Short Communication

Body Mass Index and Risk of Leukemia in Older Women

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Abstract

Overweight [body mass index (BMI) 25.0-29.9 kg/m^2] and obesity (BMI ≥ 30 kg/m^2) are risk factors for several malignancies. The Iowa Women's Health Study was examined to determine whether increased BMI was associated with leukemia development. Over 40,000 Iowa women (ages 55-69 years) completed a self-administered lifestyle and health questionnaire in 1986 that included current height and weight. Two hundred women developed leukemia during the period 1986 to 2001 including 74 acute myelogenous leukemia (AML) and 88 chronic lymphocytic leukemia. The risk of AML was increased among women who reported being overweight or obese (relative risk, 1.9; 95% confidence interval, 1.0-3.4; relative risk, 2.4; 95% confidence interval, 1.3-4.5; P_{trend} = 0.006) compared with women of normal weight. There was little evidence of a positive association for chronic lymphocytic leukemia (P_{trend} = 0.6). Given the prevalence of overweight and obesity in the United States, the population attributable risk of AML due to obesity could approach 30%. (Cancer Epidemiol Biomarkers Prev 2004;13(11):1810–3)

Introduction

Overweight and obesity are risk factors for several malignancies including colon, breast, kidney, and endometrium (1). A few prospective studies have reported a potential positive association between obesity and risk of adult leukemia, but these studies had either a few cases (<75 total) and/or a relatively short follow-up period (2-4). We examined the potential association between obesity and risk of leukemia in the Iowa Women's Health Study (IWHS), a prospective cohort study of lifestyle and health risks in older women.

Materials and Methods

In 1986, a questionnaire was completed by 41,386 of 98,030 randomly selected women between ages 55 and 69 years who had a valid Iowa drivers' license in 1985 (5). Nonresponders were 3 months younger than responders, 0.4 kg/m^2 heavier, and slightly less likely to live in rural counties of Iowa (6). The baseline questionnaire collected information on demographic characteristics as well as lifestyle behaviors including smoking status, diet, and physical activity level. Enclosed with the questionnaire were a paper tape measure and written instructions to have a friend measure waist (2.5 cm above the umbilicus) and hip (maximal protrusion) circumferences. This protocol is accurate (7).

Cancer incidence between 1986 and 2001 was ascertained by computer linkage to the Iowa Cancer Registry, part of the National Cancer Institute's Surveillance, Epidemiology, and End Results program (8). Incident cases between 1986 and 2001 were identified through computer matching on name, zip code, birth date, and social security number. Data from follow-up surveys indicate that the migration rate from Iowa among cohort members is <1% annually. Topographical and morphologic data from the *International Classification of Diseases for Oncology, Third Edition* (9) were used to classify incident leukemia in the cohort. Women were excluded who self-reported at baseline a cancer at any site other than skin (n = 3,830) or if they had a body mass index (BMI; calculated using baseline weight in kilograms and height in meters squared) <18.5 kg/m^2 (n = 379). Following these exclusions, 37,627 women remained.

Differences in baseline characteristics according to leukemia status were evaluated by t tests (for continuous variables) or χ^2 tests (for categorical variables). Multivariate-adjusted relative risks (RR) and their 95% confidence intervals (95% CI) were computed using Cox proportional hazards regression with the SAS program PHREG (10). Linear tests for trend were done by using categorical variables that represented the median value within each category and modeling them as continuous variables. Population attributable risk percentage was calculated as $p(RR - 1) / p(RR - 1) + 1$, where p represents the prevalence of exposure in the

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general population (11). Incident end points of interest were all leukemias, acute myelogenous leukemia (AML), and chronic lymphocytic leukemia (CLL). Person-years of follow-up were calculated as the time elapsed from the completion of the 1986 questionnaire to either date of incident cancer, emigration from Iowa, death, or December 31, 2001.

Results

Over a mean of 14.3 years of follow-up, 200 women developed leukemia. Women diagnosed with leukemia were slightly older (62.3 versus 61.6 years; $P = 0.02$), more likely to be overweight or obese (72% versus 61%; $P = 0.009$), and somewhat less likely to report regular leisure time physical activity compared with noncases (36% versus 42%; $P = 0.09$). Leukemia incidence was unrelated to educational attainment, marital status, residence, diabetes, alcohol consumption, or cigarette smoking (data not shown).

As shown in Table 1, there was an increased risk of leukemia for overweight and obese women compared with women of normal weight, with multivariate-adjusted RRs of 1.6 (95% CI, 1.1-2.3) and 1.6 (95% CI, 1.1-2.4), respectively ($P_{trend} = 0.01$). Separate analyses were done for the two largest subgroups of cases, AML ($n = 74$) and CLL ($n = 88$). An increased risk of leukemia with increasing categories of BMI was observed for AML ($P_{trend} = 0.006$) but not for CLL ($P_{trend} = 0.6$). The multivariate-adjusted RRs of AML was 1.9 for overweight (95% CI, 1.0-3.4) and 2.4 for obesity (95% CI, 1.3-4.5). Excluding cases diagnosed in the first 2 years of follow-up did not weaken these associations (data not shown). Results were also similar in supplemental analysis using time-dependent analysis of follow-up weights.

Discussion

Few prospective studies have explored the potential association between obesity and leukemia. In a recent record linkage study of 28,000 hospital patients from Sweden, a 20% excess incidence of leukemia ($n = 39$ cases) was observed in obese individuals compared with that expected (2). A Danish linkage study, which included nearly 44,000 individuals, reported a statistically significant 30% increased risk of leukemia associated with obesity, although average follow-up time for the majority of the cohort was <5 years (4). In a cohort study of 23,000 Icelanders who self-reported anthropometric variables, Tulinius et al. (3) reported an increased RR (1.09) of leukemia with each 1 kg/m^2 increase in BMI for males only. Finally, in a follow-up of over 900,000 cancer-free U.S. adults who completed a questionnaire in 1982, Calle et al. (12) showed that increasing BMI was significantly ($P_{trend} < 0.001$) associated with leukemia death in men only, although specific subtypes of leukemia were not analyzed.

Table 1. Multivariate-adjusted RRs of leukemia in relation to baseline anthropometric characteristics, the IWHS, 1986-2001

	Person-years	Leukemia			AML			CLL		
		Cases*	RR (95% CI)	P_{trend}†	Cases*	RR (95% CI)	P_{trend}†	Cases*	RR (95% CI)	P_{trend}†
Height (m)										
≤62 (≤1.58)	142,475	50	1.0	0.05	20	1.0	0.25	19	1.0	0.05
63-65 (1.59-1.66)	233,989	74	0.9 (0.6-1.3)		25	0.8 (0.4-1.4)		33	1.1 (0.6-1.9)	
≥66 (>1.67)	152,992	70	1.4 (0.9-2.0)		27	1.3 (0.7-2.3)		32	1.7 (0.9-2.9)	
Weight (kg)										
≤137 (≤62)	172,830	49	1.0	0.007	13	1.0	0.01	27	1.0	0.33
138-160 (63-73)	184,559	65	1.2 (0.9-1.8)		26	1.8 (0.9-3.6)		24	0.8 (0.5-1.5)	
≥161 (>73)	172,068	80	1.6 (1.1-2.3)		33	2.3 (1.2-4.4)		33	1.2 (0.8-2.1)	
BMI (kg/m^2) WHO categories										
18.5-24.9	206,030	54	1.0	0.01	16	1.0	0.006	26	1.0	0.61
25.0-29.9	199,143	85	1.6 (1.1-2.3)		30	1.9 (1.0-3.4)		40	1.6 (1.0-2.6)	
≥30.0	124,284	55	1.6 (1.1-2.4)		26	2.4 (1.3-4.5)		18	1.1 (0.6-2.1)	
Waist (m)										
≤31.8 (<0.81)	179,281	53	1.0	0.10	20	1.0	0.04	26	1.0	0.79
31.9-36.3 (0.81-0.92)	175,483	67	1.2 (0.9-1.8)		16	0.8 (0.4-1.5)		33	1.2 (0.7-2.1)	
≥36.4 (>0.92)	172,799	74	1.4 (1.0-1.9)		36	1.6 (0.9-2.8)		25	1.0 (0.6-1.7)	
Waist-to-hip ratio										
≤0.79	176,766	60	1.0	0.58	23	1.0	0.60	28	1.0	0.48
0.80-0.87	188,011	68	1.0 (0.7-1.4)		22	0.8 (0.5-1.5)		33	1.1 (0.6-1.7)	
≥0.88	162,472	66	1.1 (0.8-1.6)		27	1.1 (0.6-2.0)		23	0.8 (0.5-1.4)	

NOTE: RRs were adjusted for age (continuous) and regular physical activity (yes/no). Except for BMI, anthropometric characteristics are represented as tertiles.

*Subjects with missing values for any of the covariates were not included in the final regression totals.

†Tests for trend were done by treating the medians within categories as a continuous variable in the model.

In a previous analysis from the IWHS that examined anthropometric factors and risk of non–Hodgkin's lymphoma and B-cell CLL, we reported a weak, non-statistically significant positive association between baseline BMI and CLL (13). With an additional 3 years of follow-up data, the present analysis confirms little association between higher BMI and risk of CLL.

It is unknown why higher BMI would be associated with leukemia, particularly AML. A general mechanism that could explain this observation involves impaired immune function associated with obesity (14, 15). Alternatively, there is evidence from animal studies that suggests caloric restriction inhibits cell proliferation (16). The positive findings with AML and not CLL, however, suggest a more specific mechanism of action. For malignancies of the breast and endometrium, it has been speculated that alterations in sex hormones (such as estrogens and androgens) and growth factors (such as insulin-like growth factor-I) may be important (1). A metabolic consequence of obesity is insulin resistance followed by an increase in insulin secretion. This increase results in a decrease in insulin-like growth factor-I binding proteins and an increase in insulin-like growth factor-I activity (1). Insulin-like growth factor-I not only is important in hematopoeisis but also seems to promote the survival of myeloid cells (17, 18). Thus, it is possible that obesity-related disruptions in the insulin-like growth factor-I axis may offer a proliferative advantage to hematopoeitic cells predisposed to become malignant. Leptin may play a similar role. Circulating free leptin plasma levels are highest in obese individuals (19). Importantly, leptin receptors are expressed on peripheral blood mononuclear cells and leptin seems to promote survival of circulating blood monocytes (20, 21). Thus, myeloid cells may be particularly responsive to the stimulating effects of leptin.

We reported recently that CLL and chronic myeloid leukemia incidence rates in the United States have declined from 1973 to 1998, particularly in middle-aged and older adults (22). However, the incidence rate for AML, particularly in persons over age 65 years, increased significantly by ~0.4% per year. Furthermore, 5-year survival rates for AML are extremely poor, with overall rates of ~12% and 3% for middle-aged and elderly adults, respectively. Thus, the identification of modifiable risk factors for adult AML is of public health importance.

There are some limitations to our study. The IWHS examined postmenopausal, mostly White, women. Thus, these results may not be generalizable to other populations. BMI was calculated using self-reported weight and height, which could be subject to some degree of imprecision. However, self-reported height and weight are generally accurate (7) and do not contribute substantially to errors in measuring BMI (23, 24). Some people tend to overreport their height and underreport their weight, which could lead to a possible underestimation of overweight and obese individuals in this study. However, given that self-report occurred prior to the development of leukemia, the overall effect would be nondifferential. BMI might also not reflect true body mass, as it does not distinguish fat mass from lean mass. Nevertheless, BMI is the standard for population-based studies; importantly, increased BMI among IWHS participants has been associated with risk of kidney, breast, and endometrial cancers (5, 25, 26), similar to findings reported in other prospective studies (1). There is also the possibility that underlying disease may have affected current weight. Analyses that excluded cases diagnosed in the first 2 years of follow-up, however, did not attenuate these associations.

Our prospective study considered the two largest subgroups of adult leukemia (AML and CLL) separately with respect to obesity. Given the population prevalence of obesity in the United States, these data suggest that the population attributable risk of AML due to obesity may approach 30% (11). Although confirmation in additional prospective studies is needed, reducing obesity may be important in preventing adult AML.

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