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Medical conditions and risk of adult myeloid leukemia

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Abstract

Purpose—Although a few previous studies have reported positive associations between adult myeloid leukemia and a history of certain medical conditions, the etiology of most cases remains largely unknown. Our purpose was to examine associations between certain medical conditions and adult myeloid leukemia.

Methods—Using logistic regression, we evaluated associations between 16 self-reported medical conditions and myeloid leukemia in a case–control study of 670 cases [including 420 acute myeloid leukemia (AML) and 186 chronic myelogenous leukemia (CML)] and 701 population-based controls.

Results—We observed significant positive associations between AML and ulcerative colitis (odds ratio (OR) = 3.8; 95 % confidence interval (CI), 1.1–13) and between CML and peptic ulcer (OR = 2.0; 95% CI, 1.1–3.8). A personal cancer history increased both AML (OR = 2.6; 95% CI,

1.7–3.9) and CML (OR = 3.5; 95% CI, 2.0–5.8) risk even after excluding individuals who reported prior radiation and/or chemotherapy treatment.

Conclusion—Certain inflammatory medical conditions and a personal history of cancer, independent from therapy, are associated with an increased risk of myeloid leukemia.

Keywords

Acute myeloid leukemia; Chronic myeloid leukemia; Autoimmune disorders; Medical conditions

Introduction

Positive associations between adult leukemia and medical conditions including inflammatory bowel diseases (ulcerative colitis (UC) and Crohn's disease), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), polymyalgia, cardiovascular disease, celiac disease, and pernicious anemia have been reported. However, with the exception of one large US study of autoimmune conditions and risk of adult myeloid leukemia that linked Surveillance, Epidemiology and End Results registry cases to Medicare data [1], most studies have examined cancer incidence in cohorts with medical conditions that have included very few adult myeloid leukemia cases [2–7]. Characterizing myeloid leukemia risks associated with medical conditions may illuminate etiology and assist in identifying high-risk populations for targeted prevention strategies.

Methods

Study population

Cases—Eligibility criteria for cases (see [8] for complete description of study methods) included: (1) alive at contact, (2) Minnesota resident aged 20–79 years at diagnosis during 1 June 2005–30 November 2009, (3) diagnosis of AML, CML, chronic myelomonocytic leukemia (CMML), or other myeloid leukemia, and (4) ability to speak either English or Spanish. The population-based Minnesota state cancer registry identified 1178 pathologically confirmed incident cases of adult myeloid leukemia, of whom 271 were not referred (death soon after diagnosis ($N = 230$), physician and/or patient refusal ($N = 41$)). Of the 907 referrals, we were unable to confirm contact information for 52 patients, and 22 died before contact, resulting in contacts with 833 patients, of whom 16 % declined to participate and 3 % did not meet eligibility criteria (i.e., cognitively impaired, language, age or diagnosis ineligible, not a Minnesota resident, or deceased), yielding an overall cooperation rate of 83 % and a participation rate of 58 % [9]. Central review determined final pathologic-genetic classification of all cases, resulting in 420 AML (3 additional AML cases enrolled but died before questionnaire completion), 186 CML, and 64 CMML/other myeloid leukemia (including not otherwise specified) cases. Study results are given for myeloid leukemia overall, AML, and CML.

Controls—Controls were identified through the Minnesota State Driver's License/Identification Card list containing nearly all (>98 %) Minnesota residents aged 16–85 years (unpublished data by our group). Controls were selected on a quarterly basis throughout the study and were frequency-matched to cases on age in deciles. Control eligibility criteria were as follows: (1) alive at contact, (2) Minnesota resident, aged 20–79 years, (3) English or Spanish speaker, and (4) no prior myeloid leukemia diagnosis. Of 1020/1200 identified controls contacted, 106 did not meet eligibility criteria, 213 declined to participate, and 701 enrolled, for a total participation rate of 64 %.

Data collection

Medical conditions in cases and controls were assessed through self-report. The 30-min self-administered questionnaire included questions (yes, no, not sure; if yes, age at diagnosis) regarding diagnosis of the following: hyperthyroidism; hypothyroidism; peptic ulcer; ankylosing spondylitis; heart disease, angina or heart attack; high blood pressure; non-gestational diabetes mellitus (Type I vs. II were not ascertained); rheumatoid arthritis; osteoarthritis; Crohn's disease; UC; celiac disease; Sjogren's disease or sicca syndrome; lupus or SLE; polymyositis, dermatomyositis, or polymyalgia rheumatica; eczema; contact dermatitis; cirrhosis of the liver or liver damage; infectious mononucleosis; chronic fatigue syndrome; and/or epilepsy (convulsions or seizures not related to high fever). Participants were also asked whether they had ever been diagnosed with cancer including cancer type, diagnosis age, and treatment type(s) (surgery, radiation, chemotherapy, other, none, or don't know).

The Institutional Review Boards of the University of Minnesota, the Mayo Clinic, and the Minnesota Department of Health, and the 19 participating hospitals approved the study. All participants gave informed consent.

Statistical analysis

Unconditional logistic regression (SAS v9.1, 9.2 (Cary, NC)) was used to model adjusted associations between each medical condition and adult myeloid leukemia if at least 3 cases and 3 controls reported the condition. Potential confounders and interactions between variables were also assessed. All models were adjusted for age decile, sex, and body mass index (categorical); p values ≤ 0.05 were considered significant. To limit the possibility that medical conditions became clinically apparent as a consequence of cancer development, we conducted two sets of analyses where individuals were excluded who reported that their medical condition was diagnosed within one and 3 years of their myeloid leukemia diagnosis or date of questionnaire completion for controls. We also conducted analyses that excluded individuals who reported having a previous cancer diagnosis within 5 years of their leukemia diagnosis or questionnaire completion for controls. A small number of individuals were excluded from regression analyses due to missing data (as noted in Tables 2, 3).

Results

Case and control frequencies were similar across age categories, the matching variable (Table 1). Cases were more likely to be male and less likely to be non-Hispanic White. CML cases were more likely to report having less than a high school education and an income $< \$40,000$ per year. Both AML and CML cases were more likely to report ever having smoked, being overweight or obese, and having been exposed to benzene or other solvents.

No significant associations were found between myeloid leukemia overall, AML, or CML, and any autoimmune conditions except for UC (Table 2). There was an increased risk of myeloid leukemia associated with UC (OR = 3.5; 95% CI, 1.1–11), which was stronger for AML (OR = 3.8; 95% CI, 1.1–13) than for CML (OR = 2.0; 95% CI, 0.4–11). For CML, we observed a significant increased risk of peptic ulcer (OR = 2.0; 95% CI, 1.1–3.8). Adjusting for regular aspirin use did not materially change the risk estimate (data not shown).

We also conducted more stringent analyses that excluded individuals who reported that their medical condition occurred within 3 years of their leukemia diagnosis or questionnaire completion date for controls. Stronger associations, although less precise, were observed between UC and myeloid leukemia overall (OR = 4.5; 95% CI, 1.2–16.4) and for AML (OR = 5.2; 95% CI, 1.3–20.1) but not for CML (OR = 1.3; 95% CI, 0.1–13.5). For peptic ulcer, similar results were obtained to the results reported in Table 2 for myeloid leukemia overall

(OR = 1.5; 95% CI, 0.9–2.4), AML (OR = 0.9; 95% CI, 0.5–1.7), and CML (OR = 2.0; 95% CI, 1.0–3.8).

A personal history of cancer increased the risk of myeloid leukemia overall (OR = 2.6; 95% CI, 1.8–3.7), AML (OR = 2.6; 95% CI, 1.7–3.9), and CML (OR = 3.5; 95% CI, 2.0–5.8) (Table 3). The associations remained significant after adjusting for previous radiation or chemotherapy treatment for myeloid leukemia overall (OR = 2.1; 95% CI, 1.3–3.5), AML (OR = 1.8; 95% CI, 1.0–3.1), and CML (OR = 3.6; 95% CI, 1.9–7.0). Exclusion of reported prior hematopoietic malignancies did not materially change results (data not shown). In models that excluded individuals who reported a previous cancer diagnosis within 5 years or their leukemia diagnosis or questionnaire completion date for controls, associations remained significant for myeloid leukemia overall (OR = 2.8; 95% CI, 1.8–4.4), AML (OR = 2.9; 95% CI, 1.8–4.7), and CML (OR = 2.8; 95% CI, 1.4–5.5). Radiation treatment only for a prior cancer significantly increased the risk of CML (OR = 2.7; 95% CI, 1.0–7.3) only. Previous chemotherapy treatment was associated with stronger risks than radiation treatment for myeloid leukemia overall (OR = 4.1; 95% CI, 1.3–12.6), AML (OR = 5.1; 95% CI, 1.6–16.5), and CML (OR = 3.6; 95% CI, 0.9–15.1). Past cancer treatment with both radiation and chemotherapy increased the risk of myeloid leukemia overall by fivefold (95% CI, 2.0–12.3), of AML by sixfold (95% CI, 2.4–15.4), and of CML by 2.2-fold (95% CI, 0.5–9.5) (Table 3). No particular pattern emerged for types of cancers reported by cases versus controls, with prostate and breast cancer reported most frequently by men and women, respectively, in both groups (data not shown).

Discussion

A few population-based studies have examined the associations between UC and adult myeloid leukemia. In a Swedish cohort of 27,559 patients with UC, approximately twofold increased risks for both AML and CML were reported [4]. Another Swedish study of UC patients reported a significant standardized incident ratio (SIR) for CML (SIR, 3.0; 95% CI, 1.4–5.3), but not AML, for cases hospitalized at least 1 year before their leukemia diagnosis [5]. A US study of adult leukemia ($n = 7924$ AML and 2174 CML cases) using data from the Surveillance Epidemiology and End Results Medicare database reported a significant increased risk of AML (OR = 1.7), but not CML (OR = 0.7), associated with UC [1]. Finally, a large 2011 Swedish study that linked the cancer and inpatient registries reported no association between AML and UC (OR = 0.8) [6]. However, data on UC were obtained from the inpatient patient registry; thus, only severe cases requiring hospitalization would be captured. We used a case–control study design that collected data through survey methods, which strengthen the existing evidence for a positive relationship between UC and myeloid leukemia, particularly AML.

A relationship between inflammatory bowel diseases (UC and Crohn's disease) and leukemia may result from thiopurine treatment [10]. Azathioprine, an immune suppressant, has been classified as a carcinogen for non-Hodgkin lymphoma and skin cancer [11]. An increased frequency of somatic mutations in the hypoxanthine phosphoribosyltransferase (HPRT) locus has been detected in the T lymphocytes of thiopurine-treated inflammatory bowel disease patients [12]. Interestingly, a Nordic study of childhood leukemia survivors reported significant associations between duration and intensity of 6-MP/Methotrexate maintenance therapy and development of secondary AML [13]. However, leukemia cases have also been noted in association with UC in the absence of thiopurine treatment [14], perhaps due to coincidence or to underlying biological factors predisposing to both conditions. It will be important in future studies to collect information on medical treatment for UC and Crohn's disease to determine whether thiopurines or other drugs used to treat UC and Crohn's disease increase the risk of myeloid leukemia.

Patients with myeloproliferative disorders have been reported as having a higher prevalence of gastric ulcers [15], but there are no known reported associations between peptic ulcer and CML, which is classified as a myeloproliferative neoplasm. Gastric ulcers are associated with aspirin use and *Helicobacter (H.) pylori* infection, both inducing stomach lining inflammation. Aspirin use was not a confounder in our study. *H. pylori* infection has not been linked to CML specifically, although it has been linked with other adult hematologic malignancies [16] and with childhood leukemia [17], with the underlying biology remaining unclear.

Three studies [1, 6, 7] found significant positive associations between rheumatoid arthritis and myeloid leukemia, which we did not confirm.

Finally, a previous cancer diagnosis and treatment with radiation or chemotherapy were strongly related to both AML and CML. Cancer treatment with radiation, alkylating agents, and DNA topoisomerase II inhibitors has been linked to therapy-related AML (t-AML) [18]. Both AML and CML have been associated with radiation exposure in studies of atomic bomb survivors [19, 20], and evidence also suggests an association with previous cancer radiation treatment [21–23]. We note that in our study, previous radiation treatment for cancer was not significantly associated with AML, which is in contrast to studies of atomic bomb survivors that have indicated an age of exposure-dependent increased risk of AML in association with radiation exposure. The differences between our results and those of atomic bomb survivors could be due to age at exposure since no significant effect of radiation exposure on AML risk was observed in individuals who were older than 30 years at the time of the atomic bombings [20]. Evidence also indicates an increased risk of CML in association with cytotoxic therapy [18, 24]. It is noteworthy that a personal history of cancer was an independent predictor for both AML and CML in models that controlled for therapy. One possible explanation for this finding is that genetic factors that influence susceptibility to multiple cancers may be involved.

Strengths of our study include a large population-based study design with data collected from patients directly, rather than from surrogate respondents. Participation rates and sociodemographic factors were also similar for cases and controls; nevertheless, selection bias could have influenced our results if controls who participated in the study were less likely to have medical conditions than individuals in the source cohort. It is also possible that our findings could be due to chance, given multiple comparisons and small numbers of exposed subjects. Cases may be more likely than controls to remember past medical conditions. Differential reporting may also have occurred due to symptoms (such as UC) varying over time [25]. Notably, UC prevalence among controls was higher than that expected from previous estimates [26]. Finally, generalizability is limited to adult myeloid leukemia patients with relatively longer survival times.

In summary, we found significant increased risks between a history of certain medical conditions and adult leukemia. UC significantly increased the risk of AML, while for CML, peptic ulcer significantly increased the risk. A personal history of cancer strongly increased the risk of AML and especially CML with our estimates indicating that chemotherapy was a stronger risk factor than radiation therapy. The increased risk of myeloid leukemia in association with a personal history of cancer that is independent from therapy suggests that some individuals with leukemia may have an underlying genetic susceptibility to cancer.

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Table 1

Characteristics of study participants

Characteristic	Controls (N = 701) No. (%)	Myeloid leukemia (N = 670) No. (%)	AML (N = 420) No. (%)	CML (N = 186) No. (%)
<i>Age (years)^a</i>				
20–29	45 (6.4)	42 (6.3)	26 (6.2)	12 (6.5)
30–39	53 (7.6)	48 (7.2)	32 (7.6)	15 (8.1)
40–49	102 (14.6)	102 (15.2)	64 (15.2)	33 (17.7)
50–59	157 (22.4)	143 (21.3)	90 (21.4)	48 (25.8)
60–69	205 (29.2)	195 (29.1)	129 (30.7)	48 (25.8)
70–79	139 (19.8)	140 (20.9)	79 (18.8)	30 (16.1)
<i>Sex</i>				
Male	343 (48.9)	392 (58.5)	249 (59.3)	107 (57.5)
Female	358 (51.1)	278 (41.5)	171 (40.7)	79 (42.5)
<i>Race/ethnicity</i>				
White, non-Hispanic	671 (95.7)	629 (93.9)	394 (93.8)	172 (92.5)
Other	30 (4.3)	41 (6.1)	26 (6.2)	14 (7.5)
<i>Education</i>				
High school graduate	231 (33.0)	212 (31.6)	122 (29.1)	67 (36.0)
Some post-high school	240 (34.2)	236 (35.2)	161 (38.3)	55 (29.6)
College graduate	230 (32.8)	222 (33.1)	137 (32.6)	64 (34.4)
<i>Income (US dollars)^b</i>				
<\$40,000	255 (36.9)	260 (39.7)	149 (36.4)	80 (43.7)
\$40,000–\$80,000	281 (40.7)	246 (37.6)	165 (40.3)	64 (35.0)
>\$80,000	155 (22.4)	149 (22.8)	95 (23.2)	39 (21.3)
<i>Smoking status</i>				
Never	358 (51.7)	288 (43.4)	179 (43.2)	81 (43.8)
Ever	334 (48.3)	375 (56.6)	235 (56.8)	104 (56.2)
<i>Married</i>				
Yes	513 (73.2)	481 (71.8)	315 (75.0)	122 (65.6)
No	188 (26.8)	189 (28.2)	105 (25.0)	64 (34.4)
<i>BMI category^c</i>				
Normal	227 (32.5)	152 (22.8)	96 (22.9)	41 (22.2)
Overweight	242 (34.7)	231 (34.6)	147 (35.1)	59 (31.9)
Obese	229 (32.8)	285 (42.7)	176 (42.0)	85 (46.0)
<i>History of Benzene or other solvent exposure</i>				
No	651 (93.3)	560 (84.0)	343 (82.1)	164 (88.2)
Yes	47 (6.7)	107 (16.0)	75 (17.9)	22 (11.8)

^a Matching variable

^b Income may include retirement income

^c BMI based on weight 2 years prior to diagnosis/recruitment date

Table 2

Associations between medical conditions and risk of adult myeloid leukemia

		Controls		Myeloid leukemia		AML		CML	
		<i>N</i> (%)		<i>N</i> (%)	OR ² (95% CI)	<i>N</i> (%)	OR ² (95% CI)	<i>N</i> (%)	OR ² (95% CI)
<i>Autoimmune conditions^b</i>									
Any autoimmune condition ^c	No	587 (51.5)		552 (49.5)	1.0	354 (37.6)	1.0	150 (83.3)	1.0
	Yes	102 (50.5)		100 (49.5)	1.1 (0.8–1.6)	56 (35.4)	1.0 (0.7–1.5)	30 (22.7)	1.3 (0.8–2.2)
Rheumatoid arthritis	No	639 (94.0)		614 (95.3)	1.0	395 (96.6)	1.0	164 (93.2)	1.0
	Yes	41 (6.0)		30 (4.7)	0.8 (0.5–1.3)	14 (3.4)	0.6 (0.3–1.1)	12 (6.8)	1.3 (0.6–2.5)
Hypothyroidism	No	635 (94.0)		603 (93)	1.0	384 (94.6)	1.0	180 (98.4)	1.0
	Yes	41 (6)		42 (7)	1.2 (0.8–2.0)	22 (5.4)	1.0 (0.6–1.8)	14 (7.7)	1.5 (0.8–3.0)
Hyperthyroidism	No	655 (96.0)		627 (97)	1.0	392 (96.8)	1.0	169 (92.4)	1.0
	Yes	683 (99.4)		641 (98.2)	1.0	402 (98)	1.0	182 (98.9)	1.0
Ulcerative colitis	No	683 (99.4)		641 (98.2)	1.0	402 (98)	1.0	182 (98.9)	1.0
	Yes	4 (0.6)		12 (1.8)	3.5 (1.1–11)	8 (2.0)	3.8 (1.1–13)	2 (1.1)	2.0 (0.4–11)
<i>Other conditions^b</i>									
Heart disease	No	611 (90.5)		553 (86.8)	1.0	353 (87.8)	1.0	153 (85.5)	1.0
	Yes	64 (9.5)		84 (13.2)	1.3 (0.9–1.9)	49 (12.2)	1.2 (0.8–1.8)	26 (14.5)	1.7 (1.0–2.8) ^d
High blood pressure	No	418 (63.4)		397 (62.7)	1.0	258 (64.7)	1.0	104 (59.8)	1.0
	Yes	241 (37)		236 (37)	0.9 (0.7–1.2)	141 (35)	0.8 (0.6–1.1)	70 (40.2)	1.2 (0.8–1.8)
Diabetes mellitus	No	611 (52.3)		557 (87.3)	1.0	352 (87.6)	1.0	153 (86.4)	1.0
	Yes	71 (10.4)		81 (12.7)	1.1 (0.7–1.8)	50 (12.4)	1.1 (0.7–1.6)	24 (13.6)	1.2 (0.7–2.0)
Osteoarthritis	No	584 (87.3)		573 (89.7)	1.0	362 (90.5)	1.0	162 (90)	1.0
	Yes	85 (12.7)		66 (10.3)	0.8 (0.5–1.1)	38 (9.5)	0.7 (0.5–1.1)	18 (10.0)	0.8 (0.5–1.4)
Eczema	No	620 (91.5)		598 (93.2)	1.0	380 (93.8)	1.0	164 (91.6)	1.0
	Yes	58 (8.5)		44 (6.9)	0.8 (0.6–1.3)	25 (6.2)	0.8 (0.5–1.2)	15 (8.4)	1.1 (0.6–1.9)
Contact dermatitis	No	650 (95.3)		626 (96.8)	1.0	398 (97.1)	1.0	171 (96.1)	1.0
	Yes	32 (4.7)		21 (3.3)	0.7 (0.4–1.2)	12 (2.9)	0.6 (0.3–1.3)	7 (3.9)	0.8 (0.4–1.9)
Peptic ulcer	No	652 (95)		608 (94)	1.0	392 (95.8)	1.0	166 (91.2)	1.0
	Yes	31 (5)		42 (6)	1.4 (0.9–2.3)	17 (4.2)	0.9 (0.5–1.6)	16 (8.8)	2.0 (1.1–3.8)
Cirrhosis	No	679 (98.7)		644 (98.9)	1.0	407 (99.0)	1.0	178 (98.3)	1.0
	Yes	9 (1.3)		7 (1.1)	0.7 (0.3–2.0)	4 (1.0)	0.7 (0.2–2.2)	3 (1.7)	1.2 (0.3–4.6)
Mononucleosis	No	634 (92.7)		600 (92.0)	1.0	380 (92.7)	1.0	168 (91.8)	1.0
	Yes	50 (7.3)		52 (8.0)	1.2 (0.8–1.8)	30 (7.3)	1.0 (0.6–1.7)	15 (8.2)	1.2 (0.6–2.0)
Chronic fatigue syndrome	No	682 (99.4)		642 (99.1)	1.0	409 (99.8)	1.0	175 (97.8)	1.0
	Yes	4 (0.6)		6 (0.9)	1.6 (0.4–5.8)	1 (0.2)	0.4 (0.0–4.0)	4 (2.2)	4.2 (1.0–18) ^d
Epilepsy	No	679 (99.0)		644 (98.6)	1.0	406 (98.8)	1.0	181 (98.9)	1.0
	Yes	7 (1.0)		9 (1.4)	1.4 (0.5–3.7)	5 (1.2)	1.2 (0.4–3.8)	2 (1.1)	1.1 (0.2–5.5)

Medical conditions diagnosed within 1 year of leukemia diagnosis (cases) or 1 year of recruitment date (controls) were excluded Bold values represent statistical significance at the $p < 0.05$ level

^aModels adjusted for age (deciles), sex, and BMI (underweight/normal weight, overweight, obese)

^bThe number of cases and controls for each condition does not add up to the total number of cases ($n = 670$) and controls ($n = 701$) due to missing data for the particular medical condition

^cIncludes the following conditions: polymyositis, rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus, hypothyroidism, hyperthyroidism, ankylosing spondylitis, Crohn's disease, ulcerative colitis, and celiac disease

^dHeart disease and chronic fatigue syndrome are rounded to 1.0 for the lower CI; thus, they are not significant at $\alpha < 0.05$

Table 3

Associations between personal history of cancer/cancer treatment(s) and risk of myeloid leukemia

		Controls	Myeloid leukemia		AML		CML	
		<i>N</i> (%)	<i>N</i> (%)	OR (95% CI)	<i>N</i> (%)	OR (95% CI)	<i>N</i> (%)	OR (95% CI)
<i>Personal history of cancer^{a,b}</i>								
No	645 (95.8)	557 (92.1)	1.0	353 (93.1)	1.0	152 (89.4)	1.0	
Yes	50 (7.2)	106 (15.8)	2.1 (1.3–3.5)	65 (16)	1.8 (1.0–3.1)	32 (17.2)	3.6 (1.9–7.0)	
<i>Radiation and/or chemotherapy treatment^{b,c}</i>								
None	673 (96.4)	605 (90.6)	1.0	379 (90.5)	1.0	170 (91.9)	1.0	
Radiation alone	12 (1.7)	18 (2.7)	1.6 (0.8–3.4)	9 (2.2)	1.3 (0.6–3.2)	7 (3.8)	2.7 (1.0–7.3)	
Chemotherapy alone	4 (0.6)	15 (2.3)	4.1 (1.3–12.6)	11 (2.6)	5.1 (1.6–16.5)	4 (2.2)	3.6 (0.9–15.1)	
Both	6 (0.9)	25 (3.7)	5.0 (2.0–12.3)	19 (4.5)	6.0 (2.4–15.4)	3 (1.6)	2.2 (0.5–9.5)	

Bold values represent statistical significance at the $p < 0.05$ level^aORs adjusted for age (deciles), sex, and BMI (underweight/normal weight, overweight, obese), radiation or chemotherapy treatment (yes vs. no)^bThree controls and five cases each had missing data on personal history of cancer, radiation treatment, and chemotherapy treatment^cORs adjusted for age (deciles), sex, and BMI (underweight/normal weight, overweight, obese)