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Adult Weight Gain and Adiposity-Related Cancers: A Dose-Response Meta-Analysis of Prospective Observational Studies

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Abstract

Background: Adiposity, measured by body mass index, is implicated in carcinogenesis. While adult weight gain has diverse advantages over body mass index in measuring adiposity, systematic reviews on adult weight gain in relation to adiposity-related cancers are lacking.

Methods: PubMed and Embase were searched through September 2014 for prospective observational studies investigating the relationship between adult weight gain and the risk of 10 adiposity-related cancers. Dose-response meta-analyses were performed using a random-effects model to estimate summary relative risk (RR) and 95% confidence interval (CI) for each cancer type. All statistical tests were two-sided.

Results: A total of 50 studies were included. For each 5 kg increase in adult weight gain, the summary relative risk was 1.11 (95% CI = 1.08 to 1.13) for postmenopausal breast cancer among no- or low-hormone replacement therapy (HRT) users, 1.39 (95% CI = 1.29 to 1.49) and 1.09 (95% CI = 1.02 to 1.16) for postmenopausal endometrial cancer among HRT nonusers and users, respectively, 1.13 (95% CI = 1.03 to 1.23) for postmenopausal ovarian cancer among no or low HRT users, 1.09 (95% CI = 1.04 to 1.13) for colon cancer in men. The relative risk of kidney cancer comparing highest and lowest level of adult weight gain was 1.42 (95% CI = 1.11 to 1.81). Adult weight gain was unrelated to cancers of the breast (premenopausal women, postmenopausal HRT users), prostate, colon (women), pancreas, and thyroid. An increase in risk associated with adult weight gain for breast cancer was statistically significantly greater among postmenopausal women ($P_{\text{heterogeneity}} = .001$) and HRT nonusers ($P_{\text{heterogeneity}} = .001$); that for endometrial cancer was alike among HRT nonusers ($P_{\text{heterogeneity}} = .04$).

Conclusions: Avoiding adult weight gain itself may confer protection against certain types of cancers, particularly among HRT nonusers.

Introduction

Obesity has reached epidemic proportions worldwide, with more than one billion adults (about one third of world adults age 20 years and older) either overweight or obese in 2008 (1). Excess adiposity is a major contributor to chronic diseases including type 2 diabetes, cardiovascular diseases, and some types of cancer (2). According to American Institute for Cancer Research or the National Cancer Institute, cancers of the breast (BC), endometrium (EC), colorectum (CRC), kidney (KC), pancreas (PaC), esophagus (EsC), gallbladder (GC), ovaries (OC), thyroid (TC), and possibly prostate (PC) are classified as obesity-related cancers (3,4). Considerable meta- or pooled analyses of excess adiposity, measured by body mass index (BMI), and such obesity-related cancers have been published, strengthening the evidence for a role of obesity in carcinogenesis (5–15).

While BMI is the most widely used metric of adiposity in adults, adult weight gain may be a better metric for several reasons. First, adult weight gain captures the dynamic pattern of weight trajectory throughout adult life. Adults follow upward-sloping weight trajectories with a mean annual weight gain of 0.5 kg/year across all BMI categories (16), and thus adult weight gain represents a pattern of weight gain accumulated over time. Considering that carcinogenesis spans over a long period, such a time-integrated metric may be relevant to cancer risk. Second, as adults gain weight mostly through accumulating fat mass (17), adult weight gain is a good surrogate of body fatness. In contrast, BMI captures a mixture of fat mass and lean body mass and it even correlates more strongly with lean body mass in the elderly (18). Thus, validity of BMI to measure adiposity is highly sensitive to the sex and age distribution of study populations. Third, unlike adolescent adipose gain that is distributed primarily on the hips and thighs (pear-shaped), during adulthood fat accumulates preferentially around the waist (apple-shaped) (17), which is more detrimental metabolically (19). Thus, adult weight gain incorporating both fatness and the harmful type of fat distribution may be the best measure of adiposity in predicting adiposity-related cancer risk, which has utility in the clinical setting. Finally, as adult weight gain is a simpler and more intuitive concept to the general public than BMI, public health recommendations based on adult weight gain are more effectively communicated.

Despite the aforementioned advantages, systematic reviews or meta-analyses on cancer using adult weight gain are sparse. Thus, we conducted dose-response meta-analyses of adult weight gain and each of the obesity-related cancers in order to identify the shape of the dose-response relationships and to quantify the risks associated with an increase in adult weight gain.

Methods

The Meta-analysis Of Observational Studies in Epidemiology (MOOSE) checklist was followed for the design, analysis, and reporting of this meta-analysis (20). Two

authors (DL, RK) participated in literature search, study selection, and data extraction independently. Inconsistency was checked by a third author (NK).

Literature Search

PubMed and Embase databases were searched through September 2014. Detailed search terms are provided (Supplementary Table 1, available online). The language was limited to English, and no other restrictions were imposed. Abstracts and unpublished results were not included. The reference lists of selected reviews and meta-analyses and all the articles included in our analysis were also reviewed for additional studies.

Study Selection

Studies were included if they met the following criteria: being a prospective observational study; investigating the relationship between adult weight gain, defined as increase in weight from early adulthood (mostly age 18 to 25 years) to study enrollment and the risk of the 10 obesity-related cancers as defined in the introduction; providing the estimates of RR (risk ratio, hazard ratio) and 95% confidence interval. To be eligible for dose-response meta-analysis, studies had to provide further information: for at least three categories, a quantitative measure (kg or lb) of weight gain during adulthood, relative risks (risk ratio, hazard ratio), 95% confidence intervals, category-specific or total number of cases, and category-specific or total number of either person-years or noncases. When there were duplicate publications, the publication most closely relevant to our topic was selected. Three relevant publications (21–23) reported adult weight gain in kg/year(s), which was converted to kg by multiplying the time interval between age of early weight recalled and mean age of the study cohort at baseline. However, for one study (21), this approximation led to a wide range of adult weight gain for the reference category (-22.5–22.5 kg) and an unrealistic range of adult weight gain for the highest category (46–90 kg), and thus the publication was excluded from this analysis. The first author of one publication (24) was contacted and provided the requested information.

Data Extraction

From each study, the following information was extracted: definition and category-specific range of adult weight gain, the most fully adjusted relative risks and their 95% confidence intervals, category-specific or total number of cases, category-specific or total number of person-years, first author's name, publication year, characteristics of study cohort (eg, name, country, sex, baseline age), follow-up period, method of weight assessment (time points of weight assessment, whether

weight had been self-reported or measured, whether self-reported weight had been validated), and variables adjusted for.

Statistical Analysis

Across obesity-related cancers affecting both men and women, the harmful effect of excess adiposity has been hypothesized to be stronger among men, because men have a propensity toward metabolically harmful obesity (ie, deposit fat centrally rather than peripherally; have more visceral fat than subcutaneous fat) (25). Thus, for such cancers, meta-analyses were presented separately for men and women, wherever possible, along with an overall pooled estimate.

Similarly, for cancers of the breast, endometrium, and ovary on which estrogen has a dominant influence (26–28), a marked contrast in circulating estrogen level between pre- and postmenopausal period is expected to modify the relationship between adiposity and cancer risk. Heterogeneity in the relationship by menopausal status is well established for BC (29), but it is less so for EC and OC, and the number of studies on adult weight gain and these two cancers is stratified by menopausal status was small. Thus, while meta-analyses were performed separately by menopausal status for EC and OC, sensitivity analyses were performed by including studies conducted in a mixed population of pre- and postmenopausal women. In particular, during the postmenopausal period when adipocytes become a major site of estrogen synthesis, influx of exogenous estrogens from hormone replacement therapy (HRT) may obscure the effect of adiposity on such cancers. Thus, the primary analysis for postmenopausal cancer of these sites was conducted among non-HRT users.

Linear and nonlinear dose-response meta-analyses were conducted. For linear dose-response meta-analyses assuming a linear relationship between adult weight gain and cancer risk, the method described by Greenland and Longnecker (30) was used to calculate appropriate study-specific relative risks (linear slopes) and 95% confidence intervals from the relative risks and 95% confidence intervals extracted across categories of adult weight gain. In brief, this provides a method for combining observational studies with different exposure category definitions by estimating a linear dose-response curve for each study, whilst still adjusting for confounding. In estimating linear trends, several approximations were made: the midpoint of adult weight gain in each category was assigned to the corresponding RR; if the lowest category was within ± 3 kg, the midpoint was set to 0 to denote a stable weight, but if not the midpoint was calculated by setting the lowest bound to 0; the width of the open-ended highest category was assumed to be the same as that of the adjacent interval; when studies did not provide distributions of person-years but analyzed based on quantiles, person-years were equally divided across the quantiles; for one study (31) that used the second lowest category of adult weight gain as the reference, the method by Hamling et al. (32) was used to estimate new relative risks and 95% confidence intervals setting the lowest category as the new reference.

Finally, the estimated study-specific relative risks and variances were pooled using the DerSimonian-Laird random effects model (33) to calculate the summary relative risk and 95% confidence interval. Forest plots of the linear dose-response meta-analysis were presented for relative risks for each 5 kg increment in adult weight gain.

Potential nonlinear relationship between adult weight gain and cancer risk was examined using a set of second-order fractional polynomials (34). The best-fitting curve was determined as the one with the lowest deviance. A likelihood ratio test was used to test statistical significance of nonlinearity. To allow adequate information for the robust estimation of the curve, this nonlinear meta-analysis was applied when five or more studies contributed toward dose-response meta-analysis.

Heterogeneity in the relationship across studies was assessed by Cochran's Q test (35) and quantified by I^2 , which represents the proportion of total variation attributable to true between-study heterogeneity rather than random chance (36). I^2 values of 25%, 50%, and 75% are often used to classify low, moderate, and high heterogeneity, respectively. To explore sources of heterogeneity and to assess study quality, subgroup analyses and meta-regression were conducted by a priori selected variables related to etiologic heterogeneity (stage at diagnosis), by potential effect modifiers (menopausal status, HRT use, sex, geographical location, mean age of the cohort at baseline, age at early weight assessment), and by variables concerning methodological characteristics (number of total cases, duration of follow-up, methods of weight assessment, validation of self-reported weight at baseline, update of adult weight change over follow-up, adjustment for potential confounders). As small number of studies precludes meaningful subgroup analyses, they were performed when the number of studies was greater than three. Potential for small study effects (37), such as publication bias, was tested using Egger's test (38). As Egger's test may be low powered, small study effects were not assessed if the number of studies was less than three.

Diverse sensitivity analyses, including the influence analysis, were performed to explore robustness of the findings. A secondary analysis was conducted based on non-dose-response meta-analysis that pooled RRs for the highest vs lowest category of adult weight gain, using the DerSimonian-Laird random effects model. For cancers with no eligible studies for dose-response meta-analyses, meta-analysis comparing highest vs lowest adult weight gain was considered as a primary analysis. This highest vs lowest meta-analysis allows for inclusion of studies providing insufficient information for dose-response meta-analysis, but has less interpretability and additional heterogeneity because of inconsistent exposure categories across studies.

For statistical significance, two-sided significance level was set at $\alpha = 0.05$. All statistical analyses were conducted using STATA 12 (StataCorp, College Station, TX).

Results

The results of the literature search and study selection are summarized in Figure 1. After screening 20 123 publications related to 10 adiposity-related cancers, a total of 46 publications (22–24,31,39–80) were included in this meta-analysis. For cancers of the gallbladder and esophagus, no studies met our inclusion criteria. Thus, this meta-analysis examined eight cancer sites (breast, prostate, colon, endometrium, ovary, pancreas, kidney, and thyroid) in relation to adult weight gain. Out of the eight cancer sites, dose-response meta-analyses could be performed only for six cancers (breast, prostate, colon, endometrium, ovary, and pancreas) including 32 studies (from 30 publication) (22–24,31,39–64); highest vs lowest meta-analyses were performed for all the eight cancers, including 18 additional studies (from 16 publications) (65–80). Characteristics of the included studies are provided in Supplementary Table 2 (available online).

Primary Analysis: Dose-Response Meta-Analysis

Breast Cancer

For postmenopausal BC, a total of 13 studies (23,24,31,39–48) were eligible for dose-response meta-analyses. Only five studies (24,45–48) provided results among non-HRT users. Yet, among the remaining eight studies (23,31,39–44), one study (23) stated that the results in mixed populations of HRT users and nonusers were not substantially different from the results in non-HRT users; one study (39) was conducted in Japan where the prevalence of HRT use was relatively low (approximately 10%). Thus, the two studies that contained HRT users were additionally included, leading to a total of seven studies (23,24,39,45–48) contributing to the primary dataset (4570 cases, range of midpoint of category-specific adult weight gain = 0–35 kg).

In the linear dose-response analysis, each 5 kg increase in adult weight gain was associated with an approximately 11% increased risk of postmenopausal BC among non-HRT users (RR = 1.11, 95% CI = 1.08 to 1.13, $I^2 = 21.7\%$, $P_{\text{heterogeneity}} = .26$) (Figure 2A). Several sensitivity analyses were performed: restricting the analysis to the five studies (24,45–48) conducted purely among non-HRT users did not change the results materially (Figure 2B); repeating the analysis in the dataset including all the 13 studies (23,24,31,39–48) showed consistent results, while heterogeneity increased substantially because of the combining of HRT users and nonusers (RR = 1.08, 95% CI = 1.06 to 1.10, $I^2 = 69.6\%$, $P_{\text{heterogeneity}} < .001$, $Q = 39.51$, $df = 12$) (data not shown). Consistent with a priori biological heterogeneity by HRT use, there was no evidence of a linear trend among ever-users of HRT (Figure 2B) and the heterogeneity was statistically significant ($P_{\text{heterogeneity}} = .001$). There was no evidence of nonlinear association ($P_{\text{nonlinearity}} = .53$) (Figure 2C).

For premenopausal BC, three studies (46,47,49) were included (2409 cases, range of midpoint of category-specific adult weight gain = 0–27.5 kg). There was no

evidence of a linear relationship (RR = 0.99, 95% CI = 0.95 to 1.03, $I^2 = 36.4\%$, $P_{\text{heterogeneity}} = .21$) (Figure 2A). The heterogeneity by menopausal status at BC diagnosis was statistically significant ($P_{\text{heterogeneity}} = .001$).

For both pre- and postmenopausal BC, small study effects, such as publication bias, were not indicated (PEgger = 0.75, 0.77, respectively); the results were robust to the influence of any single study included in sensitivity analyses omitting one study at a time.

Prostate Cancer

Four studies (50–53) were included in linear dose-response meta-analysis (6882 cases, range of midpoint of category-specific adult weight gain = 0–25 kg). There was no evidence of a linear association between adult weight gain and total PC (RR = 0.98, 95% CI = 0.94 to 1.02, $I^2 = 46.4\%$, $P_{\text{heterogeneity}} = .13$) (Figure 3A). To address the highly heterogeneous nature of PC, potential etiologic heterogeneity was explored. First, by stage of PC at diagnosis, the summary RR per 5 kg increase in adult weight gain was 0.96 (95% CI = 0.92 to 1.00, $I^2 = 37.7\%$, $P_{\text{heterogeneity}} = .19$) for localized PC and was 1.04 (95% CI = 0.99 to 1.09, $I^2 = 0.0\%$, $P_{\text{heterogeneity}} = .46$) for advanced PC (Figure 3B). No evidence of heterogeneity between localized and advanced PC was indicated ($P_{\text{heterogeneity}} = .13$). Second, indolent and clinically significant PCs were compared using a high prostate-specific antigen (PSA) screening rate of the country as a marker of indolent PC. Among studies (52,53) conducted in the United States where PSA screening rates are high, a statistically significant inverse relationship was observed (RR = 0.96, 95% CI = 0.92 to 0.99, $I^2 = 0.0\%$, $P_{\text{heterogeneity}} = .47$) (Figure 3C). In contrast, among studies (50,51) conducted in Europe where PSA screening rates are relatively low, there was no evidence of a linear association (RR = 1.01, 95% CI = 0.98 to 1.05, $I^2 = 0.0\%$, $P_{\text{heterogeneity}} = .93$) (Figure 3C). Yet, heterogeneity between indolent and clinically significant PCs was not statistically significant ($P_{\text{heterogeneity}} = .15$). Small study effects, such as publication bias, were not indicated (PEgger = .68). In sensitivity analyses omitting one study at a time, excluding the study by Bassett et al. (50) led to a statistically significant inverse relationship with total PC (RR = 0.96, 95% CI = 0.93–0.99, $I^2 = 0\%$, $P_{\text{heterogeneity}} = .16$, $Q = 0.87$, $df = 2$) (data not shown).

Colon Cancer

Four studies (22,54–56) were eligible for linear dose-response meta-analysis. Three studies (22,55,56) investigated colon cancer (CC) only, while the remaining one (54) examined both CC and CRC. Thus, this meta-analysis was confined to CC (2909 cases, range of midpoint of category-specific adult weight gain = 0–29kg).

Each 5 kg increase in adult weight gain was associated with an approximately 6% increased risk of CC (RR = 1.06, 95% CI = 1.03 to 1.10, $I^2 = 0.0\%$, $P_{\text{heterogeneity}} = .52$) (Figure 4). While there was no evidence of heterogeneity by sex ($P_{\text{heterogeneity}} = .17$),

the association was statistically significant only among men (RR = 1.09, 95% CI = 1.04 to 1.13, $I^2 = 0.0\%$, $P_{\text{heterogeneity}} = .76$) (Figure 4). Small study effects, such as publication bias, were not indicated (PEgger = .96). The results were robust to the influence of any single study included.

Postmenopausal Endometrial Cancer

Three studies (57–59) were eligible for linear dose-response meta-analysis, but one (59) of them investigated EC among a mixed population of pre- and postmenopausal women. Thus, the primary dataset consisted of two studies (57,58) conducted among postmenopausal women stratified by HRT use (285 cases, range of midpoint of category-specific adult weight gain = 2–28 kg).

Among no HRT users, each 5 kg increase in adult weight gain was associated with an approximately 39% increased risk of EC (RR = 1.39, 95% CI = 1.29 to 1.49) with no evidence of heterogeneity ($I^2 = 0.0\%$, $P_{\text{heterogeneity}} = .42$) (Figure 5). In a sensitivity analysis including all of the three studies, the results were consistent, albeit more heterogeneous (data not shown). Among HRT users, the linear association was markedly attenuated (RR = 1.09, 95% CI = 1.02 to 1.16, $I^2 = 0.0\%$, $P_{\text{heterogeneity}} = .96$) (Figure 5). Heterogeneity by HRT use was statistically significant ($P_{\text{heterogeneity}} = .04$).

Postmenopausal Ovarian Cancer

Three studies (60–62) were eligible for linear dose-response meta-analysis. One (60) of them included both pre- and post-menopausal women. The remaining two studies were conducted among women assumed to be mostly postmenopausal. While one (62) of the two studies did not stratify the population by HRT use, the prevalence of HRT use was relatively low (approximately 10%). Thus, the two studies conducted among postmenopausal women constituted the primary dataset (217 cases, range of midpoint of category-specific adult weight gain = 2–27 kg).

Among postmenopausal women of no/low HRT users, each 5 kg increase in adult weight gain was associated with an approximately 13% increased risk of OC (RR = 1.13, 95% CI = 1.03 to 1.23, $I^2 = 0.0\%$, $P_{\text{heterogeneity}} = .48$) (Figure 6). In a sensitivity analysis including all of the three studies, the results did not change materially (data not shown).

Pancreatic Cancer

Two studies (63,64) (324 cases, range of midpoint of category-specific adult weight gain = 1–16 kg) conducted in combined populations of men and women were included. While no evidence of a linear association between adult weight gain and PaC (RR = 1.05, 95% CI = 0.87 to 1.26) was indicated, moderate degree of

heterogeneity ($I^2 = 49.5\%$, $P_{\text{heterogeneity}} = .16$) (Figure 7) was indicated, precluding a definitive conclusion.

Secondary Analysis: Meta-Analysis Comparing Highest vs Lowest Adult Weight Gain

For cancers for which dose-response meta-analyses were performed, 13 studies (from 11 publications) were (65–75) additionally eligible for this highest vs lowest meta-analysis. For each cancer outcome, results were consistent across the primary and secondary meta-analyses; results from this analysis including only the studies used in dose-response meta-analysis were similar to those including all eligible studies, indicating the reasonable representativeness of the studies included in dose-response meta-analysis (Supplementary Table 3, available online).

Only highest vs lowest meta-analysis was available for cancers of the kidney (two studies [79,80]) and thyroid (three studies [76–78]). People with greater adult weight gain were associated with an increased risk of KC (RR = 1.42, 95% CI = 1.11 to 1.81, $I^2 = 9.3\%$, $P_{\text{heterogeneity}} = .33$) relative to those with less adult weight gain (Supplementary Table 3, available online). In contrast, there was no evidence of an association between adult weight gain and TC risk (RR = 1.06, 95% CI = 0.82 to 1.38, $I^2 = 0.0\%$, $P_{\text{heterogeneity}} = .42$) (Supplementary Table 3, available online). Small study effects, such as publication bias, were not indicated in the TC analysis (PEgger = .14).

Subgroup Analyses

Given the limited number of studies included in dose-response meta-analysis consistent results between the primary and secondary meta-analyses, subgroup analyses were performed based on highest vs lowest meta-analysis. There was no evidence of between-subgroup heterogeneity when stratified by variables concerning etiologic heterogeneity, effect modifiers, and methodological characteristics. (Supplementary Table 3, available online). For CC, a statistically significant direct association was observed more consistently among men than women.

Discussion

In this dose-response meta-analysis of prospective observational studies, each 5 kg increase in adult weight gain was related to a statistically significant increase in risk by 11% (up to 35 kg) for postmenopausal BC among HRT nonusers, by 39% and 9% (up to 28 kg) for postmenopausal EC among HRT nonusers and users, respectively, by 13% (up to 27 kg) for postmenopausal OC among no/low HRT users. In contrast, no evidence of a linear relationship was indicated with the risk of postmenopausal BC among HRT users, and for premenopausal BC. Of note, the heterogeneity

between pre- and postmenopausal BC was statistically significant; among postmenopausal women, the direct linear association with BC and EC was statistically significantly stronger among HRT nonusers than among HRT users. For PC of all types (total, advanced, localized), no strong evidence of a linear relationship was indicated. For obesity-related cancers affecting both sexes (ie, CC, PaC, KC, TC), a statistically significant direct association was found only for CC and KC, with each 5 kg increase in adult weight gain elevating CC risk by 6% (up to 29 kg). While heterogeneity by sex was not statistically significant, the association with CC was statistically significant only among men.

The biological mechanism by which excess adiposity affects the risk of these cancers may involve estrogens, insulin, and bioavailable IGF-I (81). Excess adiposity, particularly abdominal adiposity, results in hormonal and metabolic perturbations by producing estrogen (estrone) through the aromatization of androgen (androstenedione) and inducing insulin resistance, the resulting hyperinsulinemia of which suppresses hepatic production of hormonal binding proteins (eg, SHBG, IGFBP) (26). Thus, the net consequences of excess adiposity are increased circulating concentrations of total/bioavailable estrogens, insulin, and bioavailable IGF-I (26). While insulin and bioavailable IGF-1 promote carcinogenesis by enhancing proliferation of the tissues and inhibiting apoptosis, the proliferative effect of estrogens is tissue-specific (eg, estrogens generally increase the risk of cancers, but protects against CRC among women [82,83]).

To date, for these obesity-related cancers, a meta-analysis based on adult weight gain has been published only for BC outcome, which showed an increased risk of postmenopausal BC associated with a greater adult weight gain (84). Of note, the study pooled studies by estrogen and progesterone receptor (ER, PR) status and found that the association was more pronounced for ER+PR+ than ER-PR- subtype ($P_{\text{heterogeneity}} < .001$). While such incorporation of the receptor status provided mechanistic evidence to support the mediating role of estrogens, only three cohort studies (46,48,85) were eligible for the meta-analysis. Further, as the study pooled relative risks for the highest vs lowest categories of adult weight gain, it could determine only the direction of the relationship but not quantify the level of exposure to which this applied. Our meta-analysis could not perform a stratified analysis by the receptor status because of insufficient data, but incorporated four additional studies (23,39,46,47) with 3638 more cases and specifically quantified that each 5 kg increase in adult weight gain was related to an approximately 11% increased risk of postmenopausal BC.

In contrast to the paucity of meta-analyses on adult weight gain, extensive linear dose-response meta-analyses have been conducted on BMI in relation to obesity-related cancers (5–12,14). For cancers of the breast, endometrium, and ovary, the results based on adult weight gain vs BMI have been qualitatively similar. However, relative to BMI that does not distinguish fat mass from lean body mass or apple- from pear-shaped body, adult weight gain better reflecting amount and distribution of

adiposity appears to be a more sensitive predictor of disease risk. For example, for a woman with an average height (eg, 160 cm), each 5kg/m² increase in BMI converts to about 13 kg of weight gain. Thus, the BMI-based dose-response meta-analyses were equivalent to suggesting an increase in risk by 4%, 28%, and 4%, per 5 kg of weight gain for postmenopausal BC, EC among HRT nonusers, and OC among HRT nonusers, respectively (6,9,14). The risk was substantially underestimated in light of our meta-analysis that found a corresponding 11%, 39%, 13% increased risk. Of note, two studies (31,48) included in our BC meta-analysis reported how mutual adjustments of adult weight gain and current BMI affect each other in predicting postmenopausal BC risk. Both found that a statistically significant linear trend persisted for adult weight gain but not for BMI when those variables were modeled simultaneously, suggesting that adult weight gain might confer risk above and beyond attained adiposity. Altogether, the better predictability of adult weight gain compared with BMI suggests that excess adiposity may exert a continuous and cumulative influence on carcinogenesis throughout adulthood.

For BC and EC, particularly noteworthy is the observed heterogeneity by menopausal status and HRT use, as it hints at relative contributions of estrogens, progesterone, insulin, and IGF-1 in mediating the association. During the postmenopausal period, estrogens appear to be a dominant driver, as indicated by the heterogeneity by HRT use. In the absence of excess estrogens from the ovaries and HRT, variation in estrogen levels because of difference in the amount of adipocytes may be sufficient enough to differentiate the risk of those cancers. In contrast, for HRT users, in light of evidence that HRT use itself has been shown to be an independent risk factor for BC (27,86), exogenous estrogens from HRT may raise plasma estrogens to the extent that endogenous estrogens from adipocytes have little incremental effect (59). Furthermore, progesterone included in HRT may oppose the proliferative effect of endogenous estrogens, particularly for EC (59). Thus, if estrogens are the major mediator, modulation of cancer risk through adipose-induced estrogens is unlikely among HRT users, which was the case for BC. Of note, for EC, the adverse influence of adult weight gain was much weaker among HRT users, but still statistically significant. While the residual association could be because of biases such as confounding, if real, it suggests that estrogens may be the main contributing factor, but insulin and bioavailable IGF-I may play a role in mediating excess adiposity and EC risk among postmenopausal women.

With regard to the heterogeneity by menopausal status in BC analysis, the null finding for premenopausal BC can be explained by several biological mechanisms. In the premenopausal period when the ovaries are a predominant site of estrogen synthesis, additional contribution of adipocytes to the circulating pool of estrogens (ie, estrone, estradiol, estriol) may be negligible. Not only is the amount of estrogens from adipocytes far smaller, but also the form of estrogens (ie, estrone rather than estradiol) is less biologically potent (87). Furthermore, evidence suggests that there are menopause-related changes in fat distribution in such that fats are redistributed toward the abdominal region with a preferential increase in visceral fat after

menopause (88). As the hormonal and metabolic perturbations are induced particularly by abdominal adiposity (26), the adverse effect of adult weight gain on BC may be much weaker during the premenopausal period than the postmenopausal period. While some studies have observed lower circulating estrogen concentrations among heavier premenopausal women and attributed the observation to greater sequestering of estrogens to adipocytes, higher clearance by the liver and other tissues, or ovulatory insufficiency resulting in compromised estrogen production (89,90), evidence has not been consistent.

For CC, our results suggested that adult weight gain may be more deleterious for men than women, though the number of studies was small and the heterogeneity was not statistically significant. Meta-analyses of BMI also reported a substantially stronger association in men than in women (5,6). Several bio-logical mechanisms may explain this sex difference. First, an adipose-induced increase in insulin and bioavailable IGF-1 is mostly attributable to abdominal adiposity (particularly visceral fat) (26,91), and men accumulate proportionally more visceral fat than women (25). Second, evidence supports a protective effect of exogenous (82) and endogenous (92) estrogens against CRC among women. Thus, for women with a great adult weight gain, an increase in CC risk because of increased levels of insulin and bioavailable IGF-1 may be counterbalanced by protection conferred by increased concentrations of circulating estrogens; in men, obesity is associated with high estrogens but also lower testosterone, which may increase the risk of CC (92).

For PC, our null finding is inconsistent with a meta-analysis of BMI and PC that found an inverse association with localized PC and a direct association with advanced PC (7). This apparent discrepancy may reflect the relevance of early body size (rather than adult weight gain) or lean body mass, and unidentified methodological factors. However, as both analyses were consistent in the direction of the association with localized and advanced PC, the limited number of studies might have led to our null findings for PC. While differences in the underlying biological mechanisms for localized vs advanced PC remain elusive, testosterone may play a role. Excess adiposity among men is associated with lower circulating concentrations of testosterone (93), which has been hypothesized to be associated with a decreased risk of localized PC but with an increased risk of advanced PC (94). An alternative explanation relates to detection bias. That is, obese men have lower PSA levels and larger prostates that make it difficult to detect PC at an early stage, which in turn gives an opportunity for PC to progress to an aggressive stage (95).

For cancers of the pancreas, kidney, and thyroid, a statistically significant association with adult weight gain was found only for KC, while previous meta- and pooled-analyses of BMI and these cancer sites reported a positive association (10–12,15). In light of a recent finding from the Health Professionals Follow-up Study suggesting BMI at age 21 was more important than adult weight gain since age 21 for a composite outcome including colorectal, pancreatic, renal, and esophagus

cancers (96), the lack of an association with PaC and TC in our meta-analysis could be because of the inability of adult weight gain to capture early adiposity. However, the observed inconsistency appears to be more related to methodological issues. Our analysis on PaC included only two studies reporting conflicting directions of the relationship and thus, was rather inconclusive. In particular, given that the meta-analysis of BMI and PaC found no association among ever-smokers and that the two studies included in our meta-analysis were not analyzed exclusively among never-smokers, residual confounding by smoking may have driven our null finding. Alternatively, adult weight gain may not be a strong enough risk factor to manifest its effect in the presence of the predominant risk factor such as smoking. For TC, a small number of cases in our meta-analysis (<437 vs 1156 cases in the pooled analysis [15]) may partially explain the inconsistency.

This meta-analysis has several limitations. All meta-analyses of observational studies are liable to the same potential biases as the observational studies are. Measurement error in adult weight gain is particularly concerning, as dose-response meta-analyses incorporate absolute values of adult weight gain rather than ranking of it. First, within most studies, adult weight gain was calculated based on recalled past weight and self-reported current weight. Weight tends to be underreported, with the extent of underestimation greater among women than men, in recalled past weight than in self-reported current weight and with increasing current weight (97–100). As a result, the observed range of adult weight gain within each study would have been artificially wider than the true range, especially in studies with a large number of heavy women, which would have attenuated the summary relative risk from dose-response meta-analysis. Yet, as subjects who underreport current weight are also likely to underreport past weight, some measurement error in each weight would have been offset upon calculating adult weight change. Second, dose-response meta-analysis itself introduces additional measurement error, as it requires assumptions such as approximating the width of the open-ended highest category from the adjacent interval and assigning the midpoint of each category of adult weight gain to corresponding relative risk. All of the inevitable measurement error arising from diverse sources could bias the results in either direction, but is generally expected to attenuate the true effect (101), particularly because the prospective assessment of adult weight gain relative to cancer outcome is likely to make the error random with respect to disease status. Furthermore, validation studies have shown that recalled past weight and self-reported current weight were reasonably correlated with measured weight, with correlation coefficients approximately greater than 0.70 and less than 0.90 (98,99,102), respectively, suggesting a reasonable accuracy of relative risk for the highest vs lowest category of adult weight gain within each study. Thus, consistency in the direction and statistical significance of the summary relative risks between dose-response and highest vs lowest meta-analyses alleviates the concern regarding measurement error to some degree.

Additionally, studies were inconsistent in their adjustments for anthropometric measures, which affects interpretation of adult weight change. Yet, subgroup

analyses showed no evidence of heterogeneity by adjustments for height and weight or BMI at different life stages, suggesting that the effect of weight gain throughout adulthood may be consistent regardless of height and adiposity at different life stages. Although we did not find any evidence of publication bias, there were a limited number of studies in several of the analyses. The other limitations relate to inability of the meta-analysis to address issues that were not addressed within each study included. First, adult weight change was defined over different time spans across individuals, mainly because participants entered studies at different ages. While subgroup analysis by mean age at study baseline showed no evidence of between-group heterogeneity, if every study included had analyzed adult weight gain in terms of kg per year(s) accounting for differential time intervals, dose-response meta-analysis based on such unit may have provided a more specific estimate. Second, we could not address if the timing of adult weight gain has an independent effect on the cancer risk. Emerging evidence suggests that, among non-HRT users, weight gain in later premenopausal period had a stronger influence on postmenopausal BC than weight gain in peri- or postmenopausal period (24,48).

Our meta-analysis has several strengths as well. To our knowledge, this is the first analysis that identified the shape of the dose-response relationship between adult weight gain and obesity-related cancers. As meta-analysis combines multiple studies, such evaluation was made over a wider range of adult weight gain and with increased power than a single study. In particular, our meta-analysis was more robust against the influence of confounding. As weight tends to track over time, studies based on a cross-sectional measure of adiposity at a point in time are susceptible to confounding by adiposity at earlier time windows. However, as adult weight gain is a measure of time-integrated weight trajectory, studies included in our analysis virtually controlled for past adiposity. Little evidence of heterogeneity, especially for postmenopausal BC among non-HRT users, postmenopausal EC, postmenopausal OC, and CC, enhances the generalizability of our findings.

In conclusion, while overweight and obese individuals are recommended to lose weight for other health benefits, our findings suggest that avoiding further weight gain throughout adulthood itself may confer protection against postmenopausal BC, EC, and OC, as well as CC and KC. For postmenopausal BC and EC, as less women are taking HRT nowadays, our finding of a markedly stronger association among HRT nonusers is particularly alarming. Given that adults gain weight at a rate of about 0.5 kg/year across all BMI categories (16) and that the prevalence of smoking is decreasing, our finding suggests that obesity may become the number one preventable cause of cancer, particularly among women. Weight gain happens gradually and insidiously throughout adulthood (103) and our finding of the linearity of the relationship implies that even a small weight gain could increase one's risk of cancer. Thus, individuals across all weight categories are recommended to stay attentive to small changes in weight throughout life. Both physiologically and psychologically, prevention of weight gain is more feasible than losing weight and maintaining the weight loss. Clinicians and public health policies may prioritize the

goal of avoiding further weight gain for the prevention of these cancers. As physical activity is more effective in preventing weight gain than in inducing weight loss (18), incorporation of physical activity into daily routines should be emphasized. Future studies are warranted to examine if the rate or timing of adult weight gain has an effect on cancer risk, independent of the amount of weight gain.

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Figures

Figure 1. Flowchart for study selection. *Number of publications does not match number of studies, because one publication (Jonsson et al., 2003) contributed data to PC, EC, and OC (one publication but three studies); two publications (Palmer et al., 2007, Lahmann et al., 2005) contributed data to both pre- and postmenopausal BC (two publications but four studies). BC = breast cancer; BMI = body mass index; CrC = colorectal cancer; EC = endometrial cancer; EsC = esophageal cancer; GC = gallbladder cancer; HRT = hormone replacement therapy; KC = kidney cancer; OC = ovarian cancer; PaC = pancreatic cancer; PC = prostate cancer; TC = thyroid cancer.

Figure 2. Dose-response relationship between adult weight gain and breast cancer risk. The black squares and horizontal lines represent study-specific relative risks and their 95% confidence intervals. The area of each black square reflects the weight each study contributes to the meta-analysis. The middle and horizontal tips of diamonds represent summary RRs and their 95% confidence intervals, respectively. The P values were calculated from Cochran's Q test; all statistical tests were two-sided. (Heterogeneity Q statistic, degree of freedom): A) (7.66, 6) for postmenopausal women; (3.15, 2) for premenopausal women. B) (6.50, 4) for non-hormone replacement therapy (HRT) users; (2.76, 3) for HRT users. CI = confidence interval; HRT = hormone replacement therapy; RR = relative risk.

Figure 3. Dose-response relationship between adult weight gain and prostate cancer risk. The black squares and horizontal lines represent study-specific risk ratios (RRs) and their 95% confidence intervals. The area of each black square reflects the weight each study contributes to the meta-analysis. The middle and horizontal tips of diamonds represent summary relative risks and their 95% confidence intervals, respectively. The P values were calculated from Cochran's Q test; all statistical tests were two-sided. (Heterogeneity Q statistic, degree of freedom): A) (5.60, 3). B) (4.82, 3) for localized prostate cancer; (2.57, 3) for advanced prostate cancer. C) (0.01, 1) for low PSA screening rate; (0.53, 1) for high PSA screening rate. CI = confidence interval; PSA = prostate-specific antigen; RR = relative risk.

Figure 4. Dose-response relationship between adult weight gain and colon cancer risk. The black squares and horizontal lines represent study-specific relative risks (RRs) and their 95% confidence intervals (CIs). The area of each black square reflects the weight each study contributes to the meta-analysis. The middle and horizontal tips of diamonds represent summary RRs and their 95% CIs, respectively. The P values were calculated from Cochran's Q test; all statistical tests were two-sided. (Heterogeneity Q statistic, degree of freedom): (1.39, 2) for women; (1.18, 3) for men; (5.19, 6) for overall. CI = confidence interval; RR = relative risk.

Figure 5. Dose-response relationship between adult weight gain and postmenopausal endometrial cancer risk. The black squares and horizontal lines

represent study-specific relative risks (RRs) and their 95% confidence intervals (CIs). The area of each black square reflects the weight each study contributes to the meta-analysis. The middle and horizontal tips of diamonds represent summary RRs and their 95% CIs, respectively. The P values were calculated from Cochran's Q test; all statistical tests were two-sided. (Heterogeneity Q statistic, degree of freedom): (0.64, 1) for no hormone replacement therapy (HRT) users; (0, 1) for HRT users. CI = confidence interval; HRT = hormone replacement therapy; RR = relative risk.

Figure 6. Dose-response relationship between adult weight gain and postmenopausal ovarian cancer risk. The black squares and horizontal lines represent study-specific relative risks (RRs) and their 95% confidence intervals (CIs). The area of each black square reflects the weight each study contributes to the meta-analysis. The middle and horizontal tips of the diamond represent the summary RR and its 95% CI, respectively. The P value was calculated from Cochran's Q test; the statistical test was two-sided. (Heterogeneity Q statistic, degree of freedom): (0.51, 1). CI = confidence interval; RR = relative risk.

Figure 7. Dose-response relationship between adult weight gain and pancreatic cancer risk. The black squares and horizontal lines represent study-specific relative risks (RRs) and their 95% confidence intervals (CIs). The area of each black square reflects the weight each study contributes to the meta-analysis. The middle and horizontal tips of the diamond represent the summary RR and its 95% CI, respectively. The P value was calculated from Cochran's Q test; the statistical test was two-sided. (Heterogeneity Q statistic, degree of freedom): (1.98, 1). CI = confidence interval; RR = relative risk.

Figure 1.

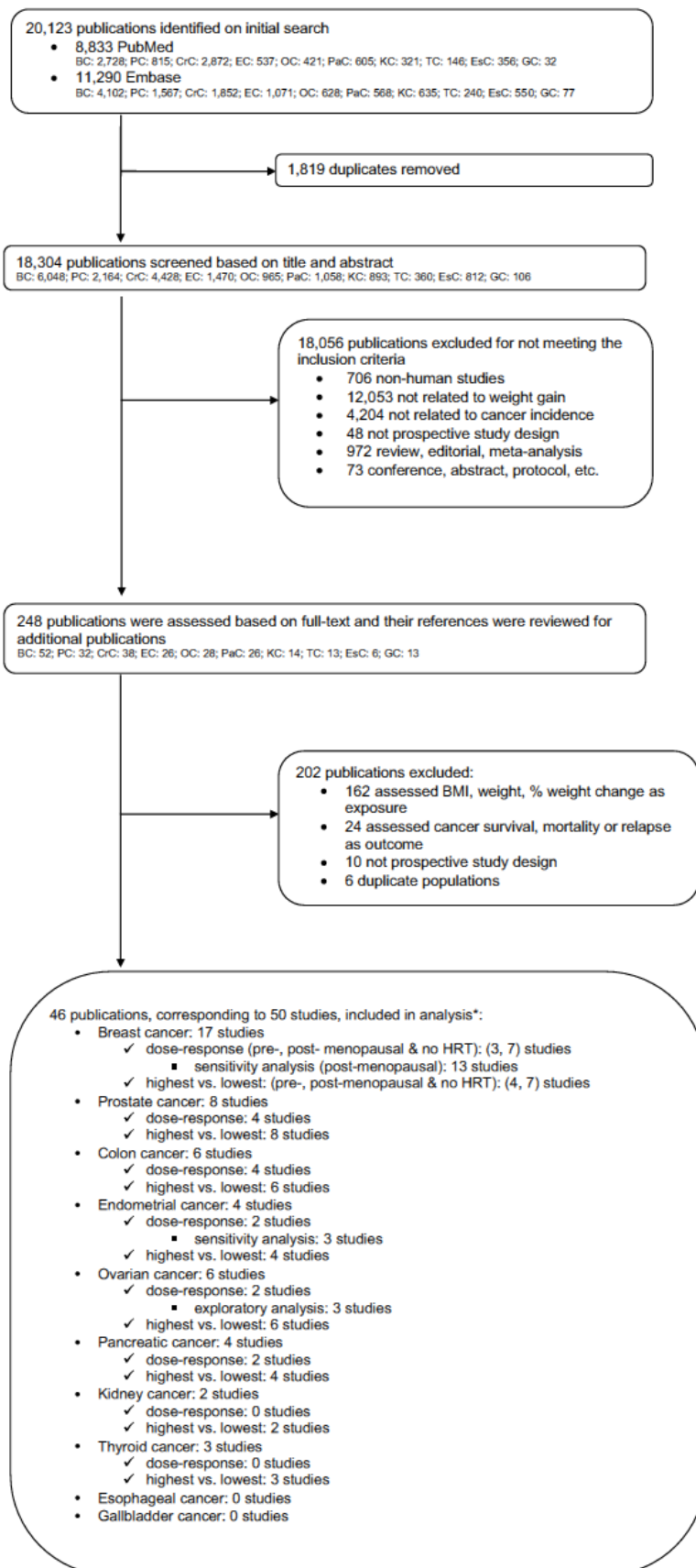


Figure 2.

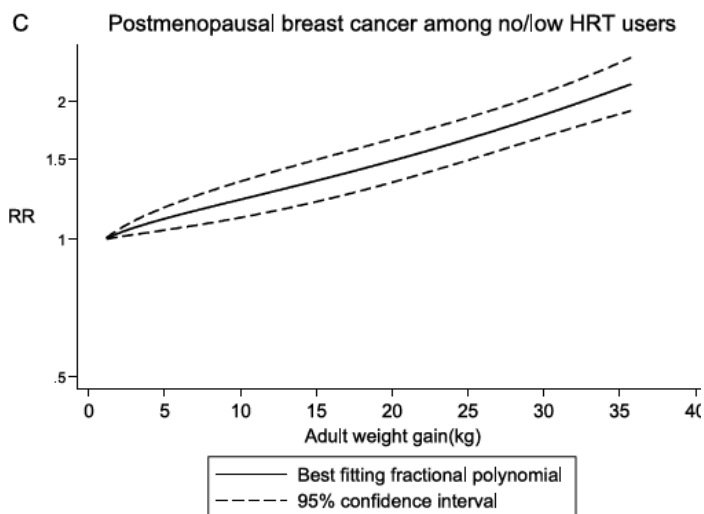
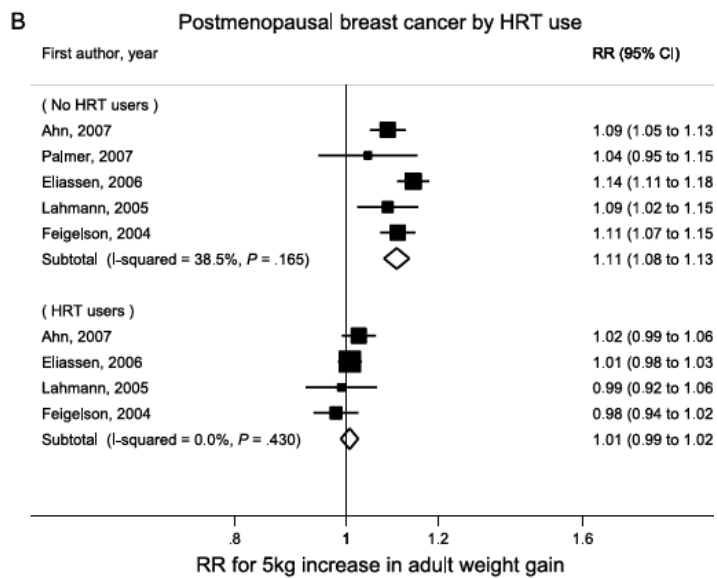
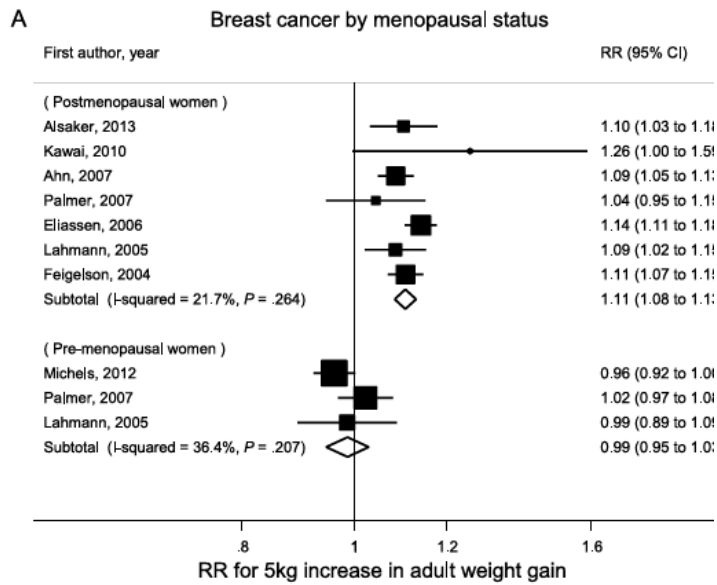


Figure 3.

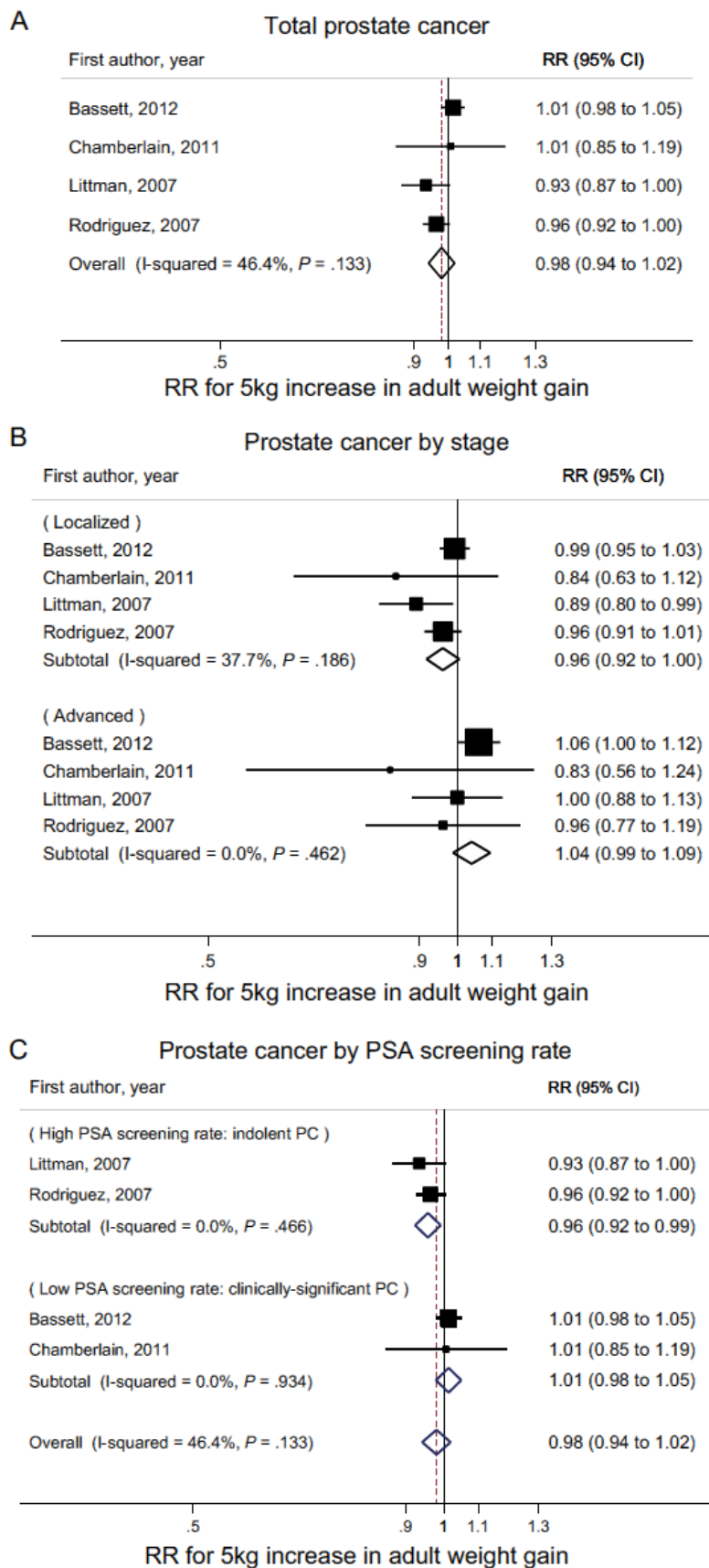


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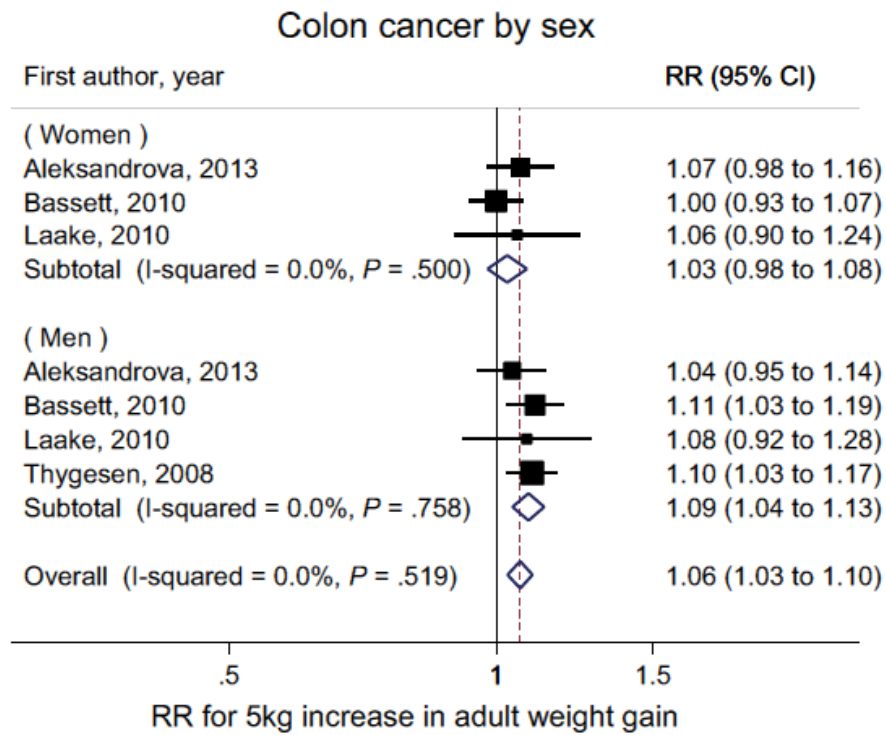


Figure 5.

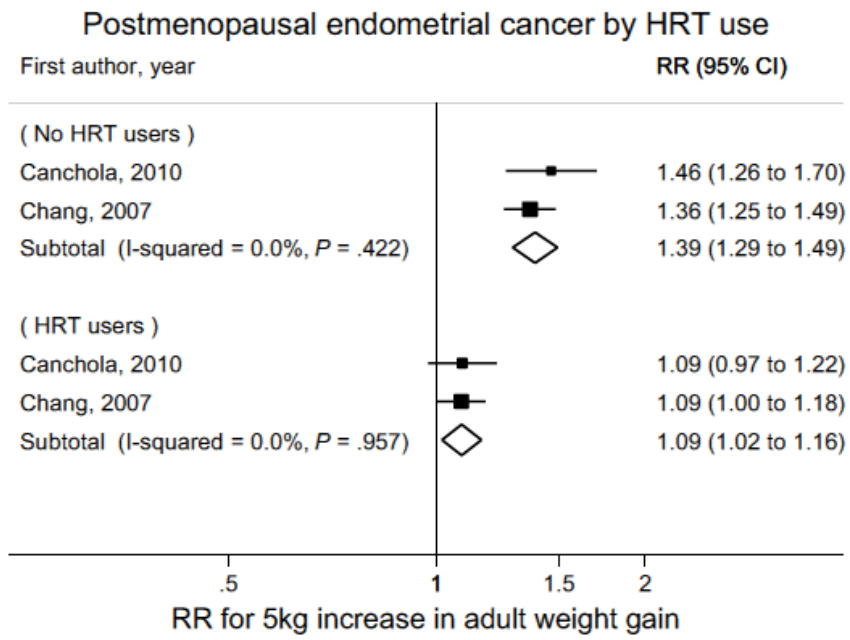


Figure 6.

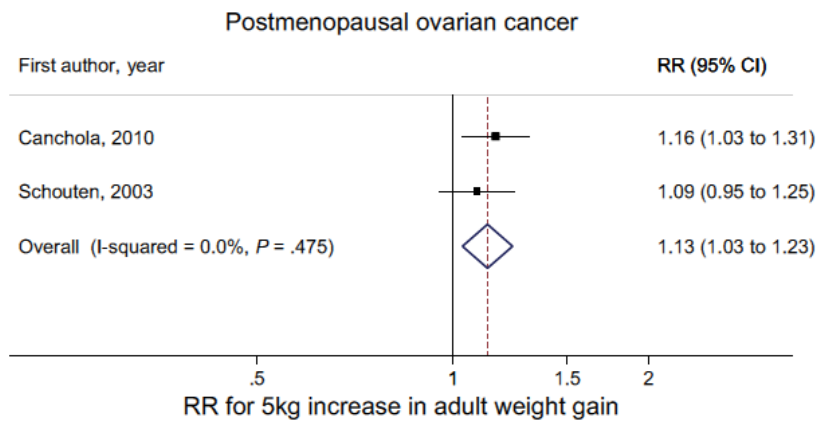


Figure 7.

