Allostatic Load and Risk of Obesity-Related and Total Cancer in Postmenopausal Women

Insights from the Women's Health Initiative

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Background

Allostatic load (AL), a combined indicator of physiological stress, has been linked to chronic illnesses, yet its connection to cancer, especially those related to obesity, is not well-explored in large, varied populations. This study examined the link between initial AL and the occurrence of obesity-related cancers and overall cancer risk in postmenopausal women participating in the Women's Health Initiative (WHI).

Methods and Materials

From 161,805 WHI participants, we identified 28,102 women with baseline AL data and no prior cancer. AL was calculated from eight biomarkers (pulse, SBP/DBP, BMI, waist circumference, CRP, fasting glucose, total cholesterol) and categorized into tertiles (0–2, 3–5, 6–8). Cox proportional hazards and Fine–Gray models estimated associations of AL with incident obesity-related cancers (13 sites) and overall cancer (excluding non-melanoma skin cancer), adjusting for sociodemographic, behavioral, and reproductive factors.

Results

Over a median follow-up of 18.6 years, 3,953 obesity-related cancers (14.1%) and 6,255 total cancers (22.3%) occurred. In fully adjusted models, women in the highest vs lowest AL tertile had higher risk of obesity-related cancer (HR 1.20, 95% CI 1.01–1.42; p=0.044), with a 4% increase in risk per 1-point higher AL (HR 1.04, 95% CI 1.00–1.07; p=0.028). AL was not significantly associated with overall cancer incidence (HR_high vs low 1.07, 95% CI 0.92–1.24; p=0.39), and competing-risk analyses gave similar results. Associations did not differ by race/ethnicity (interaction p>0.5), although Black and Hispanic women had higher AL scores than White women.

Table 1. Number (%) that achieved 1 pt for each of the eight biomarkers

AL	Low risk	High risk
Pulse rate	27609	493 (1.75%)
Systolic blood pressure	11210	16892 (60.11%)
Diastolic blood pressure	17051	11051 (39.32%)
BMI	17325	10777 (38.35%)
Waist circumference	14169	13933 (49.58%)
CRP	5413	22689 (80.74%)
Glucose	22619	5483 (19.51%)
Total cholesterol	15241	12861 (45.77%)

Table 2: Associations between Allostatic Load and Risk of Cancer: High, medium, and low AL correspond to groups based on AL tertiles.

Outcome		Adjusted Analysis [a]		
		HR (95% CI)	Contrast p-value [b]	Overall p-value [c]
Obesity-related cancer	Medium vs. Low AL	1.17 (1.04, 1.31)	0.009	0.023
	High vs. Medium AL	1.02 (0.88, 1.19)	0.772	
	High vs. Low AL	1.20 (1.01, 1.42)	0.044	
	AL score (1 pt increase)	1.04 (1.00, 1.07)		0.028
All cancer	Medium vs. Low AL	1.13 (1.02, 1.24)	0.015	0.049
	High vs. Medium AL	0.95 (0.83, 1.08)	0.435	
	High vs. Low AL	1.07 (0.92, 1.24)	0.388	
	AL score (1 pt increase)	1.02 (1.00, 1.05)		0.079

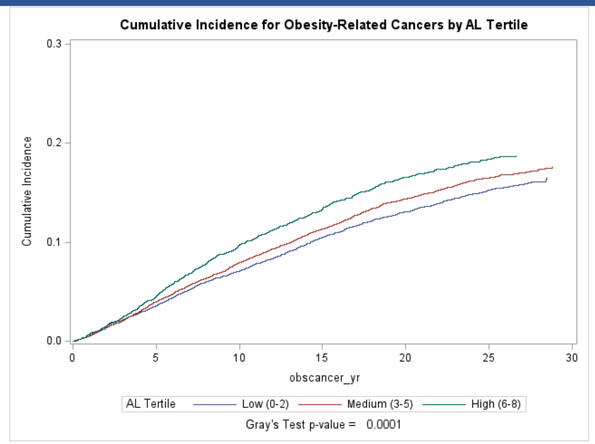


Figure 1 Cumulative Incidence of Obesity-Related Cancers

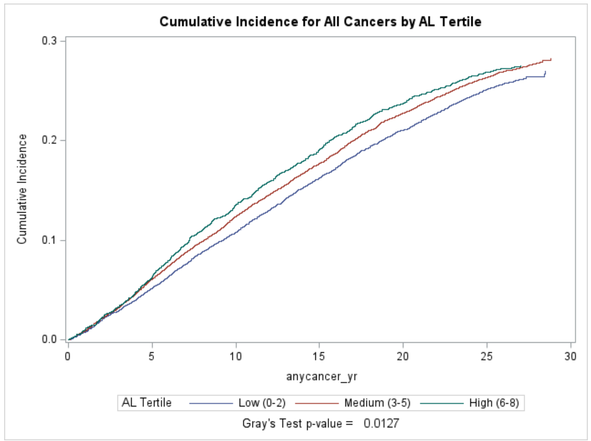


Figure 2 Cumulative Incidence for All Cancers

Discussion

In this large cohort of postmenopausal women, higher baseline allostatic load (AL)—a composite of metabolic, cardiovascular, and inflammatory dysregulation—predicted greater risk of obesity-related cancers over ~19 years: women in the highest AL tertile had ~20% higher hazard than those with low AL, with ~4% higher risk per AL unit. AL was not associated with overall cancer, suggesting specificity to obesity-linked pathways (hormonal, insulin/IGF, inflammatory) that AL captures, and the effect size (HR ≈1.2) is comparable to a ~5 kg/m² BMI increase. Associations were similar across racial/ethnic groups, but higher average AL among Black women suggests a disproportionate burden and highlights the importance of addressing upstream social determinants.

Conclusions

Increased allostatic load, indicating multi-system biological stress, independently predicted a slight rise in the risk of obesity-related cancers in postmenopausal women. This relationship remained after accounting for lifestyle and reproductive factors and was consistent across racial/ethnic groups. These findings underscore the potential role of accumulated chronic stress in cancer development beyond the impact of obesity alone. AL could be a valuable composite biomarker for identifying individuals at higher risk for certain cancers.

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