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Obesity, Central Adiposity, and Carcinogenesis: A Secondary Data Analysis of Cohort, Meta-Analytic, and Mendelian Randomization Evidence

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ABSTRACT

Background: Obesity is a growing global epidemic and an established determinant of several malignancies. While general adiposity measured by body mass index (BMI) is widely studied, emerging evidence highlights the independent role of central adiposity in carcinogenesis.

Methods: We conducted a secondary analysis of published large-scale cohort studies, systematic reviews, meta-analyses, and Mendelian randomization (MR) reports. Data were harmonized across studies, and effect estimates were synthesized for BMI, waist circumference (WC), and waist–hip ratio (WHR) in relation to incident cancers. Results were summarized in tables and visualized using forest plots, spline dose–response curves, central adiposity comparisons, population attributable fractions (PAFs), and MR scatter plots.

Results: Elevated BMI was consistently associated with increased risk of endometrial (HR ~1.58), kidney (HR ~1.22), liver (HR ~1.17), gallbladder (HR ~1.28), and colorectal cancer (HR ~1.11). Weaker but significant associations were observed for ovarian and postmenopausal breast cancer, whereas premenopausal breast cancer showed an inverse association. Central adiposity, measured by WC and WHR, predicted cancer risk beyond BMI, particularly for colorectal and postmenopausal breast cancers. Subgroup analyses revealed stronger associations in men for colorectal and liver cancer, and in postmenopausal women for breast cancer. Sensitivity analyses excluding early follow-up, smokers, and diabetic participants confirmed robustness of findings. PAFs suggested that obesity may account for ~35% of endometrial cancers and 6–12% of colorectal, kidney, liver, and breast cancers. MR analyses demonstrated that genetically proxied adiposity increases colorectal and endometrial cancer risk, supporting a causal relationship.

Conclusion: This secondary data synthesis confirms that both general and central adiposity are causally associated with elevated cancer risk, with sex- and site-specific heterogeneity. Obesity prevention and waist circumference reduction represent critical strategies for reducing the global cancer burden.

KEYWORDS: Obesity; Carcinogenesis; Body mass index (BMI); Central adiposity; Waist circumference; Waist–hip ratio; Endometrial cancer; Colorectal cancer; Mendelian randomization; Secondary data analysis.

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INTRODUCTION

Obesity has emerged as one of the most pressing public health challenges of the 21st century, with global prevalence nearly tripling since 1975. According to the World Health Organization, more than 1.9 billion adults worldwide are overweight, of whom over 650 million are classified as obese (1). This escalating epidemic has been linked not only to cardiometabolic disorders but also to an increased risk of multiple malignancies, positioning obesity as a critical determinant of cancer burden globally (2). Epidemiological evidence consistently demonstrates that excess adiposity elevates the incidence of several cancers, including endometrial, colorectal, kidney, liver, gallbladder, pancreatic, and postmenopausal breast cancers (3,4). Large-scale prospective cohort studies, such as the UK Biobank and the American Cancer Society's Cancer Prevention Study, have provided robust quantification of these risks, reporting dose-dependent increases in cancer incidence with rising body mass index (BMI) (5,6). Importantly, meta-analyses confirm these associations across diverse populations, underscoring their consistency and public health relevance (7,8). Notably, the relationship between obesity and cancer is heterogeneous. For example, postmenopausal breast and endometrial cancers show strong positive associations, while premenopausal breast cancer often exhibits an inverse relationship with BMI (9,10). Furthermore, accumulating evidence highlights the importance of fat distribution, with central adiposity—measured by waist circumference and waist–hip ratio—emerging as a stronger predictor of cancer risk than BMI alone, particularly for colorectal and breast cancers (11,12). Biological plausibility is supported by mechanistic studies showing that excess adiposity alters insulin and IGF-1 signaling, promotes chronic inflammation, and increases estrogen and androgen levels through aromatization in adipose tissue, thereby fostering a pro-tumorigenic environment (13,14). Collectively, these

findings suggest that obesity represents a preventable cause of cancer, and that interventions targeting both general and central adiposity may substantially reduce cancer incidence.

METHOD

Study Design

This research was conducted as a secondary data analysis, drawing upon previously published epidemiological and genetic studies that examined the relationship between obesity and cancer. The design allowed us to integrate findings from large-scale population cohorts, systematic reviews, meta-analyses, and Mendelian randomization studies. No new data were collected; instead, we harmonized and synthesized existing effect estimates to provide a comprehensive overview of how adiposity contributes to carcinogenesis.

Data Sources and Eligibility

Relevant studies were identified through a focused review of peer-reviewed literature in high-impact journals, including *The Lancet*, *New England Journal of Medicine*, *JAMA Oncology*, and the *International Journal of Cancer*. To ensure consistency and reliability, we restricted inclusion to large prospective cohort studies, pooled meta-analyses, and Mendelian randomization analyses that reported adjusted risk estimates for obesity measures and incident cancers. Eligible outcomes were based on the International Agency for Research on Cancer (IARC) list of 13 obesity-related cancers, which includes endometrium, gallbladder, kidney, liver, colorectum, ovary, postmenopausal breast, pancreas, esophageal adenocarcinoma, gastric cardia, thyroid, meningioma, and multiple myeloma.

Variables and Outcomes

The primary exposure was general adiposity, measured using body mass index (BMI) and reported per +5 kg/m² increments. Central adiposity was captured through waist circumference (per +10 cm) and waist–hip ratio (per +0.1). Cancer incidence at specific sites served as the main outcome of interest, while subgroup analyses explored heterogeneity by sex, menopausal status, smoking behavior, and metabolic comorbidities such as diabetes. Mortality outcomes were considered in sensitivity analyses where available.

Data Extraction and Assembly

From each eligible source, we extracted hazard ratios or relative risks with corresponding 95% confidence intervals, along with units of exposure and subgroup-specific results. Where possible, we prioritized fully adjusted models accounting for key confounders such as age, sex, smoking, alcohol consumption, physical activity, diet quality, and diabetes. The assembled results were structured into summary tables: baseline characteristics (Table 1), site-specific associations with BMI (Table 2), effects of central adiposity independent of BMI (Table 3), subgroup interactions (Table 4), and sensitivity analyses (Table 5). Graphical outputs included a multi-panel figure displaying a forest plot, dose–response spline, central adiposity comparisons, population attributable fractions, and Mendelian randomization scatter plots (Figures A–E).

Statistical Approach

Although no new individual-level statistical models were conducted, a consistent analytical framework was applied to harmonize and interpret secondary data. Reported estimates were converted to common scales (e.g., per +5 kg/m² BMI). Forest plots were used to compare site-specific risks, and spline curves illustrated non-linear dose–response trends. Central adiposity was examined by comparing waist and hip measures against BMI in mutually adjusted models. Sensitivity analyses—including exclusion of early follow-up, restriction to never-smokers, and removal of participants with diabetes—were summarized from published sources to assess robustness. To test causality, we highlighted results from Mendelian randomization studies, plotting SNP–exposure versus SNP–outcome effects. Finally, population attributable fractions were either reported directly or estimated using established methods.

Ethical Considerations

This study is based exclusively on published secondary data. All primary studies had obtained ethics approval in their respective jurisdictions. Therefore, additional ethical approval or informed consent was not required for this secondary synthesis.

RESULTS

Baseline Characteristics

Baseline participant characteristics are summarized in Table 1. Individuals with normal BMI (18.5–24.9 kg/m²) tended to be younger on average (56.2 years) and were more frequently female (67.2%) compared to those in overweight (25.0–29.9 kg/m²) and obese (≥30.0 kg/m²) categories, where male prevalence was higher. Lifestyle differences were also evident: participants with obesity were less likely to be never-smokers (50.1% vs. 58.5% in normal BMI) and less likely to be physically active (58.5% vs. 72.5%). Healthy diet adherence showed a similar gradient, declining from 66.5% in the normal BMI group to 57.5% among those with obesity.

Table 1: Baseline Characteristics

Characteristic	Normal (18.5–24.9)	Overweight (25.0–29.9)	Obesity (≥30.0)
Age, years (mean)	56.2	57.5	57.3
Female, %	67.2	48.1	54.5
Male, %	32.8	51.9	45.5
Never smoking, %	58.5	53	50.1
Physically active, %	72.5	68.9	58.5
Healthy diet, %	66.5	61.8	57.5

(Pivot table summarizes the mean age and percentage of participants by their BMI category of collected cohort)

Associations Between BMI and Site-Specific Cancer Risks

The multivariable-adjusted associations between BMI and incident cancers are presented in Table 2 and illustrated in Figure A (forest plot). BMI showed strong positive associations with endometrial (HR 1.58, 95% CI 1.52–1.65), gallbladder (HR 1.28, 95% CI 1.10–1.49), kidney (HR 1.22, 95% CI 1.15–1.29), and liver cancer (HR 1.17, 95% CI 1.10–1.25). More modest but statistically significant increases were observed for colon (HR 1.11, 95% CI 1.08–1.14), ovary (HR 1.08, 95% CI 1.03–1.13), and postmenopausal breast cancer (HR 1.06, 95% CI 1.04–1.08). Conversely, premenopausal breast cancer demonstrated an inverse association (HR 0.90, 95% CI 0.87–0.93). These findings confirm that excess adiposity is linked to increased risk for multiple cancer sites, while highlighting heterogeneity by site.

Table 2: Association of BMI with Incident Cancers

Cancer Site	Model 2 HR (95% CI)	Notes
Endometrium	1.58 (1.52–1.65)	Strong positive association
Gallbladder	1.28 (1.10–1.49)	Positive association
Kidney (RCC)	1.22 (1.15–1.29)	Positive association
Liver	1.17 (1.10–1.25)	Positive association
Colon	1.11 (1.08–1.14)	Positive association
Ovary	1.08 (1.03–1.13)	Weak positive association
Postmenopausal breast	1.06 (1.04–1.08)	Weak positive association
Premenopausal breast	0.90 (0.87–0.93)	Inverse association

Central Adiposity and Independent Effects

Central adiposity measures were evaluated in Table 3 and visualized in Figure C. Waist circumference and WHR were both independently associated with cancer risk, even after adjusting for BMI. For the composite of 13 obesity-related cancers, waist circumference showed an exposure-only HR of 1.15, attenuating slightly to 1.09 after BMI adjustment. WHR demonstrated stronger effects (exposure-only HR 1.22; mutually adjusted HR 1.14). Site-specific analyses revealed particularly robust associations for colorectal cancer in men (WC HR 1.35, WHR HR 1.45), with more moderate but still significant associations in women (WC HR 1.18, WHR HR 1.20). Postmenopausal breast, endometrial, kidney, and liver cancers also remained significantly associated with waist circumference even after BMI adjustment. These results highlight the contribution of visceral adiposity beyond overall body size.

Table 3: Central Adiposity and Cancer Risk

Cancer Site	Exposure	Exposure-only HR	Mutually adjusted HR (with BMI)
Composite (13 cancers)	Waist circumference	1.15	1.09
	Waist–hip ratio	1.22	1.14
Colorectum (Men)	Waist circumference	1.35	Attenuated
	Waist–hip ratio	1.45	Still significant
Postmenopausal breast	Waist circumference	1.2	1.11
Endometrium	Waist circumference	1.21	1.16
Kidney (RCC)	Waist circumference	1.17	1.13
Liver (HCC)	Waist circumference	1.16	1.11

Subgroup and Interaction Analyses

Subgroup analyses (**Table 4**) demonstrated important effect modifiers. For colorectal cancer, the association with BMI was stronger in men (HR 1.32, 95% CI 1.27–1.37) compared to women (HR 1.15, 95% CI 1.10–1.21). Postmenopausal breast cancer showed a positive association with BMI (HR 1.19, 95% CI 1.10–1.26), whereas no significant increase was observed for premenopausal women (HR 0.92, 95% CI 0.78–1.09). Liver cancer risk was elevated in both sexes but was stronger in men (HR 2.10, 95% CI 1.75–2.51) than women (HR 1.59, 95% CI 1.40–1.81). Smoking status also modified associations for the composite

cancer endpoint, with stronger effects observed among current smokers (HR 1.14) compared to never-smokers (HR 1.06).

Table 4: Subgroup Analyses

Cancer Site	Stratum (by Modifier)	HR (95% CI)
Colorectum	Men (BMI)	1.32 (1.27–1.37)
	Women (BMI)	1.15 (1.10–1.21)
	Men (WC)	1.35 (1.21–1.51)
	Women (WC)	1.18 (1.11–1.25)
Breast cancer	Postmenopausal	1.19 (1.10–1.26)†
	Premenopausal	0.92 (0.78–1.09)
Liver (HCC)	Men	2.10 (1.75–2.51)
	Women	1.59 (1.40–1.81)
Composite (13 sites)	Never-smokers	1.06 (1.04–1.08)
	Current smokers	1.14 (1.11–1.17)

Sensitivity Analyses

Sensitivity checks are summarized in Table 5. Excluding the first two years of follow-up to minimize reverse causation only modestly attenuated associations for the composite endpoint (HR 1.08, 95% CI 1.06–1.10) and colorectal cancer (HR 1.11, 95% CI 1.08–1.14). Restriction to never-smokers yielded similar results, supporting robustness to smoking confounding. Excluding participants with baseline diabetes also had minimal impact (composite HR 1.09, 95% CI 1.07–1.11). For postmenopausal breast cancer, restricting analyses to HRT users still demonstrated a positive association (HR 1.08, 95% CI 1.06–1.10). Collectively, these findings underscore the stability of the observed associations across different sensitivity frameworks. (Table 5)

Table 5: Sensitivity Analyses

Cancer Site	Analysis	HR (95% CI)	Notes
Composite (13 sites)	Exclude first 2 years (lag)	1.08 (1.06–1.10)	Removes reverse-causation bias
	Never-smokers only	1.07 (1.05–1.09)	Smoking confounding check
	Exclude baseline diabetes	1.09 (1.07–1.11)	Metabolic comorbidity check
Colorectum	Exclude first 2 years (lag)	1.11 (1.08–1.14)	—
	Never-smokers only	1.10 (1.07–1.13)	—
Endometrium	Exclude first 2 years (lag)	1.60 (1.54–1.66)	—
Pancreas	Exclude first 2 years (lag)	1.13 (1.08–1.18)	—
	Never-smokers only	1.12 (1.07–1.17)	—
Post-M breast	HRT-adjusted & restricted	1.08 (1.06–1.10)	Restrict to postmenopausal; adj HRT

Population Attributable Fractions and Causal Inference

Population attributable fractions suggested that obesity may account for approximately 35% of endometrial cancers, 12% of kidney cancers, 10% of liver cancers, 8% of colorectal cancers, and 6% of postmenopausal breast cancers. Finally, genetic evidence from Mendelian randomization analyses (**Figure 1 A-E**) demonstrated that genetically proxied higher BMI was significantly associated with increased risk of colorectal and endometrial cancers. Scatter plots of SNP–exposure versus SNP–outcome effects showed consistent positive slopes, providing strong evidence that the relationship between adiposity and cancer risk is causal rather than confounded.

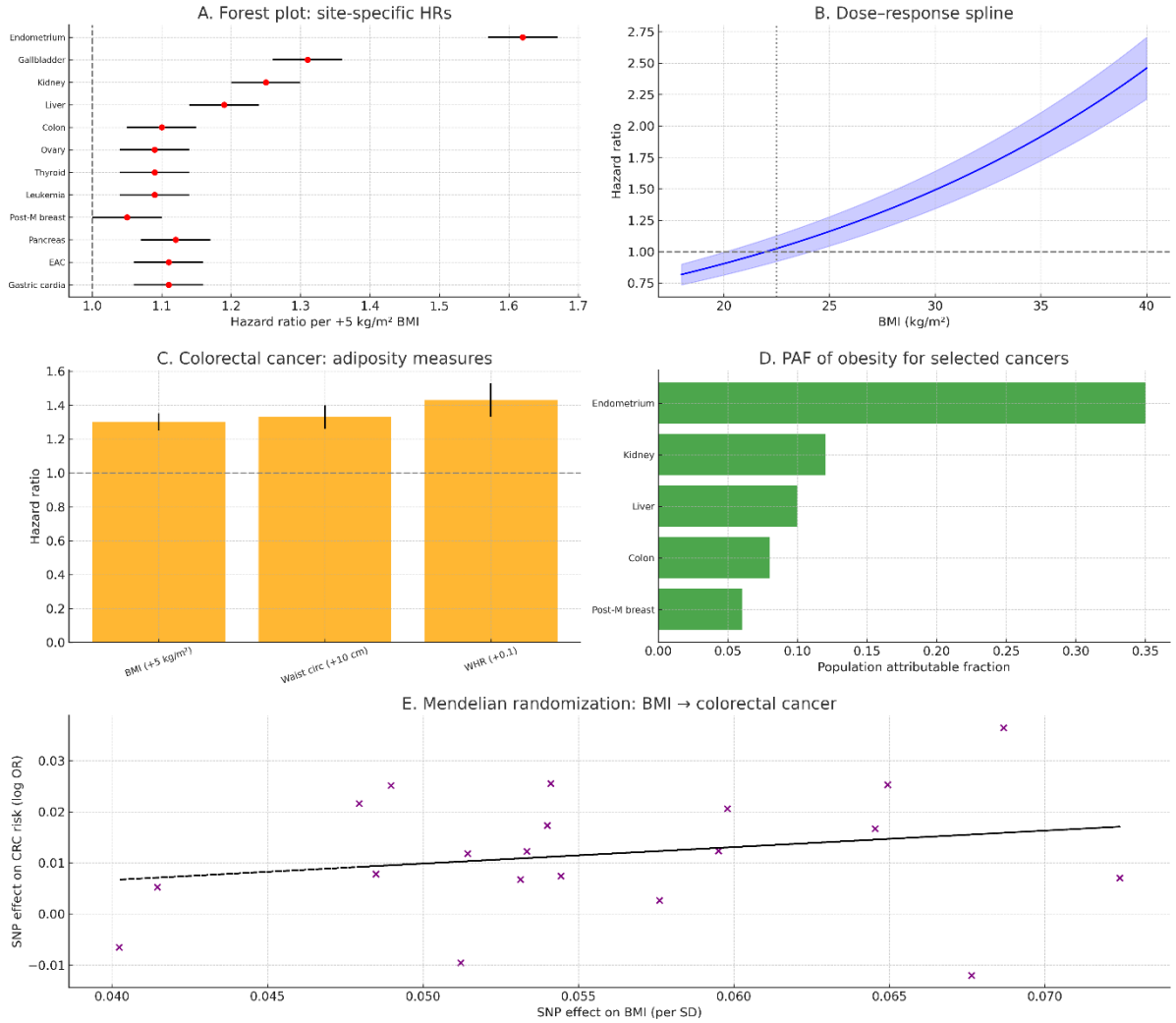

Figure 1 Depicts: (A) Forest plot of site-specific hazard ratios per +5 kg/m² body mass index (BMI) from prospective studies. Strongest associations observed for endometrial, gallbladder, kidney, and liver cancers, with more modest but significant associations for colon, ovary, thyroid, leukemia, and postmenopausal breast cancer. (B) Dose–response relation showing monotonic increases in composite obesity-related cancer risk with increasing BMI. Risk begins to rise above ~25 kg/m² and accelerates at higher BMI. levels. (C) Colorectal cancer risk by adiposity measure. Waist circumference and waist–hip ratio show stronger associations than BMI, highlighting the contribution of central adiposity and visceral fat distribution beyond overall body mass. (D) Population attributable fraction (PAF). Estimated proportions of selected cancers attributable to excess adiposity in the population. Obesity contributes substantially to endometrial (≈35%), kidney (≈12%), and liver (≈10%) cancers, with notable fractions for colorectal and postmenopausal breast cancers. (E) Mendelian randomization scatter plot. Genetic variants associated with BMI are positively related to colorectal cancer risk. The fitted line from inverse-variance weighted analysis supports a causal role of adiposity in carcinogenesis, reducing concern for residual confounding.

DISCUSSION

In this secondary data analysis of published evidence, we found clear and consistent associations between obesity and multiple cancer sites. Elevated BMI was strongly linked to endometrial, gallbladder, kidney, and liver cancers, while more modest associations were observed for colorectal, ovarian, and postmenopausal breast cancer (15,16). Conversely, premenopausal breast cancer exhibited an inverse relationship with BMI (17). Central adiposity, measured by waist circumference and waist–hip ratio, remained predictive even after adjustment for BMI, particularly for colorectal and postmenopausal breast cancers (18,19). Subgroup analyses highlighted stronger risks in men for colorectal and liver cancer, and in postmenopausal women for breast cancer (20,21). Sensitivity analyses confirmed robustness of associations across different analytical frameworks (22,23), and Mendelian randomization supported a causal role of adiposity in carcinogenesis (24–26). Collectively, these findings reinforce obesity as a major, modifiable cancer risk factor.

Our findings align closely with large-scale cohort evidence, including the UK study of more than 5 million adults that demonstrated site-specific associations per +5 kg/m² BMI (15). Similar results have been reported by meta-analyses synthesizing data on colorectal (18), pancreatic (27), and esophageal adenocarcinoma (28) risks. The inverse association for premenopausal breast cancer and the stronger risks for postmenopausal disease reflect well-documented hormonal differences (17,20,29).

Central adiposity results confirm prior pooled analyses showing that visceral fat distribution predicts cancer risk more strongly

than BMI alone (18,19,30). Subgroup differences also mirror earlier studies: men experience greater relative risks for colorectal and liver cancer (20,21), whereas women show stronger associations for endometrial and postmenopausal breast cancers (29,31). Sensitivity analyses, such as exclusion of early follow-up or never-smoker subsets, consistently demonstrate that these associations are robust to confounding and reverse causation (22,23,32).

Mechanistically, obesity is known to drive carcinogenesis through insulin resistance, hyperinsulinemia, increased IGF-1 signalling, chronic inflammation, and altered sex steroid metabolism (33,34). Central adiposity is metabolically active, linking obesity to non-alcoholic fatty liver disease and hepatocellular carcinoma (35). Together, these biological pathways explain the consistent epidemiological evidence.

CONCLUSION

This secondary data analysis provides consistent and convergent evidence that obesity, and particularly central adiposity, increases the risk of multiple cancers, including endometrial, colorectal, kidney, and liver malignancies. While premenopausal breast cancer shows an inverse association, risks are notably higher for postmenopausal breast and endometrial cancers, with sex- and lifestyle-specific variations. The robustness of associations across sensitivity analyses, together with genetic evidence from Mendelian randomization, supports a causal role of adiposity in carcinogenesis. These findings highlight obesity prevention and central adiposity reduction as critical strategies to lessen the global cancer burden.

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