Short Communication

Obesity, Weight Gain, and Risk of Chronic Myeloid Leukemia

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Abstract

To date, little is known about the risk factors for the development of chronic myeloid leukemia (CML). Obesity, measured as body mass index, has been identified as a possible risk factor for several solid tumors as well as some adult hematopoietic malignancies. This case-control study (N = 253 cases and 270 controls), conducted at the University of Texas M. D. Anderson Cancer Center, investigated the role of obesity and adulthood weight gain in CML risk. Cases and controls were similar with respect to smoking, alcohol consumption, and occupational solvent and ionizing radiation exposure. Cases were significantly more likely to have a history of occupational exposure to agricultural chemicals (11% cases versus 3% controls, P = 0.001). Cases were more likely to be obese during adulthood compared with controls at age 25 [odds ratios (OR) = 4.29; 95% confidence intervals (95% CI), 1.63-11.3], at age 40 (OR = 5.12; 95% CI, 1.92-13.6), and at diagnosis (OR = 3.09; 95% CI, 1.56-6.13). Obesity at all ages was found to be an independent risk factor, with a significant dose-response effect. Among participants ≥45 years, cases gained significantly more weight each year between ages 25 and 40 compared with controls (0.78 versus 0.44 kg/y, P < 0.001) with the association strongest among those who gained >1 kg/y between 25 and 40 years of age (OR, 3.63; 95% CI, 1.46-9.04). Our results suggest that obesity and adulthood weight gain play important roles in CML risk. Several plausible biological mechanisms have been proposed and warrant further investigation. In the future, cancer prevention interventions aimed at reducing the incidence of CML could be developed.(Cancer Epidemiol Biomarkers Prev 2009;18(5):1501–6)

Introduction

Chronic myeloid leukemia (CML) is a clonal disorder of multipotent hematopoietic stem cells that accounts for 10% of all leukemias. The Philadelphia chromosome, a reciprocal translocation between chromosomes 9 and 22, t(9;22)(q34;q11.2), is the hallmark of this rare leukemia (1).

Little is known about the clinical features that may predispose or be linked to CML etiology. Several risk factors have been evaluated in a few studies with mixed results. Exposure to high-dose radiation is the only established risk factor thus far (2). Smoking, pesticides, benzene/solvents, hair dye, and extremely low frequency electromagnetic fields (3-7) have been postulated as potential risk factors, but the results are inconclusive.

Accumulating evidence suggests that obesity may increase the risk of several adult solid tumors, as well as adult hematopoietic cancers (8). The association between obesity and multiple myeloma has been well-established, as reviewed by Larsson and Wolk in a recent meta-analysis (9). Obesity has reached epidemic proportions in the United States; determining the role that this modifiable condition plays in the risk of many different types of cancer is a significant public health issue. Because data on CML risk and obesity is scarce and conflicting, we conducted a case-control study at the University of Texas M. D. Anderson Cancer Center to investigate the role that obesity and adulthood weight gain play in CML risk.

Materials and Methods

A total of 294 adult patients with a diagnosis of *de novo* CML cases and 318 controls were identified between 1999 and 2006 as potential participants. Among cases, 253 (86%) were willing to participate. Reasons for nonenrollment included: non-U.S. resident (3%), refusal (8%), or unable to interview (4%). Cases were identified at their first visit and prospectively enrolled. Clinical data were abstracted from charts and the clinical database. CML diagnosis was based on cytogenetic and molecular evaluation of bone marrow.

Cases and controls were accrued concurrently. Controls for this study were recruited from among friends and family members of patients at various M. D. Anderson Cancer Center outpatient clinics, as previously described (10). Controls were frequency-matched on age ±5 years, gender, and ethnicity, and they had no previous history of cancer. To avoid overmatching on exposures or family history of hematopoietic cancers, we did not recruit controls in the leukemia or lymphoma clinics. Potential controls were identified and eligibility and willingness to participate in the study were determined. Approximately 85% of eligible controls

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agreed to participate (N = 270): 40% were friends, 36% were spouses, and 24% were other family members.

Informed consent was obtained according to institutional review board guidelines. Participants completed a self-administered validated questionnaire that assessed demographic information: medical, smoking, alcohol, and occupational history; and family history of hematopoietic cancer (lymphoma, multiple myeloma, and leukemias); as well as height and weight at different ages (at 25, 40, and at diagnosis).

Data Analysis. Body mass index (BMI; kg/m^2) was calculated from the self-reported weight and height at ages 25, 40, and at time of CML diagnosis/interview (controls) from the questionnaire. BMI was analyzed continuously and categorically. BMI was categorized as underweight/normal, BMI $\leq$ 24.9 kg/m^2; overweight, 25 to 29.9 kg/m^2; mildly obese, 30 to 34.9 kg/m^2; and moderately/severely obese, $\geq$35.0 kg/m^2. Underweight and normal weight groups were combined for the analyses because there were very few underweight (BMI $\leq$ 18 kg/m^2) individuals in this study (12 at age 25, 2 at age 40, and 4 at diagnosis/interview). The prevalence of underweight individuals was not significantly different between cases and controls at any age (data not shown). Annualized weight change over different age intervals was calculated by averaging the total weight gained/lost over each time period and categorized as lost weight, no change, gained 0.1 to 0.5 kg/y, gained 0.5 to 1.0 kg/y, and gained >1.0 kg/y.

Smokers were those who smoked >100 cigarettes in their lifetime and further categorized as ''current smokers'' or ''former smokers'' (quit >1 year prior to diagnosis/interview). Pack-years were the average packs smoked per day $\times$ years smoked. Alcohol drinkers were those who drank one or more alcoholic beverage per week of any type of alcohol for at least 1 year.

The National Cancer Institute job exposure matrix was used to estimate occupational exposure to chemicals and ionizing radiation for each job held full-time for >1 year (11). In the job exposure matrix, each job title is associated with an intensity level: none (0), low (1), medium (2), and high (3). Exposure to ionizing radiation was calculated from occupational sources and reported therapeutic radiation; it was analyzed as a dichotomous variable (not exposed versus exposed).

Descriptive analyses were conducted using χ^2 and Student's t tests. Unconditional logistic regression was used to assess variables of interest as possible predictors

Table 1. Demographic/clinical characteristics by cases and controls

	Cases (n = 253)	Controls (n = 270)	P
Age (y)			
Mean (range)	47.9 (16-83)	49.0 (20-82)	NS
<50	137 (54%)	128 (47%)	
≥50	116 (46%)	142 (53%)	NS
Sex			
Female	121 (48%)	126 (47%)	
Male	132 (52%)	144 (53%)	NS
Ethnicity			
White	208 (82%)	225 (83%)	
Hispanic	26 (10%)	24 (9%)	
African American	17 (7%)	17 (6%)	
Others	2 (1%)	4 (2%)	NS
Education			
<High school	11 (4%)	14 (5%)	
High school/some college	128 (51%)	106 (39%)	
Bachelor/graduate	113 (45%)	134 (50%)	NS
Family history of hematopoietic cancer*			
No	232 (92%)	259 (96%)	0.03
Yes	21 (8%)	10 (4%)	
Smoking			
Never	150 (59%)	146 (54%)	
Ever	103 (41%)	124 (46%)	0.23
Mean pack-years	18.0	17.1	0.69
Alcohol			
Never	112 (44%)	108 (40%)	
Ever	141 (56%)	162 (60%)	0.32
Solvent exposure			
None	137 (54%)	160 (61%)	
Low/medium	87 (35%)	80 (30%)	
High	28 (11%)	24 (9%)	0.35
Agrochemical exposure			
None	225 (89%)	257 (97%)	
Low/medium	15 (6%)	4 (2%)	
High	12 (5%)	3 (1%)	0.001
Ionizing radiation exposure			
No	190 (75%)	210 (81%)	
Yes	62 (25%)	54 (19%)	0.26

NOTE: Data missing for some participants due to incomplete information.
Abbreviation: NS, not significant.
*Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, or leukemia in first-degree relatives.

Table 2. Multivariate logistic regression analyses: BMI overall and by gender

Variables	Overall (n = 523)			Men (n = 276)			Women (n = 247)		
	Cases (n = 253)	Controls (n = 270)	OR* (95% CI)	Cases (n = 132)	Controls (n = 144)	OR* (95% CI)	Cases (n = 121)	Controls (n = 126)	OR* (95% CI)
BMI at age 25 †									
Under/normal	155 (66%)	158 (78%)	1.00	68 (56%)	56 (62%)	1.00	87 (76%)	102 (90%)	1.00
Overweight	58 (25%)	40 (20%)	1.53 (0.93-2.53)	41 (34%)	32 (35%)	1.17 (0.63-2.16)	17 (15%)	8 (7%)	2.58 (1.03-6.47)
Mildly obese	17 (7%)	3 (2%)	4.29 ‡ (1.63-11.3)	8 (7%)	1 (1%)	5.13 ‡ (1.20-21.9)	9 (8%)	2 (2%)	4.07 ‡ (1.05-15.8)
Moderately/severely obese	5 (2%)	3 (2%)		4 (3%)	2 (2%)		1 (1%)	1 (1%)	
			P-trend = 0.002			P-trend = 0.07			P-trend = 0.008
BMI at age 25 (continuous)			1.09 (1.03-1.15)			1.09 (1.01-1.19)			1.08 (1.00-1.16)
BMI at age 40 †									
Under/normal	73 (40%)	101 (55%)	1.00	23 (23%)	46 (45%)	1.00	50 (60%)	55 (66%)	1.00
Overweight	62 (34%)	68 (37%)	1.30 (0.79-2.14)	50 (50%)	45 (44%)	2.13 (1.10-4.12)	12 (14%)	23 (28%)	0.59 (0.25-1.38)
Mildly obese	28 (15%)	10 (5%)	3.83 (1.69-8.68)	19 (19%)	7 (7%)	4.89 (1.76-13.6)	9 (11%)	3 (4%)	3.26 (0.75-14.2)
Moderately/severely obese	22 (12%)	6 (3%)	5.12 (1.92-13.6)	9 (9%)	4 (4%)	4.35 (1.19-15.9)	13 (16%)	2 (2%)	7.19 (1.43-36.2)
			P-trend < 0.001			P-trend = 0.001			P-trend = 0.02
BMI at age 40 (continuous)			1.11 (1.05-1.16)			1.12 (1.05-1.21)			1.09 (1.02-1.17)
BMI at diagnosis/interview									
Under/normal	71 (28%)	103 (40%)	1.00	26 (20%)	46 (33%)	1.00	45 (37%)	57 (48%)	1.00
Overweight	95 (38%)	105 (40%)	1.28 (0.83-1.97)	61 (47%)	66 (47%)	1.50 (0.81-2.76)	34 (28%)	39 (33%)	1.11 (0.59-2.10)
Mildly obese	51 (20%)	37 (14%)	2.12 (1.24-3.65)	28 (21%)	22 (16%)	2.22 (1.04-4.75)	23 (19%)	15 (13%)	2.11 (0.96-4.67)
Moderately/severely obese	35 (14%)	16 (6%)	3.09 (1.56-6.13)	16 (12%)	7 (5%)	3.79 (1.34-10.7)	19 (16%)	9 (8%)	2.65 (1.06-6.64)
			P-trend < 0.001			P-trend = 0.004			P-trend = 0.01
BMI at diagnosis/interview (continuous)			1.08 (1.04-1.12)			1.11 (1.05-1.17)			1.06 (1.02-1.11)

*Adjusted for gender, ethnicity, age, and agrochemical exposure.

† The number of cases and controls in these categories are less than the total number for the study due to exclusion of subjects younger than the age cutpoints.

‡ OR calculated for mildly obese and moderately/severely obese combined due to the small number of individuals in these categories.

of CML risk by calculating odds ratios (OR) and 95% confidence intervals (95% CI). Variables with ORs $P < 0.1$ were evaluated for inclusion in a multivariate model constructed in a forward stepwise manner that estimated ORs simultaneously adjusting for all variables. For variables with three or more categories, a trend for proportions (Cochran-Armitage trend test) was used. Tests for linear trend were done on ordinal variables by including them in logistic regression models as continuous variables. Population-attributable risk percentage was calculated as $p(\text{OR-1}) / p(\text{OR-1}) + 1$, where p represents the prevalence of obesity in the general population assuming that our ORs associated with BMI were causal (12). All statistical tests were two-sided with statistical significance determined at $P \leq 0.05$ and done using SPSS (version 15.0, SPSS, Inc.).

Results

Table 1 shows the demographic, clinical, and lifestyle characteristics of the study subjects. Because of successful matching, cases and controls were similar with respect to age (47.9 versus 49.0), gender (52% versus 53% male), ethnicity (82% versus 83% whites), and education. Cases were significantly more likely than controls to have a family history of hematopoietic cancer (8% versus 4%, $P = 0.03$). However, there were no case-control differences with respect to having a first degree relative with leukemia (3% versus 2%, $P = 0.49$).

No case-control differences were found with respect to smoking, alcohol consumption, occupational solvent exposure, or ionizing radiation exposure. History of occupational exposure to agricultural chemicals (fertilizers, herbicides, or pesticides) was significantly higher in cases compared with controls (11% versus 3%, respectively, $P = 0.001$). There were no significant differences in any of these exposures by gender (data not shown).

The associations between CML risk and obesity at different ages were evaluated overall and by gender (Table 2). Cases were more likely to be obese at all three ages compared with controls. At age 25, being obese was associated with a 4-fold increase in risk (OR = 4.29; 95% CI, 1.63-11.3). Being moderately/severely obese at age 40 was associated with a 5-fold increase in risk (OR = 5.12; 95% CI, 1.92-13.6). At the time of diagnosis, moderate/severe obesity was associated with a 3-fold increase in risk (OR = 3.09; 95% CI, 1.56-6.13). In multivariate analyses, obesity at all ages was found to be an independent risk factor for CML with a significant dose-response effect. Results stratified by gender showed that being obese at any age was associated with a statistically significant increased risk for both men and women. Parallel analyses conducted using BMI as a continuous variable showed similar results (Table 2).

We analyzed the role of weight gain between ages 25 and 40, and diagnosis among 361 participants who were at least 45 years old at the time of diagnosis/interview (Table 3). We chose age 45 as the cutpoint to minimize the effect on weight change due to prediagnostic weight loss at least 5 years prior to diagnosis. Weight gain during each time period was consistently associated with increased risk. Cases gained significantly more weight each year between ages 25 and 40 compared with controls (0.78 versus 0.44 kg/y, $P < 0.001$). The strongest association was with gaining >1 kg/y between 25 and 40 years of age (OR = 3.63; 95% CI, 1.46-9.04). We found that losing weight between age 40 and diagnosis was associated with a borderline significant increase in risk, most likely due to preclinical disease. There were no significant differences in weight change between men and women (data not shown).

Discussion

In this report from the first case-control study from the United States, we assessed obesity and weight gain as

Table 3. Weight gain: multivariate regression among participants age 45+

Weight change from	Cases (%)	Controls	OR (95% CI)
Ages 25 to 40			
Lost (≥ 0.1 kg/y)	4 (3%)	12 (8%)	0.38 (0.09-1.54)
No change (0 ± 0.1 kg/y)	13 (9%)	22 (14%)	1.00
Gain (0.1-0.5 kg/y)	49 (35%)	71 (46%)	1.07 (0.48-2.39)
Gain (0.5-1 kg/y)	33 (24%)	31 (20%)	1.62 (0.67-3.92)
Gain (>1 kg/y)	40 (29%)	18 (12%)	3.63 (1.46-9.04)
Mean change (kg/y)	0.78	0.44	$P < 0.001$
Age 25 to diagnosis/interview			
Lost (≥0.1 kg/y)	6 (4%)	7 (5%)	1.02 (0.27-3.88)
No change (0 ± 0.1 kg/y)	17 (12%)	23 (15%)	1.00
Gain (0.1-0.5 kg/y)	48 (35%)	73 (47%)	0.85 (0.41-1.80)
Gain 0.5-1 kg/y	53 (38%)	40 (26%)	1.78 (0.81-3.90)
Gain >1 kg/y	15 (11%)	12 (8%)	1.66 (0.58-4.79)
Mean change, kg/y	0.52	0.42	$P = 0.05$
Age 40 to diagnosis/interview			
Lost (≥0.1 kg/y)	31 (22%)	17 (11%)	2.43 (0.99-5.96)
No change (0 ± 0.1 kg/y)	21 (15%)	29 (18%)	1.00
Gain (0.1-0.5 kg/y)	43 (30%)	51 (32%)	1.26 (0.60-2.63)
Gain (0.5-1 kg/y)	28 (20%)	44 (28%)	0.86 (0.39-1.89)
Gain (>1 kg/y)	20 (14%)	17 (11%)	1.57 (0.61-4.04)
Mean change (kg/y)	0.30	0.43	$P = 0.2$

NOTE: Adjusted for age, sex, ethnicity, agrochemical exposure, family history, and weight at ages 25 and 40.

risk factors for CML. We found that obesity was associated with 2-fold to 3-fold statistically significant increased risk of CML with a statistically significant trend with increasing BMI. In addition, this study is the first to analyze the role of adulthood weight gain in CML risk. Among those ≥45 years old, gaining more than 1 kg/y between age 25 and diagnosis was associated with a nonsignificant increase in risk and gaining more than 1 kg/y during early adulthood was associated with a 4-fold increased risk.

Most studies that investigated the association between obesity and leukemia risk have analyzed all leukemias combined, whereas the risk by specific leukemia has been evaluated in a few studies (13-16). A meta-analysis of the three published cohort studies found obesity associated with a slight statistically significant increase in relative risk (1.26; 95% CI, 1.09-1.46; ref. 8). In a large Norwegian population-based cohort, risk increased with increasing BMI categories in both men and women (P trend = 0.009 and 0.02, respectively; ref. 13). In the cohorts of veterans from the United States and in Swedish construction workers, both of which included only men, obesity was associated with a nonsignificant increase in CML risk (14, 15). In the only published case-control study of 169 Canadian cases; authors reported a 2-fold increase in risk (OR = 2.3; 95% CI, 1.5-2.4) associated with obesity (16). Our results are similar in magnitude to these previous reports. Based on our findings, being overweight/obese accounted for 28.5% of overall risk for CML (35.6% among men and 23.0% among women) similar to those reported in the Canadian study (24.8%; ref. 16).

Weight gain has been suggested to play a role in several types of solid tumors (17-20), but no studies have been conducted in leukemias. Gaining weight throughout adulthood was associated with a more than 3-fold increase of endometrial cancer (17) and a 2-fold increase in ovarian cancer (18). The authors postulate that these associations may be attributable to alterations in the endogenous hormonal milieu.

Different biological mechanisms may provide plausible explanations for this association between obesity and CML risk. Alterations in obesity-related hormones such as leptin and adiponectin have been shown to play a role in hematopoietic disorders (21-23). Leptin, involved in fat metabolism, stimulates myeloid progenitor cell development (21) and promotes the survival of monocytes (24). In animal models, leptin enhanced CD4 T-cell proliferation and stimulated the proliferation of myeloid and primitive hematopoietic progenitor cells (25). Additionally, the leptin receptor has been found to be expressed in hematopoietic stem cells and leukemic cells from CML patients, with higher expression in blast crisis (25). Adiponectin, involved in glucose and fatty acid metabolism and inflammation, inhibits cytokine secretion in bone marrow, thereby regulating cell proliferation (21, 22). Insulin-resistance is associated with increased insulin and insulin-like growth factors and with decreased insulin-like growth factor binding proteins levels (8, 24). Insulin-like growth factor-I plays a role in hematopoiesis by promoting the survival of myeloid cells (24) and is mitogenic in myeloid and lymphoid leukemia cell lines (22). Other potential mechanisms include increased cell proliferation, inhibition of apoptosis, impaired immune function, and chronic inflammation (8, 16, 24, 26). Future studies designed to identify the specific mechanism by which obesity and weight gain modulate CML risk are indicated.

This study has several strengths, including a large sample size of well-defined cases and well-matched controls, along with the use of the same validated risk factor questionnaires for cases and controls. To minimize the potential for selection and recall bias, controls were chosen from among visitors accompanying patients to various M. D. Anderson Cancer Center clinics, excluding the leukemia and lymphoma clinics (10). Patients were enrolled at the time of registration; avoiding the need for proxy interviews. As in any case-control study that uses self-reported measurements of past exposures (i.e., height and weight), there is potential for misclassification of BMI. However, we do not expect cases and controls to differentially report weight; therefore, bias is likely to be nondifferential, resulting in an attenuation of the effect. In addition, several studies have shown self-reported measurements to be reliable (10, 16). It is possible that an unknown underlying comorbidic condition(s) associated with obesity may actually be responsible for the observed association in this study; however, we did not have these data to assess for confounding. In addition, residual confounding caused by imperfect exposure assessment and/or effects of unknown factors cannot be ruled out.

In summary, our findings suggest that obesity and adulthood weight gain play important roles in the development of CML. The identification of obesity, a modifiable risk factor, is of special public health relevance due to the aging of the population and raising obesity rates. In the future, cancer prevention interventions aimed at reducing the incidence of CML could be developed.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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