH" OR "postmenopausal hormonal therapy". Additional studies were obtained through citations of review articles and reports of meta-analyses including the report prepared by the World Cancer Research Fund (5). Article titles and abstracts were reviewed to determine relevance. Only published English-language articles that provided estimates of relative risk for breast cancer were reviewed for potential inclusion in this meta-analysis; abstracts and unpublished reports were not considered.

Papers were screened and evaluated for eligibility (by G. C.) in the meta-analysis to exclude studies that did not present results according to categories of body mass index or type of hormone use, studies with mortality as the endpoint, and studies limited to special populations (e.g., *BRCA* mutation carriers, men, mother-daughter pairs, and so on). The remaining papers were then involved in a qualitative synthesis (by M. F. M.) to exclude studies that presented results according to incompatible risk group definitions. For example, for the analysis of body mass index, we excluded studies that used weight or waist-to-hip ratio rather than body mass index, body mass index measured on a continuous scale, or body mass index groups incompatible with obesity defined according to the World Health Organization (i.e., <25, 25–29.9, ≥30 kg/m^2) (23). For the analysis of estrogen-progestin therapy, we included only those studies of the use of estrogen combined with progestin and excluded studies with nonspecific hormone therapy and studies of the use of estrogen only. The qualitative synthesis also excluded hospital-based case-control studies, studies without results presented according to menopausal status, and studies without results for white, black, or Hispanic women. In other words, our analysis included clinical trials, cohort studies, case-cohort studies, nested case-control studies, and population-based case-control studies that used incident breast cancer as the endpoint and presented the findings by using comparable measures. Hospital-based case-control studies were excluded because their results were potentially influenced by too many sources of bias.

From the selected papers, we extracted author(s), study dates, study design (e.g., case-control, cohort), risk groups, number of cases, number of controls or person-years at risk, population, population size, measure of risk (e.g., odds ratio, relative risk, hazard ratio), relative risk estimates with confidence intervals, and covariates used in multivariable-adjusted relative risk estimates. When there were multiple reports from a single population, only the results of the report with the most cases or the report with the longest follow-up were included in the analysis.

Statistical analysis

Risk ratio estimates included odds ratios, rate ratios, and hazard ratios. We categorized body mass index into 3 categories: <25.0, 25.0–29.9, and ≥30.0 kg/m^2 (23). If risk ratio estimates were not presented in these categories in a paper but the paper presented data so that risk ratio estimates could be reorganized into these categories, then we did so and calculated unadjusted risk ratio estimates. Results from papers with separate underweight categories (e.g., <18.5 kg/m^2) were combined with the lowest body mass index group (<25 kg/m^2). We also included papers with body mass index categories similar to these 3 categories; adjusted risk ratio estimates were taken directly from publications if results were shown for these body mass index categories. Lowest values of

body mass index (<25 kg/m^2) served as the reference category for all analyses. We categorized estrogen-progestin use into never, ever, current, and past use of estrogen-progestin therapy. Analyses for body mass index, estrogen-progestin use, and both factors jointly were conducted according to strata of menopausal status and repeated in subgroups according to estrogen receptor and progesterone receptor (PR) status and race/ethnicity (white, black, and Hispanic).

For body mass index and for estrogen-progestin therapy, we first fit a fixed-effects model to the log of the risk ratio estimates using Stata, version 12.0, statistical software (StataCorp LP, College Station, Texas) to combine results across studies weighted by the inverse standard error of the risk ratio estimate. We used the Cochran Q test and the I^2 statistic to examine heterogeneity among the studies (24). In the presence of significant heterogeneity ($P < 0.05$), we then fit a random-effects model based on the method of DerSimonian and Laird (25). Thus, risk ratios are presented from either fixed- or random-effects models depending on the Q test P value for heterogeneity. Because 2 separate models were fit for the relationship between body mass index and breast cancer (≥30 kg/m^2 vs. <25 kg/m^2 and 25–29.9 kg/m^2 vs. <25 kg/m^2), these 2 risk ratios were not necessarily both from random (or fixed) effect models because each depended on separate Q tests. For fixed-effects models, we tested for heterogeneity between case-control and cohort studies. We also examined the probability of publication bias or small-study effects using funnel plots and Egger's test (26–30). Confidence intervals, P values, and statements of statistical significance are nominal in the sense that they are not adjusted to account for multiple comparisons. As such, they are descriptive rather than having inferential content.

RESULTS

We identified 435 candidate papers for the analysis of body mass index and, after screening and review of these papers, we included 57 papers in the analysis of body mass index (Figure 1). We identified 1,076 candidate papers for the analysis of estrogen-progestin use and, after screening and review of these papers, we included 32 papers (Figure 2). From among these 89 papers we identified 28 papers that included some analysis of the interaction of body mass index and estrogen-progestin use. Of these 28 papers, we found only

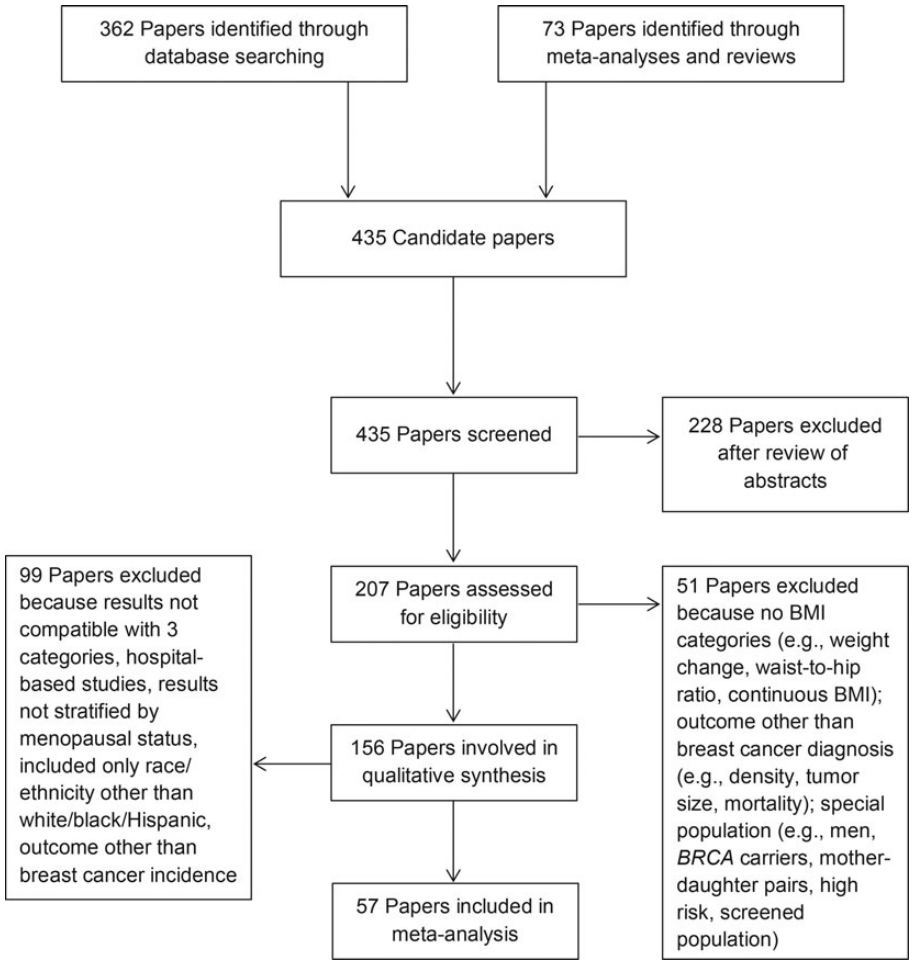

Figure 1. Identification, review, and selection of studies included in the meta-analysis of breast cancer in relation to body mass index (BMI).

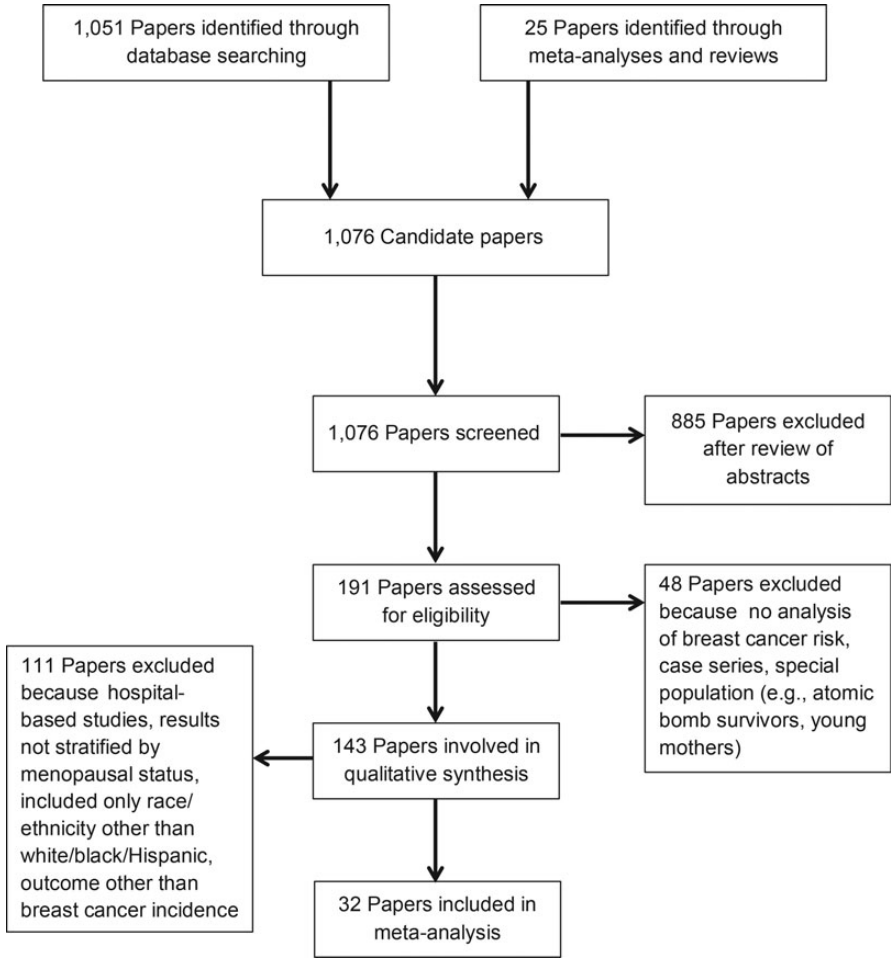

Figure 2. Identification, review, and selection of studies included in the meta-analysis of breast cancer in relation to postmenopausal hormone use.

4 papers that included analyses of estrogen plus progestin use stratified by body mass index or of body mass index stratified by estrogen plus progestin use (19, 31–33) plus 1 additional paper from a study already included in the analysis of the main effects of body mass index and estrogen-progestin use (34). These 5 papers were included in the analysis of the interaction between body mass index and estrogen-progestin use.

Premenopausal women: body mass index

Analysis of the relationship between body mass index and premenopausal breast cancer included 22 articles comprising 12,938 participants with breast cancer in reports from case-control studies and 4,469 breast cancers in reports from cohort studies (Table 1; Figure 3). Intermediate values of body mass index (25–29.9 kg/m^2) were associated with a modestly reduced risk (risk ratio (RR) = 0.95, 95% CI: 0.91, 1.00) (Figure 3) as compared with a body mass index <25 kg/m^2. Body mass index ≥30 kg/m^2 was also associated with a reduced risk ratio of premenopausal breast cancer (RR = 0.83, 95% CI: 0.75, 0.91) (Figure 4). For body mass index ≥30 kg/m^2, body mass index appeared to be related to ER-positive/PR-positive (RR = 0.78, 95% CI: 0.67, 0.92) but not ER-negative/PR-negative (RR = 1.06, 95% CI: 0.70, 1.60) premenopausal breast cancer (Table 2).

Risk ratio estimates for white women suggested similar relationships between body mass index and premenopausal breast cancer as for black and Hispanic women (Table 2). In a comparison of the third with the first category of body mass index, the summary risk ratio for white women was 0.72 (95% CI: 0.61, 0.85), whereas the comparable estimate for black women was 0.87 (95% CI: 0.70, 1.03) and for Hispanic women was 0.71 (95% CI: 0.54, 0.92). Too few studies have published results for the body mass index relationship with premenopausal breast cancer to evaluate both race/ethnicity subgroups and breast cancer subtypes by hormone receptor status.

Postmenopausal women: body mass index

Analyses of the relationship between body mass index and postmenopausal breast cancer included 39 articles comprising 43,005 participants with breast cancer in case-control

Table 1. Papers Included in Meta-analysis of Body Mass Index in Relation to Breast Cancer Risk

First Author, Year (Reference No.)	Study Type	Population[a]	Body Mass Index[b]	Age, Years	Years of Study	No. of Cases	Adjustment Variables[c,d]
Ahn, 2007 (92)	Cohort	NIH-AARP Diet and Health Study	<25 25–29 30–34 ≥35	50–71	1996–2000	204	A, AF, AM, B, E, H, M, P, S
Barlow, 2006 (93)	Case-control	BCSC	<25 25–29 30–34 ≥35	35–84	1996–2002	3,915	A, AF, B, D, F, H, P, T
Barnes, 2011 (94)	Case-control	MARIE	<25 25–29 ≥30	50–74	2002–2005	3,074	None
Berstad, 2010 (95)	Case-control	CARE	<25 25–29 30–34 ≥35	35–64	1994–1998	3,997	A, AM, F, H
Boyd, 2006 (96)	Case-control	NBSS	<25.0 25.0–27.6 >27.6	Average, 56.7	1984–1999	1,114	None
Brinton, 2008 (66)	Cohort	NIH-AARP Diet and Health Study	<25 25–29 ≥30	50–71	1995–2002	3,559	A, AF, B, F
Cerne, 2011 (97)	Case-control	Slovenia	<25 25–29 ≥30	50–69	2006–2008	530	None
Chang, 2006 (98)	Cohort	PLCO	<22.4 22.5–24.9 25.0–27.4 27.5–29.9 ≥30	55–74	1993–2003	764	None
Chlebowski, 2007 (99)	Randomized trial	Women's Health Initiative	<25 25–29 ≥30	50–79	1995–2000	1,072	A, AF, AL, AM, F, M, P, S
Cotterchio, 2003 (100)	Case-control	WHS/ECSS	≤25 25–27 >27	25–74	1995–1998	2,586	A, AF, AL, B, E, F, M, O, P, S
Cust, 2009 (101)	Case-control	Northern Sweden Health and Disease Cohort	<24.2 24.2–27.4 ≥27.4	Median, 52.5	1985–2005	533	A, AF, H
Eng, 2005 (102)	Case-control	Long Island Breast Cancer Study Project	<26.4 26.4–30.1 >30.1	20–98	1996–1997	1,002	None
Franceschi, 1996 (14)	Case-control	Italy	<25.7 25.8–28.8 >28.8	23–74	1991–1994	2,562	None
Friedenreich, 2002 (17)	Case-control	Alberta, Canada	<25.7 25.7–29.2 >29.2	<80	1995–1997	1,233	None
Gaudet, 2010 (103)	Case-control	NCI Biological Markers Project	<25 25–29 ≥30	≥47	1977–1987	229	A, AF, P
Hall, 2000 (104)	Case-control	Carolina Breast Cancer Study	14.6–24.6 24.7–30.1 >30.1	20–74	1993–1996	780	None
Harlid, 2012 (105)	Case-control	MDCS, NSHDS; Iceland	<25 25–29 ≥30	>50	1985–2007	1,962	A
Harris, 1992 (68)	Case-control	American Health Foundation	<22 22–27 >27	<30 to >80	1987–1989	604	A, F, P
Hines, 2010 (106)	Cohort	4-Corners Breast Cancer Study	<25 25–29.9 ≥30	25–79	1992–2002	2,299	A, AF, AL, AM, E, F, H, M, O, P
Hislop, 1986 (107)	Case-control	Cancer Control Agency of British Columbia	<25.6 25.6–29.3 >29.3	<70	1980–1982	512	None

Table continues

Table 1. Continued

First Author, Year (Reference No.)	Study Type	Population[a]	Body Mass Index[b]	Age, Years	Years of Study	No. of Cases	Adjustment Variables[c,d]
Huang, 1997 (12)	Cohort	Nurses' Health Study	<25 25–31 >31	30–55	1976–1992	2,517	None
Huang, 2000 (108)	Case-control	Carolina Breast Cancer Study	<23 23–31 >31	20–74	1993–1996	856	A, AL, F, H, M, O, P, S
John, 2003 (109)	Case-control	San Francisco Bay Area Breast Cancer Study	<26.1 26.1–31.9 ≥32	35–79	1995–1998	1,263	A
John, 2011 (110)	Case-control	San Francisco Bay Area, California	<25 25–29.9 ≥30	35–79	1995–2004	672	A, AL, B, F, M, P
Jumaan, 1999 (111)	Nested case-control	Sweden	<25 25–29.9 ≥30	50–70	1987–1990	273	A
Krebs, 2006 (112)	Cohort	Study of Osteopathic Fractures	<25 25–29.9 ≥30	Average, 73.5	1986–1988	350	A, B, E, F, H, M, O, P, S
Li, 2000 (113)	Case-control	King County, Washington	<25 25–29.9 ≥30	50–64	1988–1990	479	None
Li, 2006 (19)	Case-control	Seattle-Puget Sound, Washington	<25 25–29.9 ≥30	65–79	1997–1999	926	A, T
Ma, 2006 (114)	Case-control	Los Angeles County, California	<25 25–29.9 ≥30	20–49	1998–2003	1,725	None
Magnusson, 1998 (15)	Case-control	All native Swedish female residents	<25.8 25.8–28.2 >28.2	50–74	1993–1995	2,799	None
Mannisto, 1996 (45)	Case-control	Kuopio Breast Cancer Study	<25 25–28 >28	25–75	1990–1994	327	None
Meier, 2002 (115)	Case-control	UK General Practice Research Database	<25 25–29.9 ≥30	50–89	1992–1997	2,507	A, S
Michels, 2006 (116)	Cohort	Nurses' Health Study II	<25 25–29.9 ≥30	25–42	1989–2003	1,398	None
Modugno, 2006 (117)	Case-control	Women's Health Initiative	<23.8 23.8–27.4 >27.4	50–79	1993–1998	199	None
Nemesure, 2009 (118)	Case-control	Barbados	<25 25–29.9 ≥30	≥21	2002–2006	219	A, AF, B, E, F, H, M
Obi, 2009 (119)	Case-control	MARIE	<25 25–29.9 ≥30	50–74	2002–2005	3,462	None
Palmer, 2007 (120)	Cohort	Black Women's Health Study	<25 25–29.9 30–34.9	21–69	1995–2005	949	A, AF, AM, E, F, M, P
Pan, 2004 (121)	Case-control	Canada	<25 25–29.9 ≥30	20–76	1994–1997	2,362	A, AF, F, M
Peacock, 1999 (122)	Case-control	Seattle-Puget Sound, Washington	<23.3 23.3–27 >27	21–45	1983–1990	845	None
Phipps, 2011 (11)	Randomized trial/cohort	Women's Health Initiative	<25 25–29.9 ≥30	50–79	1993–1998	2,898	A, F
Rinaldi, 2006 (123)	Case-control	European Prospective Investigation into Cancer and Nutrition	<25 25–29.9 ≥30	Postmenopausal	1998–2000	613	None

Table continues

Table 1. Continued

First Author, Year (Reference No.)	Study Type	Population[a]	Body Mass Index[b]	Age, Years	Years of Study	No. of Cases	Adjustment Variables[c,d]
Rosenberg, 2006 (124)	Case-control	All native Swedish female residents	<25.9 25.9–28.2 >28.2	50–74	1993–1995	1,241	None
Sarkissyan, 2011 (125)	Cohort	South Los Angeles, California	<25 25–29.9 ≥30	>30	1995–2007	237	A
Silvera, 2006 (126)	Cohort	NBSS	<25 25–29.9 ≥30	40–59	1980–2000	1,671	A, AF, AL, B, F, H, M, O, P, S
Suzuki, 2006 (127)	Cohort	Swedish Mammography Cohort	<25 25–29.9 ≥30	Postmenopausal	1988–2004	1,284	None
Swanson, 1989 (128)	Case-control	BCDDP	<23.5 23.5–27.5 >27.5	26–93	1973–1980	1,768	None
Swanson, 1996 (129)	Case-control	Atlanta, Georgia; Seattle, Washington; New Jersey	<24.7 24.7–28.8 >28.8	20–44	1990–1992	1,588	None
Sweeney, 2004 (130)	Cohort	Iowa Women's Health Study	<26 26–29.5 >29.5	55–84	1986–2001	2,286	None
Toniolo, 1994 (131)	Case-control	NYU Women's Health Study	<23.7 23.7–26.6 >26.6	35–65	1990–1991	180	None
Tornberg, 1994 (132)	Cohort	Swedish Two County Study	<24 24–27.9 ≥28	25–74	1963–1987	1,466	None
Trentham-Dietz, 1997 (133)	Case-control	Maine, Wisconsin, Massachusetts, New Hampshire	<24.9 25–27.5 >27.5	<74	1988–1991	6,548	None
Trentham-Dietz, 2000 (13)	Case-control	Wisconsin, Massachusetts, New Hampshire	<24.0 24.0–29.4 >29.4	50–79	1992–1995	5,031	None
van den Brandt, 1997 (134)	Case-cohort	Netherlands Cohort Study	<25 25–29.9 ≥30	55–69	1986–1990	626	None
Vatten, 1992 (135)	Cohort	Norway	<24 24–27 >27	44–67	1974–1977	291	None
Weiderpass, 2004 (136)	Cohort	Norway and Sweden	<25 25–29.9 ≥30	30–50	1991–1999	716	None
White, 2012 (137)	Cohort	Multiethnic Cohort	20–24.9 25–29.9 ≥30	45–75	1993–2008	2,840	A, AF, AL, AM, E, F, H, P, S, T
Zhu, 2005 (138)	Case-control	Tennessee	<25 25–29.9 ≥30	20–64	1995–1998	271	A, AL, B, E, F, H, M, P, S

Abbreviations: BCDDP, Breast Cancer Detection Demonstration Project; BCSC, Breast Cancer Surveillance Consortium; CARE, Women's Contraceptive and Reproductive Experiences Study; ECSS, Enhanced Cancer Surveillance Study; EPIC, European Prospective Investigation into Cancer and Nutrition; MARIE, Mammary Carcinoma Risk Factor Investigation; MDCS, Malmö Diet and Cancer Study; NBSS, Canadian National Breast Screening Study; NCI, National Cancer Institute; NIH-AARP, National Institutes of Health-AARP; NSHDS, North Sweden Health and Disease Study; NYU, New York University; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; UK, United Kingdom; WHS, Women's Health Study.

[a] Studies listed more than once in the table provide data for different subgroup analyses according to menopausal status, estrogen and progesterone receptor status, and race/ethnicity.

[b] Body mass index: weight (kg)/height $(m)^2$.

[c] Adjustment variables: A, age; AF, age at first birth; AL, alcohol; AM, age at menopause; B, benign breast disease; D, breast density; E, exercise or physical activity; F, family history of breast cancer; H, postmenopausal hormone use; M, age at menarche; O, oral contraceptive use; P, parity; S, smoking; T, type of menopause.

[d] "None" indicates that sample sizes provided in the source articles were used to calculate unadjusted risk estimates for body mass index in 3 categories (<25, 25–29.9, ≥30 kg/m^2).

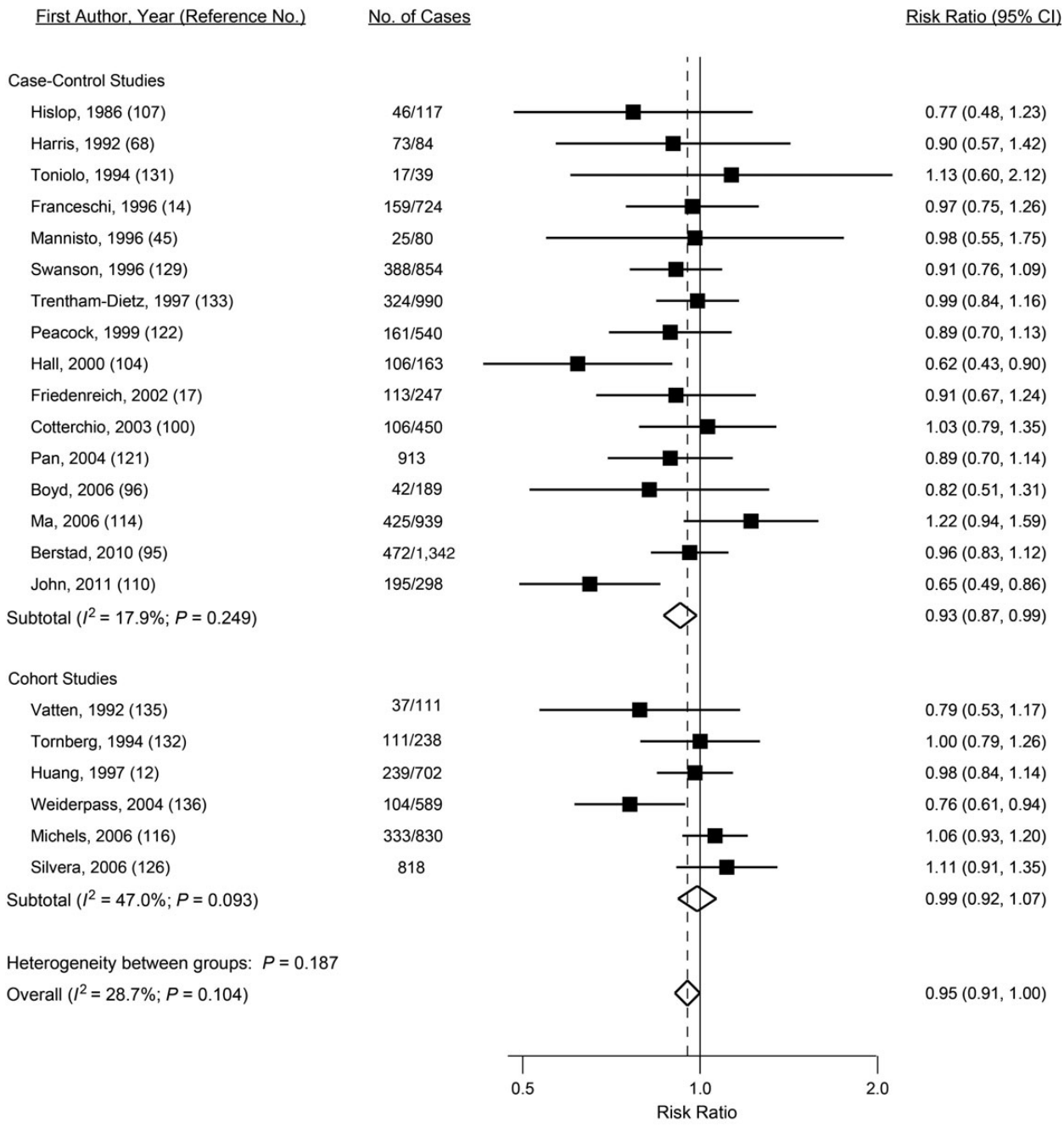

Figure 3. Summary forest plots of the association between body mass index and premenopausal breast cancer according to study design, comparing body mass index 25.0–29.9 with <25 kg/m^2 (Egger's test P = 0.08). Numbers of cases are shown for women with body mass index 25.0–29.9/<25 kg/m^2. If only 1 sample size is shown for the number of cases, then this number represents all cases in the study. CI, confidence interval.

studies and 16,180 breast cancers in eligible cohort studies (Table 1). Greater body mass index was positively associated with postmenopausal breast cancer, as shown in Figure 5 for 25–29.9 kg/m^2 (RR = 1.10, 95% CI: 1.06, 1.13) and Figure 6 for ≥30 kg/m^2 (RR = 1.18, 95% CI: 1.12, 1.25). As among premenopausal women, the relationship between body mass index ≥30 kg/m^2 and postmenopausal breast cancer appeared limited to ER-positive/PR-positive (RR = 1.39, 95% CI: 1.14, 1.70) but not ER-negative/PR-negative (RR = 0.98, 95% CI: 0.78, 1.22) breast cancer (Table 2).

Risk ratio estimates of postmenopausal breast cancer were very similar comparing relationships limited to white women and black women (Table 2). For comparing body mass index ≥30 kg/m^2 with <25 kg/m^2, risk ratio estimates were

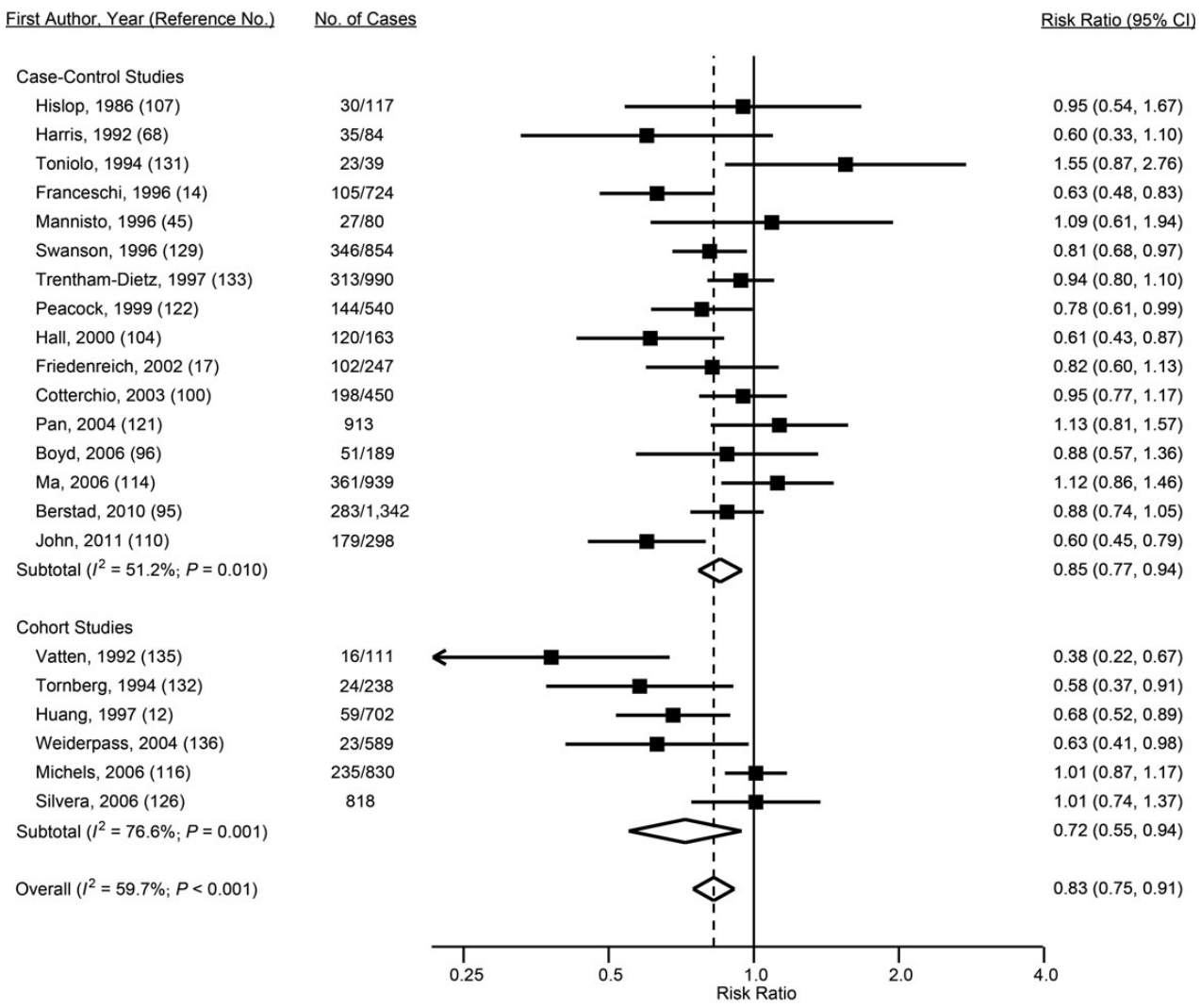

Figure 4. Summary forest plots of the association between body mass index and premenopausal breast cancer according to study design, comparing body mass index ≥30 with <25 kg/m^2 (Egger's test P = 0.14). Numbers of cases are shown for women with body mass index ≥30/<25 kg/m^2. If only 1 sample size is shown for the number of cases, then this number represents all cases in the study. CI, confidence interval.

similarly elevated for ER-positive/PR-positive breast cancer (white women: RR = 1.26, 95% CI: 0.91, 1.76; black women: RR = 1.38, 95% CI: 1.00, 1.91) and null for ER-negative/PR-negative breast cancer (white women: RR = 0.84, 95% CI: 0.55, 1.30; black women: RR = 0.73, 95% CI 0.49, 1.10). The pooled risk ratio of 1.02 (95% CI: 0.64, 1.63) for Hispanic women was null. Data were insufficient to evaluate the risk ratio of postmenopausal breast cancer jointly according to body mass index and hormone receptor status among Hispanic women.

Postmenopausal women: estrogen-progestin use

Analyses of the relationship between estrogen-progestin therapy and postmenopausal breast cancer included 32 articles comprising 32,043 participants with breast cancer from 17 reports of case-control studies and 23,541 breast cancers in 12 reports of cohort studies and 3 reports from 2 randomized trials (Table 3). Ever-use of combined estrogen-progestin hormone use was associated with an elevated risk ratio of postmenopausal breast cancer (RR = 1.34, 95% CI: 1.24, 1.46) (Table 4). The risk ratio for current estrogen-progestin use was elevated (RR = 1.72, 95% CI: 1.55, 1.92) (Table 4), whereas the risk ratio for past use was not significantly increased (RR = 1.02, 95% CI: 0.92, 1.14) (I^2 = 2%, Q test P = 0.41; data not shown). An elevated risk ratio associated with use of estrogen-progestin therapy was restricted to ER-positive/PR-positive breast cancer (ever use: RR = 1.40, 95% CI: 1.08, 1.82; current use: RR = 1.92, 95% CI: 1.60, 2.30) (Table 4). Too few studies presented results for estrogen-progestin use according to race/ethnicity with or without estrogen receptor status to conduct a meta-analysis.

Table 2. Summary Risk Estimates[a] From Meta-analysis of the Association Between Body Mass Index and Breast Cancer for Subgroups Defined by Menopausal Status, Estrogen Receptor and Progesterone Receptor Status, and Race/Ethnicity, 1980–2012

Subgroup	No. of Studies	No. of Cases	Body Mass Index[b]							
			25.0–29.9				≥30.0			
			RR	95% CI	Heterogeneity[c]		RR	95% CI	Heterogeneity[c]	
					P Value	I^2 Statistic, %			*P* Value	I^2 Statistic, %
Premenopausal Women										
ER and PR status										
ER+/PR+	4	2,486	0.94	0.76, 1.17	0.14	45	0.78	0.67, 0.92	0.67	0
ER−/PR−	4	1,360	1.26	1.07, 1.49	0.41	0	1.06	0.70, 1.60	0.004	77
ER+/PR unknown	2	800	1.02	0.85, 1.21	0.52	0	1.01	0.83, 1.24	0.56	0
ER−/PR unknown	2	347	0.98	0.74, 1.29	0.13	57	1.15	0.86, 1.55	0.08	67
Race/ethnicity[d]										
White	11	5,885	0.88	0.81, 0.96	0.91	0	0.72	0.61, 0.85	0.03	50
Black	7	1,668	0.90	0.78, 1.05	0.07	48	0.87	0.70, 1.03	0.31	16
Hispanic	3	756	0.72	0.55, 0.93	0.17	44	0.71	0.54, 0.92	0.08	61
Postmenopausal Women										
ER and PR status										
ER+/PR+	8	6,733	1.17	1.01, 1.36	0.001	74	1.39	1.14, 1.70	0.001	81
ER−/PR−	9	2,302	1.06	0.95, 1.18	0.99	0	0.98	0.78, 1.22	0.02	57
ER+/PR unknown	6	7,965	1.08	1.02, 1.15	0.09	48	1.22	1.03, 1.45	0.002	74
ER−/PR unknown	3	831	0.96	0.78, 1.17	0.28	22	1.27	1.05, 1.55	0.77	0
Race/ethnicity										
White	21	23,905	1.09	1.03, 1.15	0.01	48	1.13	1.02, 1.25	<0.001	74
ER+/PR+	4	4,123	1.11	0.95, 1.29	0.03	68	1.26	0.91, 1.76	<0.001	88
ER−/PR−	4	1,123	1.01	0.87, 1.17	0.68	0	0.84	0.55, 1.30	0.02	69
ER+/PR unknown	3	4,405	1.06	0.92, 1.23	0.05	66	1.19	0.83, 1.69	<0.001	89
Black	7	2,151	0.95	0.76, 1.20	0.04	55	1.12	0.83, 1.52	0.002	71
ER+/PR+	2	309	0.97	0.70, 1.35	0.96	0	1.38	1.00, 1.91	0.53	0
ER−/PR−	2	210	1.12	0.79, 1.60	0.79	0	0.73	0.49, 1.10	0.61	0
Hispanic[d]	3	969	0.97	0.81, 1.17	0.21	36	1.02	0.64, 1.63	0.03	73

Abbreviations: CI, confidence interval; ER, estrogen receptor; PR, progesterone receptor; RR, risk ratio; +, positive; −, negative.

[a] Estimates from fixed-effects models if heterogeneity *P* value ≥ 0.05 and random-effects models if heterogeneity *P* value < 0.05 with body mass index <25.0 kg/m^2 as the reference category.

[b] Body mass index: weight (kg)/height (m)^2.

[c] Cochran's *Q* test *P* values and the I^2 statistic to examine heterogeneity among the studies.

[d] Sample sizes were inadequate to evaluate associations according to both race/ethnicity and ER status.

Postmenopausal women: joint association of body mass index and estrogen-progestin use

Five studies presented sufficient data to examine the relationship between body mass index and postmenopausal breast cancer among subgroups defined by estrogen-progestin use. Among never users of estrogen-progestin therapy, both case-control and cohort studies consistently reported an elevated risk ratio of postmenopausal breast cancer associated with greater body mass index, as shown in Table 5 and Figure 7, where the combined risk ratio was 1.42 (95% CI: 1.30, 1.55) for ≥30 compared with <25 kg/m^2. However, among ever users of estrogen-progestin therapy (Figure 8), the summary risk ratio estimate from cohort studies was elevated for body mass index ≥30 kg/m^2 (RR = 1.26, 95% CI: 1.02, 1.56), and the summary risk ratio estimate from case-control studies was null (RR = 0.98, 95% CI: 0.68, 1.42). These risk ratio estimates were not precise so that the test for heterogeneity according to study design was not significant ($P = 0.25$).

An inadequate number of studies provided results jointly for body mass index and estrogen-progestin use in relation to breast cancer according to subgroups defined by race/ethnicity or ER status to conduct a meta-analysis.

Evaluation of bias

As a subjective measure of study quality, estimates were calculated separately for case-control and cohort studies

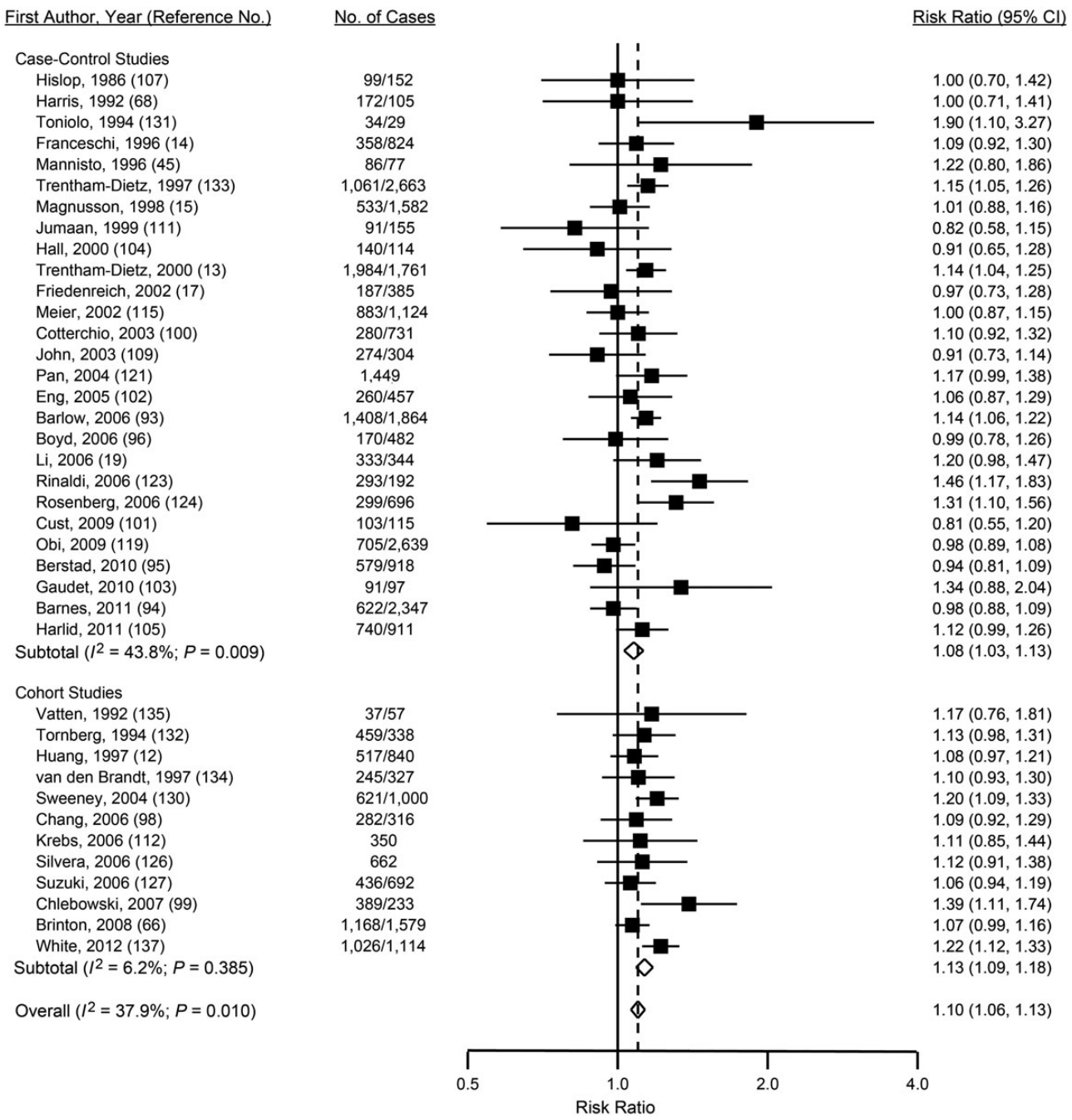

Figure 5. Summary forest plots of the association between body mass index and postmenopausal breast cancer according to study design, comparing body mass index 25.0–29.9 with <25 kg/m^2 (Egger's test $P = 0.68$). Numbers of cases are shown for women with body mass index 25.0–29.9/<25 kg/m^2. If only 1 sample size is shown for the number of cases, then this number represents all cases in the study. CI, confidence interval.

(including randomized trials). Overall, retrospective and prospective studies resulted in very similar estimates (Figures 3–7). The joint analysis of body mass index and ever use of estrogen-progestin therapy suggested that risk ratios were elevated among cohort but not all case-control studies, although the test for heterogeneity according to study design was not significant (Figure 8) ($P = 0.25$). We did not evaluate studies on the basis of whether body mass index was measured or self-reported or on the basis of the source of data—medical records or self-report—for hormone medication use.

Funnel plots were constructed as indicators of bias due to publication bias and effect measures from small studies (Web Figures 1–3 available at http://aje.oxfordjournals.org/). Visual inspection of funnel plots and Egger's test did not suggest that most funnel plots were significantly asymmetrical ($P > 0.05$) (Web Figures 1 and 3) except for the association

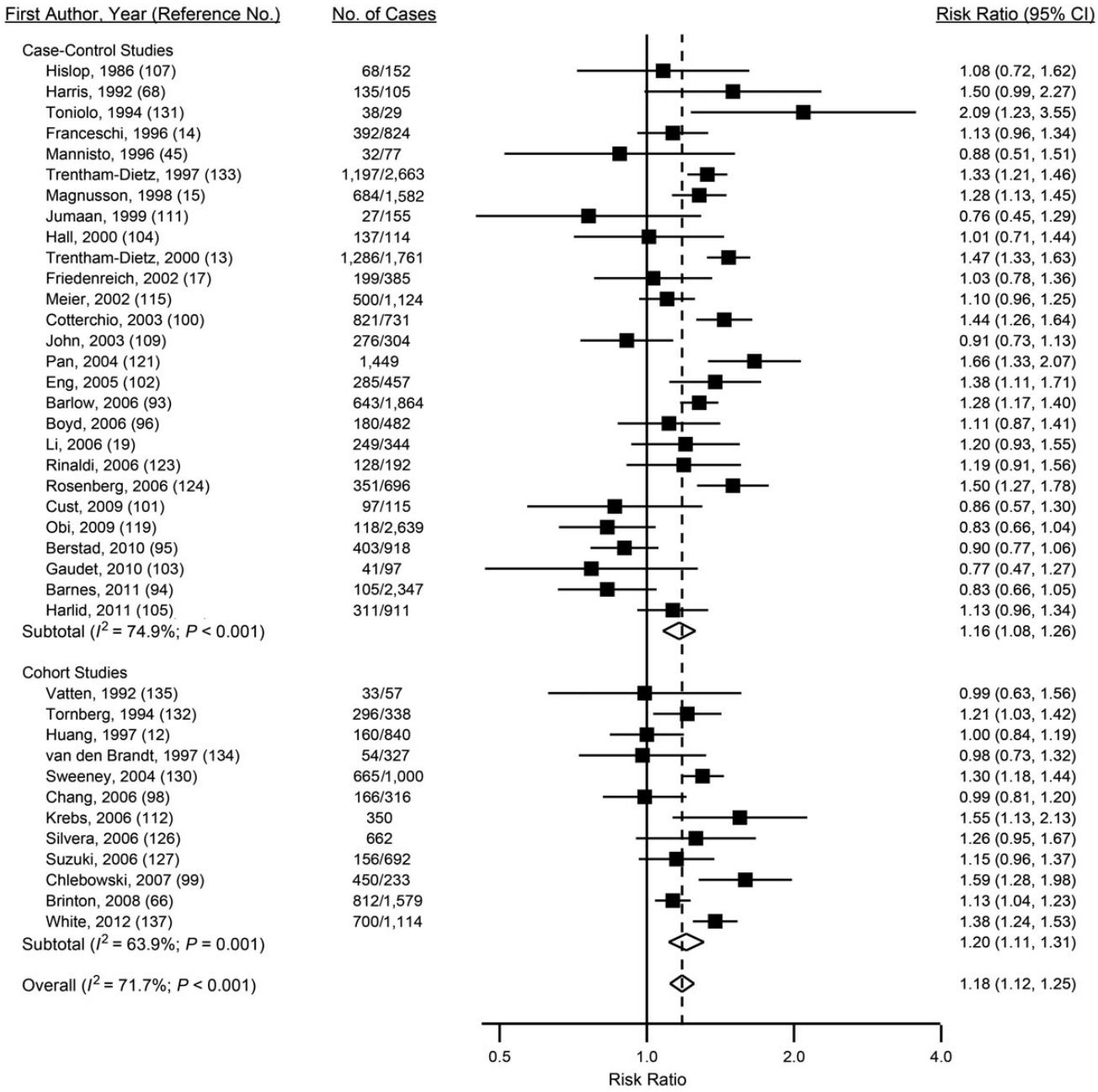

Figure 6. Summary forest plots of the association between body mass index and postmenopausal breast cancer according to study design, comparing body mass index ≥30 with <25 kg/m^2 (Egger's test $P = 0.05$). Numbers of cases are shown for women with body mass index ≥30/<25 kg/m^2. If only 1 sample size is shown for the number of cases, then this number represents all cases in the study. CI, confidence interval.

between body mass index and postmenopausal breast cancer for comparing body mass index ≥30.0 kg/m^2 versus <25.0 kg/m^2 ($P = 0.05$) (Web Figure 2).

DISCUSSION

Results of this meta-analysis suggest that obese women have a reduced risk of hormone receptor–positive premenopausal breast cancer and an increased risk of hormone receptor–positive postmenopausal breast cancer as compared with women of "normal" body mass. Risk ratios appeared attenuated for hormone receptor–negative breast cancer and, for postmenopausal breast cancer, among women using estrogen-progestin therapy. Results stratified according to race/ethnicity appeared consistent for premenopausal breast cancer and for white women and black women for postmenopausal breast cancer;

Table 3. Papers Included in Meta-analysis of Estrogen-Progestin Use in Relation to Breast Cancer Risk

First Author, Year (Reference No.)	Study Type	Population[a]	Estrogen + Progestin Use	Age, Years	Years of Study	No. of Cases	Adjustment Variables[b,c]
Bakken, 2011 (139)	Cohort	EPIC	Current	≥55	1992–2006	4,006	AF, AL, AM, BM, P, O, T
Beral, 2011 (140)	Cohort	Million Women Study	Current	50–59	1996–2001	10,419	A, AF, AL, AM, BM, P
Brinton, 2008 (66)	Cohort	NIH-AARP Diet and Health Study	Ever Current Past	50–71	1995–2002	1,886	A, AF. F
Chen, 2002 (141)	Case-control	Group Health Cooperative	Current Past	50–74	1990–1995	809	A
Chen, 2004 (142)	Cohort	Nurses' Health Study	Current	30–55	1980–2000	807	A, B, AF, AL, AM, F, M, P, T
Chlebowski, 2010 (59)	Randomized trial	Women's Health Initiative	Ever	50–79	2005–2009	569	A, DT
Ewertz, 2005 (143)	Cohort	Denmark	Ever	50–67	1989–2002	678	AF, P
Fournier, 2005 (144)	Cohort	French E3N	Ever	40–66	1990–2000	899	AL, AM, B, BM, F, P, M, O
Fournier, 2008 (145)	Cohort	French E3N	Ever	Postmenopausal	1990–2002	692	A, AF, AM, B, BM, F, M, O, P, T
Hines, 2010 (106)	Case-control	4-Corners Breast Cancer Study	Current	25–79	1999–2002	1,026	A, AF, AM, B, BM, F, M, O, P, T
Hulley, 2002 (52)	Randomized trial	HERS	Ever	Postmenopausal	1993–2000	88	A, AF, BM, F, P
Kotsopoulos, 2009 (146)	Case-control	Nurses' Health Study	Current	≥30	1971–2006	704	None
Lee, 2006 (147)	Cohort	Multiethnic Cohort Study	Past	45–75	1993–1996	746	AF, AL, AM, BM, E, F, M, P, T
Li, 2000 (148)	Case-control	King County, Washington	Current	50–64	1988–1990	22	A, T
Li, 2006 (19)	Case-control	Seattle-Puget Sound, Washington	Current	65–79	1997–1999	835	A, T
Li, 2008 (149)	Case-control	Seattle-Puget Sound, Washington	Ever Current Past	55–74	2000–2004	355	A, F
Lyytinen, 2010 (150)	Case-control	Finland	Ever	50–62	1995–2007	7,204	A, AF, P
Newcomb, 1995 (151)	Case-control	Wisconsin, Massachusetts, Maine, New Hampshire	Ever Past	≤75	1989–1991	2,345	AF, AL, AM, B, BM, F, M, T
Newcomb, 2002 (31)	Case-control	Wisconsin, Massachusetts, Maine, New Hampshire	Ever	50–79	1992–1994	5,289	A, AF, AL, AM, B, BM, E, F, M

Table continues

risk ratio estimates were null for the relationship between body mass index and postmenopausal breast cancer among Hispanic women.

Results from our analysis of the main associations of body mass index with breast cancer agree with reports from other meta-analyses and large studies. The meta-analysis of cohort studies published by Renehan et al. (7), which included the Million Women Study (35), reported a risk ratio equal to 0.92 (95% CI: 0.88, 0.97) of premenopausal breast cancer for each 5 kg/m^2 increase in body mass index. In our analysis, summary risk ratio estimates for receptor-negative premenopausal breast cancer were null, while significantly reduced risk ratio estimates were limited to receptor-positive breast cancer. These same results were found in a meta-analysis conducted by Suzuki et al. (6) and in a pooled analysis of studies participating in the Breast Cancer Association Consortium (36). However, another meta-analysis of 11 studies reported an elevated summary odds ratio for triple-negative premenopausal breast cancer comparing body mass index ≥30 kg/m^2 with <30 kg/m^2 (pooled odds ratio = 1.43, 95% CI: 1.23, 1.65) (37); the methods for this meta-analysis differed from our approach by combining results for case-case and case-control comparisons as well as evaluating risk ratios for only 2 categories of body mass index (obese vs.

Table 3. Continued

First Author, Year (Reference No.)	Study Type	Population[a]	Estrogen + Progestin Use	Age, Years	Years of Study	No. of Cases	Adjustment Variables[b,c]
Opatrny, 2008 (152)	Case-control	UK General Practices Research Database	Ever	50–75	1988–2004	5,161	AL, BM, F, O, S, T
Persson, 1999 (153)	Cohort	Uppsala Health Care Region	Ever	Average, 65	1987–1993	76	A, AF, AM, BM
Reding, 2012 (154)	Case-control	CARE	Current Past	35–64	1994–1998	534	None
Rosenberg, 2006 (124)	Case-control	Sweden	Ever	50–74	1993–1995	1,521	None
Rossouw, 2002 (21)	Randomized trial	Women's Health Initiative	Ever	50–79	1993–2002	290	A, DT
Saxena, 2010 (32)	Cohort	California Teacher's Study	Ever	≤80	1995–2006	1,646	A, AF, AL, AM, B, BM, F, M, P, S
Schairer, 1994 (155)	Cohort	Breast Cancer Detection Demonstration Project	Ever Current Past	<55–>75	1980–1989	609	A, AF, AM, B, F, T
Shantakumar, 2007 (69)	Case-control	Long Island Breast Cancer Study, New York	Ever	20–98	1996–1997	803	None
Sprague, 2008 (156)	Case-control	Wisconsin, Massachusetts, New Hampshire	Current	≥54	1997–2001	2,324	None
Stahlberg, 2004 (157)	Cohort	Danish Nurse Study	Ever	≥44	1993–1999	130	AF, AL, AM, B, BM, E, M, O, P, S
Ursin, 2002 (64)	Case-control	Los Angeles, California	Ever	55–72	1987–1996	1,298	None
Weiss, 2002 (158)	Case-control	CARE	Ever	35–64	1994–1998	1,361	A, T
Yang, 1992 (159)	Case-control	British Columbia, Canada	Ever	≤75	1988–1989	452	A, T

Abbreviations: CARE,Women's Contraceptive and Reproductive Experiences Study; EPIC, European Prospective Investigation into Cancer and Nutrition; French E3N,the French component of the European Prospective Investigation into Cancer and Nutrition; HERS, Heart and Estrogen/progestin Replacement Study; NIH-AARP,National Institutes of Health-AARP; UK, United Kingdom.

[a] Studies listed more than once in the table provide data for different subgroup analysis according to menopausal status, estrogen and progesterone receptor status, and race/ethnicity.

[b] Adjustment variables: A, age; AF, age at first birth; AL, alcohol; AM, age at menopause; B, benign breast disease; BM, body mass index; DT, diet; E, exercise or physical activity; F, family history of breast cancer; M, age at menarche; O, oral contraceptive use; P, parity; S, smoking; T, type of menopause.

[c] "None" indicates that sample sizes provided in the source articles were used to calculate unadjusted risk estimates for hormone therapy use.

nonobese). As molecular subtyping for breast cancer continues incorporating more markers than just the estrogen and progesterone receptors, increasing etiologic heterogeneity will likely be uncovered.

Meta-analysis of studies of obesity in relation to postmenopausal breast cancer overwhelmingly supports elevated relative risk in comparison with normal body mass (7). As with our study, other meta-analyses and systematic reviews using body mass index have reported increased relative risk for receptor-positive breast cancer (9). Several studies have examined different measures of body size with respect to breast cancer including weight (6, 13, 17), adult weight gain (8, 12, 13, 16, 17, 38–40), fat mass (41), and indicators of central obesity including waist circumference and waist-to-hip ratio (17, 41–46). Regardless of the measure of adiposity, relative risk estimates range close to the ones reported in this analysis for body mass index, with relative risk increased by approximately 40% for receptor-positive postmenopausal breast cancer and attenuated relative risk estimates for breast cancer overall or all other subtypes of breast cancer combined.

Limited studies have investigated the relationship between obesity and breast cancer among nonwhite populations. We found that risk ratio estimates for the relationship between obesity and pre- and postmenopausal breast cancer were similar for white women and black women. A meta-analysis of 5 studies (7) suggested that obesity may increase the risk of premenopausal breast cancer among women from Asia and the Pacific, including Japanese women in Hawaii, where the risk ratio was 1.16 (95% CI: 1.01, 1.32) per 5 kg/m^2 increase in body mass index; results for postmenopausal women were similar for all racial groups ($P = 0.09$), although there was a suggestion that the summary risk ratio estimate for Asian

Table 4. Summary Risk Estimates[a] From Meta-analysis of the Association Between Estrogen-Progestin Hormone Use and Postmenopausal Breast Cancer for Subgroups Defined by Estrogen Receptor and Progesterone Receptor Status, 1980–2012

Subgroup	No. of Studies	No. of Cases	RR	95% CI	Heterogeneity[b]	
					P Value	I^2 Statistic, %
Ever Use of Estrogen-Progestin Hormones						
Overall	21	33,677	1.34	1.24, 1.46	<0.001	79
ER+/PR+	3	1,872	1.40	1.08, 1.82	0.02	74
ER−/PR−	3	548	1.09	0.87, 1.37	0.40	0
Current Use of Estrogen-Progestin Hormones						
Overall	13	22,917	1.72	1.55, 1.92	<0.001	79
ER+/PR+	2	876	1.92	1.60, 2.30	0.11	60
ER−/PR−	2	258	1.11	0.78, 1.57	0.98	0
ER+/PR unknown	2	3,042	2.55	1.65, 3.92	0.006	87

Abbreviations: CI, confidence interval; ER, estrogen receptor; PR, progesterone receptor; RR, risk ratio; +, positive; −, negative.

[a] Estimates from random-effects (if $P < 0.05$ for heterogeneity) and fixed-effects (if $P \geq 0.05$ for heterogeneity) models with never users of postmenopausal hormones as the reference category.

[b] Cochran's *Q* test *P* values and the I^2 statistic to examine heterogeneity among the studies.

women was slightly greater than the estimates for whites in Europe and North America. For Hispanic women, only 4 studies contributed to this meta-analysis, with estimates for premenopausal breast cancer similar across race/ethnic groups. The summary risk ratio for postmenopausal breast cancer associated with obesity was null for Hispanic women. In another review, Sexton et al. (47) identified only 3 studies of body size in relation to breast cancer in Hispanic women; results from these 3 studies were also null, underscoring the need for adequately powered studies of breast cancer in Hispanic women (48–50).

Epidemiologic evidence has long suggested that estrogen-progestin use is associated with an increase in breast cancer (51). In 2002, the Women's Health Initiative (WHI) published the results of their large, placebo-controlled, randomized trial of estrogen plus progestin, finding that the risks of use outweighed the benefits (21). After approximately 5 years of follow-up, women assigned to the estrogen plus progestin arm were 26% (95% CI: 0, 59) more likely to develop breast cancer than women in the placebo arm. These findings were nearly identical to the results of the Heart and Estrogen/progestin Replacement Study (HERS) in the same year (52). Following these publications, there were rapid and dramatic reductions in postmenopausal hormone use in the United States (53–56). Nationally, prescriptions for postmenopausal hormone therapy fell by 38% in the first year following publication of the Women's Health Initiative results (57). Ravdin et al. (58) observed that breast cancer incidence in the United States fell by 6.7% in 1 year; this decrease was most evident in women over 50 years of age and in breast cancers that were estrogen receptor positive. Our meta-analysis concurred with this ecological analysis; the pooled risk ratio of 1.92 (95% CI:

Table 5. Summary Risk Estimates[a] From Meta-analysis of the Association Between Body Mass Index and Postmenopausal Breast Cancer for Subgroups Defined by Use of Estrogen-Progestin Hormones, 1980–2012

Subgroup	No. of Studies	No. of Cases	Body Mass Index[b]							
			25.0–29.9				≥30.0			
			RR	95% CI	Heterogeneity[c]		RR	95% CI	Heterogeneity[c]	
					P Value	I^2 Statistic, %			*P* Value	I^2 Statistic, %
Overall	39	59,185	1.10	1.06, 1.13	0.01	38	1.18	1.12, 1.25	<0.001	72
Hormone use										
Never	5	5,711	1.16	1.06, 1.27	0.81	0	1.42	1.30, 1.55	0.36	8
Ever	5	1,337	1.11	0.96, 1.29	0.50	0	1.18	0.98, 1.42	0.32	15

Abbreviations: CI, confidence interval; RR, risk ratio.

[a] Estimates from fixed-effects models if the heterogeneity $P \geq 0.05$ and random-effects models if the heterogeneity $P < 0.05$ with body mass index <25.0 kg/m^2 as the reference category.

[b] Body mass index: weight (kg)/height (m)^2.

[c] Cochran's *Q* test *P* values and the I^2 statistic to examine heterogeneity among the studies.

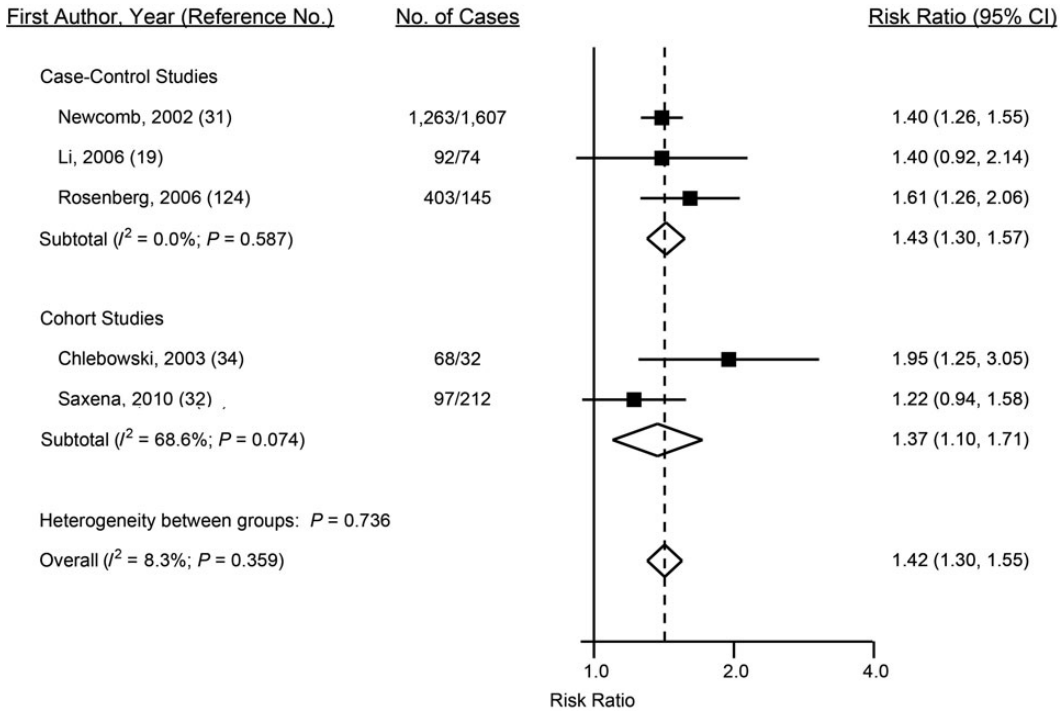

Figure 7. Summary forest plots of the association between body mass index ≥30 (reference value, <25 kg/m^2) and postmenopausal breast cancer according to study design, among never users of postmenopausal hormones (Egger's test P = 0.53). Numbers of cases are shown for women with body mass index ≥30/<25 kg/m^2. CI, confidence interval.

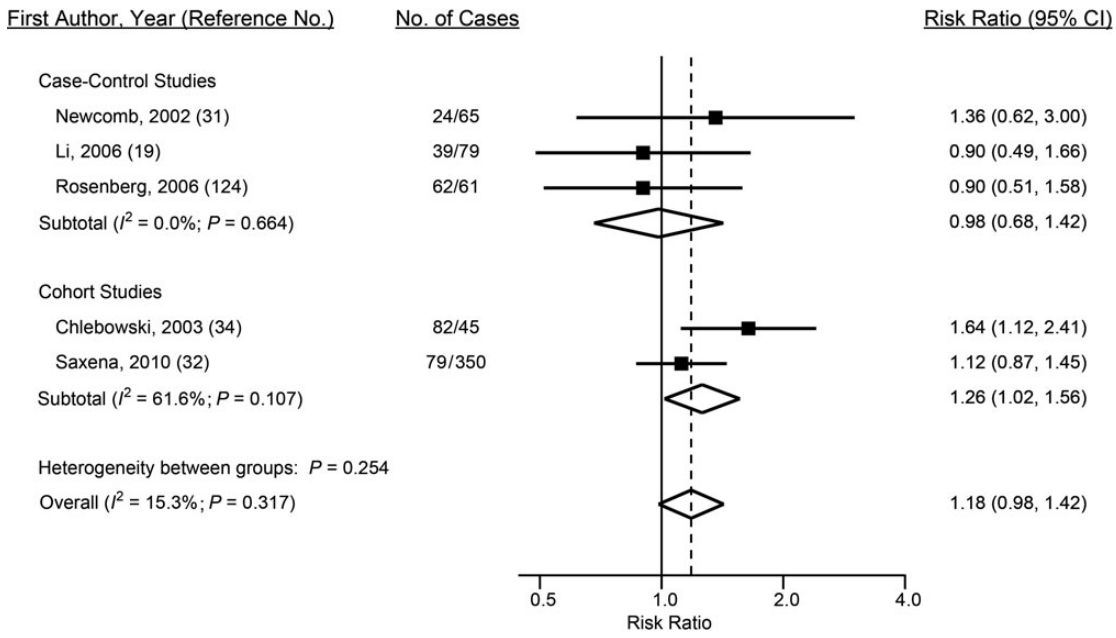

Figure 8. Summary forest plots of the association between body mass index ≥30 (reference value, <25 kg/m^2) and postmenopausal breast cancer according to study design, among ever users of postmenopausal hormones (Egger's test P = 0.84). Numbers of cases are shown for women with body mass index ≥30/<25 kg/m^2. CI, confidence interval.

1.60, 2.30) for current estrogen-progestin use in relation to hormone receptor–positive breast cancer was significantly elevated, but it was null at 1.11 (95% CI: 0.78, 1.57) for ER-negative/PR-negative breast cancer. These estimates were based on only 2 studies. Furthermore, an updated analysis of data from the Women's Health Initiative suggests that use of combined estrogen-progestin hormones is related similarly to both ER-positive and ER-negative disease ($P_{\text{difference}} = 0.81$) (59). Although the relative risk of receptor-negative postmenopausal breast cancer appears likely to be smaller than for receptor-positive disease, the evidence does not conclusively rule out a positive association for estrogen-progestin therapy (9).

The prevalence of estrogen-progestin use has continued to decline to very low levels since 2002. Trends in use of combined estrogen-progestin hormone use were described by using data from the National Health and Nutrition Examination Study (NHANES, 1999–2008) (60). The age-adjusted prevalence of estrogen-progestin use in 1999–2000 was 8.3% and declined to 2.9% in 2003–2004; by 2009–2010, estrogen-progestin use decreased to 1.7%. Synthesis of the evidence led the US Preventive Services Task Force to recommend that clinicians do not prescribe estrogen-progestin therapy for the prevention of chronic conditions (D grade) (61). Notably, our meta-analysis, based on 5 studies, suggests that risk ratio estimates for the association between body mass index and postmenopausal breast cancer are significantly elevated among never users—but not ever users—of estrogen-progestin therapy. Since substantially fewer women are now using postmenopausal hormones, obesity may consequently contribute to a greater proportion of the breast cancer burden.

Several studies that were not included in this meta-analysis have also reported on the modification of the association between body mass index and postmenopausal breast cancer according to estrogen-progestin use; the primary reason these studies were not included was due to presentation of the body mass index results in categories that were not compatible with the normal, overweight, and obese categories in this analysis. Two of the largest cohort studies reported the results of statistical tests for interaction (European Prospective Investigation into Cancer and Nutrition (EPIC): $P_{\text{interaction}} = 0.003$ (18); Women's Health Initiative: $P_{\text{interaction}} = 0.001$ (62)). Although 3 additional studies reported nonsignificant values for the formal test of interaction between body mass index and estrogen-progestin use in relation to postmenopausal breast cancer (13, 19, 63), many studies including both case-control (13–15, 17, 19) and cohort (12, 16, 18, 62, 63) studies reported attenuated relative risk estimates for body mass index among ever, former, or current users of estrogen-progestin therapy as compared with never users. Multiple reports (but not all (64)) have also suggested that the association between estrogen-progestin use and postmenopausal breast cancer is likewise attenuated among obese women (31–34, 51, 65–69).

Strengths and limitations

Interpretation of the results of this meta-analysis must consider several limitations. Publications were included in the analysis only if the results could be considered in the 3 categories according to well-recognized cutpoints for obesity based on body mass index as defined by the World Health Organization (23). For example, a report from the Vermont Breast Cancer Surveillance System (70) and a report from the Million Women Study (35) were not included because results were provided for 5 categories of body mass index that did not include those corresponding to the World Health Organization categories. Pooled analyses with individual-level data could address this limitation but may exclude studies based on data-sharing restrictions (51, 63). Studies of estrogen-only postmenopausal hormone use also were not included. Although estrogen-only hormone use was found to reduce risk of breast cancer incidence and mortality in the Women's Health Initiative, results from this randomized trial did not suggest that body mass index modifies the association between estrogen-only use and breast cancer incidence ($P_{\text{interaction}} = 0.49$) (71). Other systematic reviews, meta-analysis, or pooled analysis of data from individual studies will be necessary to confirm whether the association between obesity and postmenopausal breast cancer varies according to estrogen-only hormone use.

Results in the analysis were a combination of adjusted relative risk estimates taken directly from the published papers along with crude estimates if, for example, body mass index results were combined to align with the 3 categories. In most studies, multivariable relative risk estimates are very similar to unadjusted estimates, although adjusted estimates are frequently slightly attenuated as compared with the unadjusted risk ratios (38).

Meta-analysis relies on the quality of the individual studies. We did not evaluate each study on the basis of indicators of quality, such as participation rates or loss to follow-up. However, we did exclude hospital-based studies. Tests of heterogeneity from fixed-effects models suggest that pooled results for prospective studies were not significantly different from pooled results for retrospective studies. Thus, case-control, cohort, and randomized trials were generally in close agreement regarding the relationship among body mass index, estrogen-progestin therapy, and breast cancer.

Many studies collected information on body mass index, postmenopausal hormone use, and other factors by using self-report rather than medical records or measured values. This may especially have influenced the results of this meta-analysis for self-reported body mass index because heavier women are more likely to underreport their weight. In another meta-analysis that did evaluate the extent to which self-reporting of body mass index affected the results, the authors noted that the effect size between studies in which women self-reported body mass index and those in which weight and height were measured was 1.06 (95% CI: 1.02, 1.09) (7). However, several studies have shown satisfactory reproducibility for self-reported body weight (13, 72–77) and high validity of estrogen-progestin therapy reporting in comparison with medical records (78–81).

Publication bias is a common concern for reports of meta-analyses. In particular, studies of null findings may be missing from the literature, especially once the field appears to be nearing consensus. Funnel plots and statistical tests suggest

that publication bias did not strongly influence the results of this meta-analysis except potentially for the evaluation of obese versus normal body mass index in relation to postmenopausal breast cancer (Egger's test $P = 0.05$) (Figure 6); although results for this highest category of body mass index were more potentially susceptible to bias because of the lack of small studies with positive findings, Egger's test suggests that publication bias was less of a concern for the results comparing overweight with normal body mass index in relation to postmenopausal breast cancer (Egger's test $P = 0.68$) (Figure 5).

Biological mechanisms

The biological mechanisms underlying the association between body mass index and breast cancer are thought to primarily involve sex hormone pathways (82). Estrogen levels are positively associated with breast cancer among postmenopausal women (83); relationships between endogenous estrogens and breast cancer development appear to be more complex among premenopausal women (84). Among premenopausal women, obesity is associated with anovulation and lower levels of circulating estrogen levels (85, 86). In contrast, estrogen levels are elevated among obese postmenopausal women because adipose tissue is the primary source of estrogen production via aromatase enzyme conversion of androgenic precursors (87). An analysis of data pooled from 8 prospective studies found that the association between body mass index and postmenopausal breast cancer was essentially eliminated by adjusting for serum estrogen concentrations (88).

The results of this meta-analysis are consistent with these proposed biological mechanisms. Breast cancer subtypes characterized by ER/PR expression are thought to be etiologically distinct diseases, with ER/PR breast cancers having a predominantly hormone-sensitive etiology (9). Consistent with this hypothesis, body mass index was associated with increased ER/PR-positive, but not ER/PR-negative, breast cancer. Further, the attenuation of the risk ratios between body mass index and breast cancer among estrogen-progestin users lends further support to the hypothesis that obesity influences risk via sex hormone pathways. Circulating estrogen levels are elevated among women using estrogen-progestin therapy, and thus the impact of adipose tissue estrogen production may be expected to be minimized.

Additional mechanisms that could contribute toward the association of body mass index with breast cancer risk among postmenopausal women include chronic hyperinsulinemia (89) and altered adipocytokine production (90). These pathways could influence both ER/PR-positive and -negative subtypes.

Conclusions and implications

This study estimates that obesity is associated with a 20% reduction in receptor-positive premenopausal breast cancer relative risk and approximately 20%–40% increased relative risk of receptor-positive postmenopausal breast cancer. As molecular characterization of breast cancer tumors increases in complexity, greater etiologic heterogeneity in terms of the relationship between body mass index and breast cancer may be revealed beyond the simple categorization of tumors according to ER and PR, or basal versus luminal, subtype. Although studies to date suggest that the relationship between body mass and breast cancer is similar for white women and black women, inconsistencies in the literature suggest that additional research is needed regarding other groups, particularly for Asian and Hispanic women.

Observational studies agree with 2 randomized trials in confirming that estrogen-progestin therapy increases risk of postmenopausal hormone use by about 35% overall and potentially as much as 2-fold for hormone receptor–positive breast cancer among current estrogen-progestin users. This analysis suggests that the relationship between body mass index and postmenopausal breast cancer was strongest in women who never took estrogen-progestin therapy. With the dramatic decline in use of postmenopausal hormones, the role of body mass index in postmenopausal women is likely elevated. A Congressionally authorized panel including federal members from several agencies, nonfederal scientists and clinicians, and breast cancer advocates has recently recognized the urgent need to increase focus on breast cancer prevention (91), and avoidance of obesity after menopause is likely an effective measure to decrease the burden of breast cancer.

ACKNOWLEDGMENTS

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This work was supported in part by National Institutes of Health grants U01 CA152958 and P30 CA014520.

We would like to acknowledge the helpful contributions of the Cancer Intervention Surveillance Modeling Network (CISNET) Breast Working Group including Dr. Natasha Stout, Dr. Oguz Alagoz, and Dr. Jeanne Mandelblatt, as well as National Cancer Institute colleagues Dr. Rocky Feuer and Dr. Kathy Cronin.

Conflict of interest: none declared.

REFERENCES

1. Wang Y, Beydoun MA. The obesity epidemic in the United States—gender, age, socioeconomic, racial/ethnic, and geographic characteristics: a systematic review and meta-regression analysis. *Epidemiol Rev*. 2007;29(1):6–28.
2. State-specific prevalence of obesity among adults—United States, 2005. *MMWR Morb Mortal Wkly Rep*. 2006;55(36):985–988.
3. Wang YC, McPherson K, Marsh T, et al. Health and economic burden of the projected obesity trends in the USA and the UK. *Lancet*. 2011;378(9793):815–825.

4. Finkelstein EA, Trogdon JG, Cohen JW, et al. Annual medical spending attributable to obesity: payer- and service-specific estimates. *Health Aff (Millwood)*. 2009;28(5): w822–w831.
5. World Cancer Research Fund/American Institute for Cancer Research. *Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*. Washington, DC: American Institute for Cancer Research; 2007.
6. Suzuki R, Orsini N, Saji S, et al. Body weight and incidence of breast cancer defined by estrogen and progesterone receptor status—a meta-analysis. *Int J Cancer*. 2009;124(3): 698–712.
7. Renehan AG, Tyson M, Egger M, et al. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet*. 2008;371(9612): 569–578.
8. Vrieling A, Buck K, Kaaks R, et al. Adult weight gain in relation to breast cancer risk by estrogen and progesterone receptor status: a meta-analysis. *Breast Cancer Res Treat*. 2010;123(3):641–649.
9. Althuis MD, Fergenbaum JH, Garcia-Closas M, et al. Etiology of hormone receptor-defined breast cancer: a systematic review of the literature. *Cancer Epidemiol Biomarkers Prev*. 2004;13(10):1558–1568.
10. Phipps AI, Malone KE, Porter PL, et al. Body size and risk of luminal, HER2-overexpressing, and triple-negative breast cancer in postmenopausal women. *Cancer Epidemiol Biomarkers Prev*. 2008;17(8):2078–2086.
11. Phipps AI, Chlebowski RT, Prentice R, et al. Body size, physical activity, and risk of triple-negative and estrogen receptor-positive breast cancer. *Cancer Epidemiol Biomarkers Prev*. 2011;20(3):454–463.
12. Huang Z, Hankinson SE, Colditz GA, et al. Dual effects of weight and weight gain on breast cancer risk. *JAMA*. 1997; 278(17):1407–1411.
13. Trentham-Dietz A, Newcomb PA, Egan KM, et al. Weight change and risk of postmenopausal breast cancer (United States). *Cancer Causes Control*. 2000;11(6):533–542.
14. Franceschi S, Favero A, La Vecchia C, et al. Body size indices and breast cancer risk before and after menopause. *Int J Cancer*. 1996;67(2):181–186.
15. Magnusson C, Baron J, Persson I, et al. Body size in different periods of life and breast cancer risk in post-menopausal women. *Int J Cancer*. 1998;76(1):29–34.
16. Feigelson HS, Jonas CR, Teras LR, et al. Weight gain, body mass index, hormone replacement therapy, and postmenopausal breast cancer in a large prospective study. *Cancer Epidemiol Biomarkers Prev*. 2004;13(2):220–224.
17. Friedenreich CM, Courneya KS, Bryant HE. Case-control study of anthropometric measures and breast cancer risk. *Int J Cancer*. 2002;99(3):445–452.
18. Lahmann PH, Hoffmann K, Allen N, et al. Body size and breast cancer risk: findings from the European Prospective Investigation into Cancer and Nutrition (EPIC). *Int J Cancer*. 2004;111(5):762–771.
19. Li CI, Malone KE, Daling JR. Interactions between body mass index and hormone therapy and postmenopausal breast cancer risk (United States). *Cancer Causes Control*. 2006;17(5): 695–703.
20. Wu AH, Yu MC, Tseng CC, et al. Body size, hormone therapy and risk of breast cancer in Asian-American women. *Int J Cancer*. 2007;120(4):844–852.
21. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results. From the Women's Health Initiative randomized controlled trial. *JAMA*. 2002; 288(3):321–333.
22. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA*. 2004;291(14):1701–1712.
23. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser*. 2000;894:i–xii, 1–253.
24. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539–1558.
25. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177–188.
26. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;50(4): 1088–1101.
27. Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. *J Clin Epidemiol*. 2001;54(10):1046–1055.
28. Sterne JA, Egger M, Smith GD. Systematic reviews in health care: investigating and dealing with publication and other biases in meta-analysis. *BMJ*. 2001;323(7304): 101–105.
29. Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. *J Clin Epidemiol*. 2000;53(11):1119–1129.
30. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997; 315(7109):629–634.
31. Newcomb PA, Titus-Ernstoff L, Egan KM, et al. Postmenopausal estrogen and progestin use in relation to breast cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2002; 11(7):593–600.
32. Saxena T, Lee E, Henderson KD, et al. Menopausal hormone therapy and subsequent risk of specific invasive breast cancer subtypes in the California Teachers Study. *Cancer Epidemiol Biomarkers Prev*. 2010;19(9):2366–2378.
33. Rosenberg LU, Magnusson C, Lindstrom E, et al. Menopausal hormone therapy and other breast cancer risk factors in relation to the risk of different histological subtypes of breast cancer: a case-control study. *Breast Cancer Res*. 2006;8(1):R11.
34. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative randomized trial. *JAMA*. 2003;289(24):3243–3253.
35. Reeves GK, Pirie K, Beral V, et al. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. *BMJ*. 2007;335(7630):1134.
36. Yang XR, Chang-Claude J, Goode EL, et al. Associations of breast cancer risk factors with tumor subtypes: a pooled analysis from the Breast Cancer Association Consortium studies. *J Natl Cancer Inst*. 2011;103(3):250–263.
37. Pierobon M, Frankenfeld CL. Obesity as a risk factor for triple-negative breast cancers: a systematic review and meta-analysis. *Breast Cancer Res Treat*. 2013;137(1): 307–314.
38. Eliassen AH, Colditz GA, Rosner B, et al. Adult weight change and risk of postmenopausal breast cancer. *JAMA*. 2006;296(2):193–201.
39. London SJ, Colditz GA, Stampfer MJ, et al. Prospective study of relative weight, height, and risk of breast cancer. *JAMA*. 1989;262(20):2853–2858.
40. Harvie M, Howell A, Vierkant RA, et al. Association of gain and loss of weight before and after menopause with risk of postmenopausal breast cancer in the Iowa Women's Health

Study. *Cancer Epidemiol Biomarkers Prev*. 2005;14(3):656–661.
41. Macinnis RJ, English DR, Gertig DM, et al. Body size and composition and risk of postmenopausal breast cancer. *Cancer Epidemiol Biomarkers Prev*. 2004;13(12):2117–2125.
42. Harvie M, Hooper L, Howell AH. Central obesity and breast cancer risk: a systematic review. *Obes Rev*. 2003;4(3):157–173.
43. Schapira DV, Kumar NB, Lyman GH, et al. Abdominal obesity and breast cancer risk. *Ann Intern Med*. 1990;112(3):182–186.
44. Connolly BS, Barnett C, Vogt KN, et al. A meta-analysis of published literature on waist-to-hip ratio and risk of breast cancer. *Nutr Cancer*. 2002;44(2):127–138.
45. Mannisto S, Pietinen P, Pyy M, et al. Body-size indicators and risk of breast cancer according to menopause and estrogen-receptor status. *Int J Cancer*. 1996;68(1):8–13.
46. Huang Z, Willett WC, Colditz GA, et al. Waist circumference, waist:hip ratio, and risk of breast cancer in the Nurses' Health Study. *Am J Epidemiol*. 1999;150(12):1316–1324.
47. Sexton KR, Franzini L, Day RS, et al. A review of body size and breast cancer risk in Hispanic and African American women. *Cancer*. 2011;117(23):5271–5281.
48. Gilliland FD, Hunt WC, Baumgartner KB, et al. Reproductive risk factors for breast cancer in Hispanic and non-Hispanic white women: the New Mexico Women's Health Study. *Am J Epidemiol*. 1998;148(7):683–692.
49. Wenten M, Gilliland FD, Baumgartner K, et al. Associations of weight, weight change, and body mass with breast cancer risk in Hispanic and non-Hispanic white women. *Ann Epidemiol*. 2002;12(6):435–444.
50. Slattery ML, Sweeney C, Edwards S, et al. Body size, weight change, fat distribution and breast cancer risk in Hispanic and non-Hispanic white women. *Breast Cancer Res Treat*. 2007;102(1):85–101.
51. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. *Lancet*. 1997;350(9084):1047–1059.
52. Hulley S, Furberg C, Barrett-Connor E, et al. Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). *JAMA*. 2002;288(1):58–66.
53. Buist DS, Newton KM, Miglioretti DL, et al. Hormone therapy prescribing patterns in the United States. *Obstet Gynecol*. 2004;104(5 Pt 1):1042–1050.
54. Clarke CA, Glaser SA, Uratsu CS, et al. Recent declines in hormone therapy utilization and breast cancer incidence: clinical and population-based evidence. *J Clin Oncol*. 2006;24(33):49–50.
55. Haas JS, Kaplan CP, Gerstenberger EP, et al. Changes in the use of postmenopausal hormone therapy after the publication of clinical trial results. *Ann Intern Med*. 2004;140(3):184–188.
56. Kerlikowske K, Miglioretti DL, Buist DS, et al. Declines in invasive breast cancer and use of postmenopausal hormone therapy in a screening mammography population. *J Natl Cancer Inst*. 2007;99(17):1335–1339.
57. Hersh AL, Stefanick ML, Stafford RS. National use of postmenopausal hormone therapy: annual trends and response to recent evidence. *JAMA*. 2004;291(1):47–53.
58. Ravdin PM, Cronin KA, Howlader N, et al. The decrease in breast-cancer incidence in 2003 in the United States. *N Engl J Med*. 2007;356(16):1670–1674.
59. Chlebowski RT, Anderson GL, Gass M, et al. Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. *JAMA*. 2010;304(15):1684–1692.
60. Sprague BL, Trentham-Dietz A, Cronin KA. A sustained decline in postmenopausal hormone use: results from the National Health and Nutrition Examination Survey, 1999–2010. *Obstet Gynecol*. 2012;120(3):595–603.
61. Nelson HD, Walker M, Zakher B, et al. Menopausal hormone therapy for the primary prevention of chronic conditions: a systematic review to update the U.S. Preventive Services Task Force recommendations. *Ann Intern Med*. 2012;157(2):104–113.
62. Morimoto LM, White E, Chen Z, et al. Obesity, body size, and risk of postmenopausal breast cancer: the Women's Health Initiative (United States). *Cancer Causes Control*. 2002;13(8):741–751.
63. van den Brandt PA, Spiegelman D, Yaun SS, et al. Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. *Am J Epidemiol*. 2000;152(6):514–527.
64. Ursin G, Tseng CC, Paganini-Hill A, et al. Does menopausal hormone replacement therapy interact with known factors to increase risk of breast cancer? *J Clin Oncol*. 2002;20(3):699–706.
65. Rosenberg L, Palmer JR, Wise LA, et al. A prospective study of female hormone use and breast cancer among black women. *Arch Intern Med*. 2006;166(7):760–765.
66. Brinton LA, Richesson D, Leitzmann MF, et al. Menopausal hormone therapy and breast cancer risk in the NIH–AARP Diet and Health Study Cohort. *Cancer Epidemiol Biomarkers Prev*. 2008;17(11):3150–3160.
67. Gertig DM, Fletcher AS, English DR, et al. Hormone therapy and breast cancer: what factors modify the association? *Menopause*. 2006;13(2):178–184.
68. Harris RE, Namboodiri KK, Wynder EL. Breast cancer risk: effects of estrogen replacement therapy and body mass. *J Natl Cancer Inst*. 1992;84(20):1575–1582.
69. Shantakumar S, Terry MB, Paykin A, et al. Age and menopausal effects of hormonal birth control and hormone replacement therapy in relation to breast cancer risk. *Am J Epidemiol*. 2007;165(10):1187–1198.
70. Vacek PM, Geller BM. A prospective study of breast cancer risk using routine mammographic breast density measurements. *Cancer Epidemiol Biomarkers Prev*. 2004;13(5):715–722.
71. Anderson GL, Chlebowski RT, Aragaki AK, et al. Conjugated equine oestrogen and breast cancer incidence and mortality in postmenopausal women with hysterectomy: extended follow-up of the Women's Health Initiative randomised placebo-controlled trial. *Lancet Oncol*. 2012;13(5):476–486.
72. Davis H, Gergen PJ. The weights and heights of Mexican-American adolescents: the accuracy of self-reports. *Am J Public Health*. 1994;84(3):459–462.
73. Kushi LH, Kaye SA, Folsom AR, et al. Accuracy and reliability of self-measurement of body girths. *Am J Epidemiol*. 1988;128(4):740–748.
74. Must A, Willett WC, Dietz WH. Remote recall of childhood height, weight, and body build by elderly subjects. *Am J Epidemiol*. 1993;138(1):56–64.
75. Rimm EB, Stampfer MJ, Colditz GA, et al. Validity of self-reported waist and hip circumferences in men and women. *Epidemiology*. 1990;1(6):466–473.
76. Stewart AL. The reliability and validity of self-reported weight and height. *J Chronic Dis*. 1982;35(4):295–309.
77. Stunkard AJ, Albaum JM. The accuracy of self-reported weights. *Am J Clin Nutr*. 1981;34(8):1593–1599.

78. Goodman MT, Nomura AM, Wilkens LR, et al. Agreement between interview information and physician records on history of menopausal estrogen use. *Am J Epidemiol*. 1990; 131(5):815–825.
79. Greendale GA, James MK, Espeland MA, et al. Can we measure prior postmenopausal estrogen/progestin use? The Postmenopausal Estrogen/Progestin Interventions Trial. The PEPI investigators. *Am J Epidemiol*. 1997;146(9): 763–770.
80. Jain MG, Rohan TE, Howe GR. Agreement of self-reported use of menopausal hormone replacement therapy with physician reports. *Epidemiology*. 1999;10(3):260–263.
81. Jannausch ML, Sowers MR. Consistency of perimenopausal estrogen use reporting by women in a population-based prospective study. *Maturitas*. 1992;14(3):161–169.
82. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nat Rev Cancer*. 2004;4(8):579–591.
83. Key T, Appleby P, Barnes I, et al. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. *J Natl Cancer Inst*. 2002;94(8): 606–616.
84. Eliassen AH, Spiegelman D, Xu X, et al. Urinary estrogens and estrogen metabolites and subsequent risk of breast cancer among premenopausal women. *Cancer Res*. 2012;72(3): 696–706.
85. Potischman N, Swanson CA, Siiteri P, et al. Reversal of relation between body mass and endogenous estrogen concentrations with menopausal status. *J Natl Cancer Inst*. 1996;88(11):756–758.
86. Rich-Edwards JW, Goldman MB, Willett WC, et al. Adolescent body mass index and infertility caused by ovulatory disorder. *Am J Obstet Gynecol*. 1994;171(1):171–177.
87. Siiteri PK. Adipose tissue as a source of hormones. *Am J Clin Nutr*. 1987;45(1 suppl):277–282.
88. Key TJ, Appleby PN, Reeves GK, et al. Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. *J Natl Cancer Inst*. 2003;95(16):1218–1226.
89. Renehan AG, Frystyk J, Flyvbjerg A. Obesity and cancer risk: the role of the insulin-IGF axis. *Trends Endocrinol Metab*. 2006;17(8):328–336.
90. Rose DP, Komninou D, Stephenson GD. Obesity, adipocytokines, and insulin resistance in breast cancer. *Obes Rev*. 2004;5(3):153–165.
91. Interagency Breast Cancer and the Environment Research Coordinating Committee. Breast cancer and the environment: prioritizing prevention. Bethesda, MD: National Institutes of Health; 2013. (http://www.niehs.nih.gov/about/assets/docs/ibcercc_full_508.pdf). (Accessed August 21, 2013).
92. Ahn J, Schatzkin A, Lacey JV Jr, et al. Adiposity, adult weight change, and postmenopausal breast cancer risk. *Arch Intern Med*. 2007;167(19):2091–2102.
93. Barlow WE, White E, Ballard-Barbash R, et al. Prospective breast cancer risk prediction model for women undergoing screening mammography. *J Natl Cancer Inst*. 2006;98(17): 1204–1214.
94. Barnes BB, Steindorf K, Hein R, et al. Population attributable risk of invasive postmenopausal breast cancer and breast cancer subtypes for modifiable and non-modifiable risk factors. *Cancer Epidemiol*. 2011;35(4): 345–352.
95. Berstad P, Coates RJ, Bernstein L, et al. A case-control study of body mass index and breast cancer risk in white and African-American women. *Cancer Epidemiol Biomarkers Prev*. 2010;19(6):1532–1544.
96. Boyd NF, Martin LJ, Sun L, et al. Body size, mammographic density, and breast cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2006;15(11):2086–2092.
97. Cerne JZ, Ferk P, Leskosek B, et al. Hormone replacement therapy and some risk factors for breast cancer among Slovenian postmenopausal women. *Climacteric*. 2011;14(4): 458–463.
98. Chang SC, Ziegler RG, Dunn B, et al. Association of energy intake and energy balance with postmenopausal breast cancer in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. *Cancer Epidemiol Biomarkers Prev*. 2006; 15(2):334–341.
99. Chlebowski RT, Anderson GL, Lane DS, et al. Predicting risk of breast cancer in postmenopausal women by hormone receptor status. *J Natl Cancer Inst*. 2007;99(22): 1695–1705.
100. Cotterchio M, Kreiger N, Theis B, et al. Hormonal factors and the risk of breast cancer according to estrogen- and progesterone-receptor subgroup. *Cancer Epidemiol Biomarkers Prev*. 2003;12(10):1053–1060.
101. Cust AE, Stocks T, Lukanova A, et al. The influence of overweight and insulin resistance on breast cancer risk and tumour stage at diagnosis: a prospective study. *Breast Cancer Res Treat*. 2009;113(3):567–576.
102. Eng SM, Gammon MD, Terry MB, et al. Body size changes in relation to postmenopausal breast cancer among women on Long Island, New York. *Am J Epidemiol*. 2005;162(3): 229–237.
103. Gaudet MM, Falk RT, Gierach GL, et al. Do adipokines underlie the association between known risk factors and breast cancer among a cohort of United States women? *Cancer Epidemiol*. 2010;34(5):580–586.
104. Hall IJ, Newman B, Millikan RC, et al. Body size and breast cancer risk in black women and white women: the Carolina Breast Cancer Study. *Am J Epidemiol*. 2000;151(8):754–764.
105. Harlid S, Butt S, Ivarsson MI, et al. Interactive effect of genetic susceptibility with height, body mass index, and hormone replacement therapy on the risk of breast cancer. *BMC Womens Health*. 2012;12(17).
106. Hines LM, Risendal B, Slattery ML, et al. Comparative analysis of breast cancer risk factors among Hispanic and non-Hispanic white women. *Cancer*. 2010;116(13): 3215–3223.
107. Hislop TG, Coldman AJ, Elwood JM, et al. Relationship between risk factors for breast cancer and hormonal status. *Int J Epidemiol*. 1986;15(4):469–476.
108. Huang WY, Newman B, Millikan RC, et al. Hormone-related factors and risk of breast cancer in relation to estrogen receptor and progesterone receptor status. *Am J Epidemiol*. 2000; 151(7):703–714.
109. John EM, Horn-Ross PL, Koo J. Lifetime physical activity and breast cancer risk in a multiethnic population: the San Francisco Bay area breast cancer study. *Cancer Epidemiol Biomarkers Prev*. 2003;12(11 Pt 1):1143–1152.
110. John EM, Sangaramoorthy M, Phipps AI, et al. Adult body size, hormone receptor status, and premenopausal breast cancer risk in a multiethnic population: the San Francisco Bay area breast cancer study. *Am J Epidemiol*. 2011;173(2): 201–216.
111. Jumaan AO, Holmberg L, Zack M, et al. Beta-carotene intake and risk of postmenopausal breast cancer. *Epidemiology*. 1999;10(1):49–53.
112. Krebs EE, Taylor BC, Cauley JA, et al. Measures of adiposity and risk of breast cancer in older postmenopausal women. *J Am Geriatr Soc*. 2006;54(1):63–69.

113. Li CI, Stanford JL, Daling JR. Anthropometric variables in relation to risk of breast cancer in middle-aged women. *Int J Epidemiol*. 2000;29(2):208–213.
114. Ma H, Bernstein L, Ross RK, et al. Hormone-related risk factors for breast cancer in women under age 50 years by estrogen and progesterone receptor status: results from a case-control and a case-case comparison. *Breast Cancer Res*. 2006;8(4):R39.
115. Meier CR, Schmitz S, Jick H. Association between acetaminophen or nonsteroidal antiinflammatory drugs and risk of developing ovarian, breast, or colon cancer. *Pharmacotherapy*. 2002;22(3):303–309.
116. Michels KB, Terry KL, Willett WC. Longitudinal study on the role of body size in premenopausal breast cancer. *Arch Intern Med*. 2006;166(21):2395–2402.
117. Modugno F, Kip KE, Cochrane B, et al. Obesity, hormone therapy, estrogen metabolism and risk of postmenopausal breast cancer. *Int J Cancer*. 2006;118(5):1292–1301.
118. Nemesure B, Wu SY, Hennis A, et al. Body size and breast cancer in a black population—the Barbados National Cancer Study. *Cancer Causes Control*. 2009;20(3):387–394.
119. Obi N, Chang-Claude J, Berger J, et al. The use of herbal preparations to alleviate climacteric disorders and risk of postmenopausal breast cancer in a German case-control study. *Cancer Epidemiol Biomarkers Prev*. 2009;18(8):2207–2213.
120. Palmer JR, Adams-Campbell LL, Boggs DA, et al. A prospective study of body size and breast cancer in black women. *Cancer Epidemiol Biomarkers Prev*. 2007;16(9):1795–1802.
121. Pan SY, Johnson KC, Ugnat AM, et al. Association of obesity and cancer risk in Canada. *Am J Epidemiol*. 2004;159(3):259–268.
122. Peacock SL, White E, Daling JR, et al. Relation between obesity and breast cancer in young women. *Am J Epidemiol*. 1999;149(4):339–346.
123. Rinaldi S, Key TJ, Peeters PH, et al. Anthropometric measures, endogenous sex steroids and breast cancer risk in postmenopausal women: a study within the EPIC cohort. *Int J Cancer*. 2006;118(11):2832–2839.
124. Rosenberg LU, Einarsdottir K, Friman EI, et al. Risk factors for hormone receptor-defined breast cancer in postmenopausal women. *Cancer Epidemiol Biomarkers Prev*. 2006;15(12):2482–2488.
125. Sarkissyan M, Wu Y, Vadgama JV. Obesity is associated with breast cancer in African-American women but not Hispanic women in South Los Angeles. *Cancer*. 2011;117(16):3814–3823.
126. Silvera SA, Jain M, Howe GR, et al. Energy balance and breast cancer risk: a prospective cohort study. *Breast Cancer Res Treat*. 2006;97(1):97–106.
127. Suzuki R, Rylander-Rudqvist T, Ye W, et al. Body weight and postmenopausal breast cancer risk defined by estrogen and progesterone receptor status among Swedish women: a prospective cohort study. *Int J Cancer*. 2006;119(7):1683–1689.
128. Swanson CA, Brinton LA, Taylor PR, et al. Body size and breast cancer risk assessed in women participating in the Breast Cancer Detection Demonstration Project. *Am J Epidemiol*. 1989;130(6):1133–1141.
129. Swanson CA, Coates RJ, Schoenberg JB, et al. Body size and breast cancer risk among women under age 45 years. *Am J Epidemiol*. 1996;143(7):698–706.
130. Sweeney C, Blair CK, Anderson KE, et al. Risk factors for breast cancer in elderly women. *Am J Epidemiol*. 2004;160(9):868–875.
131. Toniolo P, Riboli E, Shore RE, et al. Consumption of meat, animal products, protein, and fat and risk of breast cancer: a prospective cohort study in New York. *Epidemiology*. 1994;5(4):391–397.
132. Tornberg SA, Carstensen JM. Relationship between Quetelet's index and cancer of breast and female genital tract in 47,000 women followed for 25 years. *Br J Cancer*. 1994;69(2):358–361.
133. Trentham-Dietz A, Newcomb PA, Storer BE, et al. Body size and risk of breast cancer. *Am J Epidemiol*. 1997;145(11):1011–1019.
134. van den Brandt PA, Dirx MJ, Ronckers CM, et al. Height, weight, weight change, and postmenopausal breast cancer risk: the Netherlands Cohort Study. *Cancer Causes Control*. 1997;8(1):39–47.
135. Vatten LJ, Kvinnsland S. Prospective study of height, body mass index and risk of breast cancer. *Acta Oncol*. 1992;31(2):195–200.
136. Weiderpass E, Braaten T, Magnusson C, et al. A prospective study of body size in different periods of life and risk of premenopausal breast cancer. *Cancer Epidemiol Biomarkers Prev*. 2004;13(7):1121–1127.
137. White KK, Park SY, Kolonel LN, et al. Body size and breast cancer risk: the Multiethnic Cohort. *Int J Cancer*. 2012;131(5):E705–E716.
138. Zhu K, Caulfield J, Hunter S, et al. Body mass index and breast cancer risk in African American women. *Ann Epidemiol*. 2005;15(2):123–128.
139. Bakken K, Fournier A, Lund E, et al. Menopausal hormone therapy and breast cancer risk: impact of different treatments. The European Prospective Investigation into Cancer and Nutrition. *Int J Cancer*. 2011;128(1):144–156.
140. Beral V, Reeves G, Bull D, et al. Breast cancer risk in relation to the interval between menopause and starting hormone therapy. *J Natl Cancer Inst*. 2011;103(4):296–305.
141. Chen CL, Weiss NS, Newcomb P, et al. Hormone replacement therapy in relation to breast cancer. *JAMA*. 2002;287(6):734–741.
142. Chen WY, Hankinson SE, Schnitt SJ, et al. Association of hormone replacement therapy to estrogen and progesterone receptor status in invasive breast carcinoma. *Cancer*. 2004;101(7):1490–1500.
143. Ewertz M, Mellemkjaer L, Poulsen AH, et al. Hormone use for menopausal symptoms and risk of breast cancer. A Danish cohort study. *Br J Cancer*. 2005;92(7):1293–1297.
144. Fournier A, Berrino F, Riboli E, et al. Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort. *Int J Cancer*. 2005;114(3):448–454.
145. Fournier A, Fabre A, Mesrine S, et al. Use of different postmenopausal hormone therapies and risk of histology- and hormone receptor-defined invasive breast cancer. *J Clin Oncol*. 2008;26(8):1260–1268.
146. Kotsopoulos J, Tworoger SS, De Vivo I, et al. *+331G/A* variant in the progesterone receptor gene, postmenopausal hormone use and risk of breast cancer. *Int J Cancer*. 2009;125(7):1685–1691.
147. Lee S, Kolonel L, Wilkens L, et al. Postmenopausal hormone therapy and breast cancer risk: the Multiethnic Cohort. *Int J Cancer*. 2006;118(5):1285–1291.
148. Li CI, Weiss NS, Stanford JL, et al. Hormone replacement therapy in relation to risk of lobular and ductal breast carcinoma in middle-aged women. *Cancer*. 2000;88(11):2570–2577.

149. Li CI, Malone KE, Porter PL, et al. Relationship between menopausal hormone therapy and risk of ductal, lobular, and ductal-lobular breast carcinomas. *Cancer Epidemiol Biomarkers Prev*. 2008;17(1):43–50.
150. Lyytinen HK, Dyba T, Ylikorkala O, et al. A case-control study on hormone therapy as a risk factor for breast cancer in Finland: intrauterine system carries a risk as well. *Int J Cancer*. 2010;126(2):483–489.
151. Newcomb PA, Longnecker MP, Storer BE, et al. Long-term hormone replacement therapy and risk of breast cancer in postmenopausal women. *Am J Epidemiol*. 1995;142(8): 788–795.
152. Opatrny L, Dell'Aniello S, Assouline S, et al. Hormone replacement therapy use and variations in the risk of breast cancer. *BJOG*. 2008;115(2):169–175; discussion 175.
153. Persson I, Weiderpass E, Bergkvist L, et al. Risks of breast and endometrial cancer after estrogen and estrogen-progestin replacement. *Cancer Causes Control*. 1999;10(4):253–260.
154. Reding KW, Chen C, Lowe K, et al. Estrogen-related genes and their contribution to racial differences in breast cancer risk. *Cancer Causes Control*. 2012;23(5):671–681.
155. Schairer C, Byrne C, Keyl PM, et al. Menopausal estrogen and estrogen-progestin replacement therapy and risk of breast cancer (United States). *Cancer Causes Control*. 1994;5(6):491–500.
156. Sprague BL, Trentham-Dietz A, Egan KM, et al. Proportion of invasive breast cancer attributable to risk factors modifiable after menopause. *Am J Epidemiol*. 2008;168(4):404–411.
157. Stahlberg C, Pedersen AT, Andersen ZJ, et al. Breast cancer with different prognostic characteristics developing in Danish women using hormone replacement therapy. *Br J Cancer*. 2004;91(4):644–650.
158. Weiss LK, Burkman RT, Cushing-Haugen KL, et al. Hormone replacement therapy regimens and breast cancer risk(1). *Obstet Gynecol*. 2002;100(6):1148–1158.
159. Yang CP, Daling JR, Band PR, et al. Noncontraceptive hormone use and risk of breast cancer. *Cancer Causes Control*. 1992;3(5):475–479.