Risk of Non-hematologic Cancer in Individuals with High Count Monoclonal B-Cell Lymphocytosis (MBL)

Benjamin M. Solomon, M.D.[1,2], **Kari G. Chaffee, M.S.**[3], **Jonathan Moreira, M.D.**[4], **Susan M. Schwager**[5,6], **James R. Cerhan, M.D., Ph.D.**[3], **Timothy G. Call, M.D.**[5,6], **Neil E. Kay, M.D.**[5,6], **Susan L. Slager, Ph.D.**[3], and **Tait D. Shanafelt, M.D.**[5,6]

[1]University of South Dakota Sanford School of Medicine

[2]Avera Medical Group Oncology and Hematology

[3]Mayo Clinic Department of Health Sciences Research

[4]Northwestern University Feinberg School of Medicine

[5]Mayo Clinic Department of Medicine

[6]Division of Hematology

Abstract

It is unknown whether individuals with monoclonal B-cell lymphocytosis (MBL) are at risk for adverse outcomes associated with chronic lymphocytic leukemia (CLL), such as the risk of non-hematologic cancer. We identified all locally-residing individuals diagnosed with high count MBL at Mayo Clinic between 1999 and 2009 and compared their rates of non-hematologic cancer to that of patients with CLL and two control cohorts: general medicine patients and patients who underwent clinical evaluation with flow cytometry but who had no hematologic malignancy. After excluding individuals with prior cancers, there were 107 high count MBL cases, 132 CLL cases, 589 clinic controls, and 482 flow cytometry controls. With 4.6 years median follow-up, 14 (13%) individuals with high count MBL, 21 (4%) clinic controls (comparison MBL p<0.0001), 18 (4%) flow controls (comparison MBL p=0.0001), and 16 (12%) CLL patients (comparison MBL p=0.82) developed non-hematologic cancer. On multivariable Cox regression analysis, individuals with high count MBL had higher risk of non-hematologic cancer than flow controls (HR=2.36; p=0.04) and borderline higher risk than clinic controls (HR=2.00; p=0.07). Patients with high count MBL appear to be at increased risk for non-hematologic cancer, further reinforcing that high count MBL has a distinct clinical phenotype despite low risk of progression to CLL.

Corresponding Author: Tait D. Shanafelt, M.D., Phone:(507) 266-1154, FAX:(507) 266-4972, ; Email: shanafelt.tait@mayo.edu

Keywords

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INTRODUCTION

Chronic lymphocytic leukemia (CLL) is one of the most common hematologic malignancies, affecting approximately 5–10 people per 100,000.(1) Population-based data indicate that patients with CLL are at increased risk for developing second cancers compared to the general population.(2–5) Specific malignancies for which patients with CLL seem to be at risk include other lymphoid malignancies, myelodysplastic syndromes, and certain solid tumors (e.g. melanoma, breast, lung).(2–4, 6, 7) In addition, patients who develop non-hematologic cancer in the setting of CLL may have inferior overall survival (OS) and cancer-specific survival (i.e. death due to breast cancer in a patient with breast cancer).(8) A variety of factors may explain the increased risk of cancer in patients with CLL including: i) shared genetic risk factors, ii) shared behavioral risks or exposures , iii) side effects of CLL treatment, iv) dysregulation of immune surveillance, and v) ascertainment bias.

The need for better understanding of the risk between CLL and the risk of second cancers has been heightened by the discovery of monoclonal B-cell lymphocytosis (MBL). MBL is a common asymptomatic condition characterized by a clonal B-cell population detected in the blood or bone marrow without cytopenias, lymphadenopathy, or organomegaly.(9) In screening studies of the population, MBL is prevalent in 3–5% of adults over age 40, and this rate increases with age.(10–13) MBL is an asymptomatic precursor state to CLL and other types of indolent non-Hodgkin lymphoma (NHL).(14) Only a small subset of patients with MBL will come to clinical attention, typically during evaluation for low grade lymphocytosis (designated now as high count MBL). The rate of progression to CLL requiring treatment among individuals with high count MBL is ~1%/year, and the vast majority of patients with high count MBL will never develop a B-cell malignancy.(10, 12, 14, 15) Recent data indicate that individuals with high count MBL are at increased risk of infection similar to CLL.(16) It is unknown whether individuals with high count MBL are at risk for other adverse outcomes associated with CLL, such as increased risk of non-hematologic cancer.(2, 3, 5, 17)

We investigated the incidence of non-hematologic cancer in a cohort of locally dwelling individuals with newly identified high count MBL compared to two control cohorts and a cohort of patients with newly diagnosed CLL.

METHODS

Mayo Clinic Rochester is located in Olmsted County, Minnesota, and is the primary center for hematologic care in a region including southeastern Minnesota, northern Iowa, and western Wisconsin. No other hematology specialty centers are available within a 50-mile

radius of Mayo Clinic. The methods to assemble our MBL, CLL, and clinic control cohorts have been previously described.(16, [18])

Patients

To explore the risk of non-hematologic cancer in a local, community dwelling cohort of individuals with CLL-phenotype high count MBL, we used the Mayo Clinic CLL database to identify all individuals with newly diagnosed high-count MBL seen in the Mayo Clinic Hematology Division between January 1, 1999 and December 31, 2009. Of the 154 high count MBL cases residing within 50 miles of Mayo Clinic, the analysis was limited to 107 high count MBL cases who did not have a prior non-hematologic cancer diagnosis at the time high count MBL was identified.

Two control cohorts were used for comparison. The first consisted of 596 adult general medicine patients (clinic controls), residing within 50 miles of Mayo Clinic, who were seen for a general medical exam, and who enrolled as controls in a prospective case-control study of non-Hodgkin lymphoma between April 25, 2004 and December 31, 2009 (clinic controls) (19). The 589 (98.8%) individuals in this cohort with no prior cancer diagnosis at the time of enrollment were included in the analysis. To account for potential bias in the types of individuals undergoing flow cytometry evaluation (e.g., the group from which individuals with MBL was identified), a second comparison cohort (flow controls) was identified which consisted of all adult residents of Olmsted County, Minnesota, without a known hematologic malignancy who underwent peripheral blood flow cytometry at Mayo Clinic during the study interval and were found to have normal flow cytometry results (e.g., no hematologic malignancy). A total of 482 individuals had approved use of their clinical records for research purposes and were included in this analysis.

Rates of non-hematologic cancer in the MBL cohort were also compared to a cohort of patients with newly diagnosed CLL seen in the same time interval as the MBL cohort and also living within 50 miles of Mayo Clinic. Of the 174 identified CLL cases fitting these criteria, 132 had no prior non-hematologic cancer and were included in the analysis.

Non-hematologic cancer diagnoses were identified using the Mayo Clinic Tumor Registry as well as review of medical records in all 4 cohorts (MBL, CLL, Clinic Controls, Flow Controls). The Mayo Clinic Tumor Registry is an information system that prospectively collects and maintains data on patients diagnosed with a malignant condition, excluding non-melanoma skin cancer, at Mayo Clinic. The registry includes demographic information, diagnostic findings, primary site of malignancy, tumor stage, and treatment/follow-up information obtained from the medical record. Patients with MBL/CLL with a non-hematologic cancer diagnosis >2 months prior to the diagnosis date of MBL/CLL were excluded from analysis. Patients who were diagnosed with a non-hematologic cancer within 2 months of diagnosis with MBL or CLL (e.g. 2 months before or 2 months after) were considered to have a "concurrent" diagnosis. Patients in the control cohorts with cancer prior to the consent date (clinic controls) or normal flow cytometry date (flow controls) were excluded from the analysis. To evaluate for possible ascertainment bias, analysis was conducted both including and excluding "concurrently" diagnosed cancers. Data on comorbid conditions was collected from the medical record as previously described.(18)

This study was conducted with approval from the Mayo Clinic Institutional Review Board and in accordance with the Declaration of Helsinki.

Differences in patient characteristics and cancers were compared between groups using chi-square or Fisher's exact tests for qualitative variables or Kruskal-Wallis test for quantitative variables. The primary endpoint was development of new non-hematologic cancer. When the death rate is high, the standard Kaplan-Meier approach will overestimate the cumulative incidence rate of second cancers, as those who die are coded as censored events; therefore, death was primarily modeled using the more conservative approach modeling death as a competing event which provides a more accurate estimate of incidence (Kaplan-Meier estimates provided in Supplemental Figures 1A and 1B).[20] Gray's test for equality of cumulative incidence functions (CIF) was used to compare time to first non-hematologic cancer between groups.[21] To access the effect of risk factors on time to non-hematologic cancer after adjusting for confounding factors such as age, sex, and major comorbidities,[18] we modeled the proportional hazards of the sub-distributions of the CIF for the disease groups.[22]

RESULTS

After excluding patients with prior cancers, there were 107 patients in the MBL cohort, 132 in the CLL cohort, 482 in the flow control cohort, and 589 in the clinic control cohort. Individuals with high count MBL and CLL tended to be older and were more likely to be male than both the clinic controls and flow cytometry controls (Table 1). A summary of co-morbid health conditions is provided in Supplemental Table 2. Individuals with high count MBL and CLL were more likely to have comorbid health conditions than clinic controls (p=0.001) but not flow cytometry controls (p=0.72).

Median follow-up of the MBL, CLL, flow control, and clinic control cohorts was 4.8 years, 4.5 years, 5.1 years, and 4.3 years, respectively. Fourteen (13%) individuals with high count MBL developed non-hematologic cancer as compared to 21 (4%) of the clinic controls (p<0.0001; Table 2). Sixteen (12%) CLL patients developed non-hematologic cancer, suggesting a similar rate to that of high count MBL patients (p=0.82; Table 2). Eighteen (4%) flow controls developed non-hematologic cancer; this rate was significantly lower than in the MBL cohort (p=0.0001; Table 3). Specifically, the MBL cohort had a higher cumulative incidence of cancer of the breast, lung, and gastrointestinal tract than both clinic (Table 2) and flow cytometry controls (Table 3). The higher rate of second cancer in individuals with MBL (11%) relative to clinic controls (4%; p=0.002) and flow controls (3%; p=0.0004) persisted when patients with concurrent diagnosed cancers were excluded from the analysis.

Time to development of non-hematologic cancer was shorter in MBL and CLL cohorts versus either the clinic controls (p-value=0.003; Figure 1A) or the flow controls (p-value=0.0001; Figure 1B). The shorter time to non-hematologic cancer in individuals with high count MBL and CLL remained when patients treated for progressive CLL (in both CLL and MBL cohort) were censored at the date of their treatment (clinic controls p=0.002, Figure 1C; flow controls p=0.0002, Figure 1D). Shorter time to non-hematologic cancer in

individuals with high count MBL also remained when patients with concurrently diagnosed cancers were excluded from the analysis (clinic controls p=0.03, Figure 1E; flow controls p=0.0006; Figure 1F).

Finally, we performed a pooled analysis of all of the MBL, CLL, and clinic controls using Cox regression (n=828) adjusting for age, sex, major comorbidities, presence of high count MBL, and diagnosis of CLL (Table 4). Age (HR each year older=1.02; 95% CI=(1.003–1.04); p=0.02) was a risk factor for non-hematologic cancer while high count MBL was borderline significant (HR=2.00; 95% CI=(0.94–4.24); p=0.07) . When multivariable analysis was repeated using the flow controls: age (HR each year older=1.03; 95% CI=(1.01–1.05); p=0.004), high count MBL (HR=2.36; 95% CI=(1.05–5.34); p=0.042), and CLL (HR=2.25; 85% CI=(1.01–5.01); p=0.047) were independent risk factors for non-hematologic cancer. The results were similar for both models when the effect of age was modeled in a non-linear (e.g. logarithmic) manner (Supplemental Table 1).

DISCUSSION

We present the first study, to our knowledge, to explore the risk of non-hematologic cancer in patients with high count MBL relative to controls. This cohort study, comparing the risk of non-hematologic cancer in individuals with high count MBL to two separate control groups, demonstrates increased risk of non-hematologic cancer in patients with high count MBL. Individuals with high count MBL were at approximately two-fold risk for non-hematologic cancer compared to both clinic controls and flow cytometry controls. The risk of non-hematologic cancer among individuals with high count MBL was similar to the risk in patients with CLL. This increased risk persisted and was of similar magnitude in multivariate analysis with flow controls adjusting for age, gender, and major comorbidities while the multi-variate analysis using clinic controls demonstrated risk of similar magnitude at the threshold of statistical significance. The results for both models were also similar when age was modeled on the logarithmic scale. In a previous analysis, we found individuals with high count MBL were at increased risk of infection requiring hospitalization,(16) suggesting immune function may be impaired in individuals with high count MBL. The increased risk of non-hematologic cancer in patients with high count MBL seen in the current study adds to the evidence that high count MBL has a clinical phenotype, despite the low risk of progression to CLL requiring treatment. In addition to increased risk of developing a second cancer, large population-based studies have demonstrated that patients with co-existent CLL and certain malignancies have inferior overall and cancer-specific survival compared to controls without CLL.(8, 23) This observation raises important questions regarding risk stratification and management of a second primary cancer in patients with CLL. It is unknown whether high count MBL may also be associated with inferior prognosis in patients with other malignancies.

Despite increased risk of non-hematologic cancer, the appropriate cancer screening approach for individuals with high count MBL or CLL is unknown. In the current study, patients with high count MBL appeared to have an increased risk of cancer of the breast, lung, and gastrointestinal tract. Among these, screening is recommended for female breast, colorectal, and lung, depending on patient age and risk factors.(24–26) At a minimum, patients with

high count MBL should be encouraged to undergo age- and gender-appropriate cancer screening consistent with national screening guidelines.

It should be noted that, prior to 2005, many individuals now classified as having high count MBL would have been diagnosed with Rai stage 0 CLL.(9, [27], [28]) Although some have debated the appropriateness of this reclassification,(29) multiple studies have demonstrated the reclassification better anchors the diagnosis of CLL to the likelihood a patient will develop clinical manifestations of their disease that actually require treatment.(10, [15], [30], [31]) Given the low rates of clinical progression among most individuals with high count MBL(12, [15]) and the fact this diagnosis does not appear to impact survival,(32) this reclassification may also decrease unnecessary anxiety and emotional distress precipitated by diagnosing individuals with "leukemia" when they have a very low risk of developing disease-related symptoms or requiring treatment during their lifetime. Despite these potentially beneficial aspects of this reclassification, the apparent increased risk of infection(16) and non-hematologic cancers suggests that individuals with high count MBL are at risk for various complications and may benefit from some of the supportive care measures (e.g., vaccination strategies, screening for skin cancer) recommended for patients with CLL.(33, [34]) Collectively, the risk of serious infection and/or non-hematologic cancer among individuals with high count MBL appear to be greater than the likelihood they will progress to require treatment for CLL.

It should be emphasized that our findings relate to patients with high count MBL. It is unknown whether the increased risk of non-hematologic cancer also applies to individuals with low count MBL. Additional studies exploring that aspect would be noteworthy, given that low count MBL impacts ~5% of the general population over the age of 40. Given this high prevalence in the general population, an increased risk of non-hematologic cancer among patients with low count MBL could have substantial population-level implications.

Our study has several limitations. First, the CLL and MBL cohorts were derived from patients residing within 50 miles of Mayo Clinic. Consistent with the demographic composition of this region, the cohorts were comprised predominately of Caucasian individuals, and these results may or may not generalize to a more diverse patient population. Second, while both the Mayo Clinic CLL database and the Mayo Clinic Cancer Registry were cross-referenced, it is possible that there was incomplete ascertainment of all new non-hematologic cancer diagnoses. We also did not have data on non-melanoma skin cancers. We did not have data on screening. Third, we were unable to adjust for socioeconomic and lifestyle factors, particularly smoking and body mass index, that could influence risk of malignancy. Although these factors do not relate to the risk of developing CLL, they do relate to the risk of developing other cancers. Fourth, the cohorts were of insufficient size to provide enough statistical power to detect small differences in the risk of uncommon malignancies.

Our study also has several strengths. First, although many studies have demonstrated increased risk of non-hematologic cancer in patients with CLL, ours is the only study to evaluate the risk of non-hematologic cancer in a community-dwelling cohort of patients with high count MBL. Second, we were able to use two separate control groups. Although we

cannot exclude a healthy volunteer bias leading to a decreased rate of non-hematologic cancer in the clinic controls, this bias would not affect the flow cytometry control cohort. The flow control cohort also provides evidence that the increased incidence of non-hematologic cancer in the MBL cohort, relative to clinic controls, was not simply due to ascertainment bias in a cohort under increased medical scrutiny. It is also notable that the hazard ratio for risk of non-hematologic cancer in high count MBL was similar regardless of which control group was used for comparison and regardless of whether age was used as a linear or logarithmic variable. Third, both control groups were drawn from the same region as the MBL and CLL cohorts, which is more appropriate than a population-based control sample which can introduce bias in the context of clinic-based case ascertainment.(19)

In summary, patients with high count MBL appear to carry a ~two-fold increased risk of non-hematologic malignancy. Growing evidence suggests that high count MBL is not only a risk factor for progression to CLL, but also a risk factor for some of the recognized complications observed in individuals with of CLL, such as infection and malignancy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

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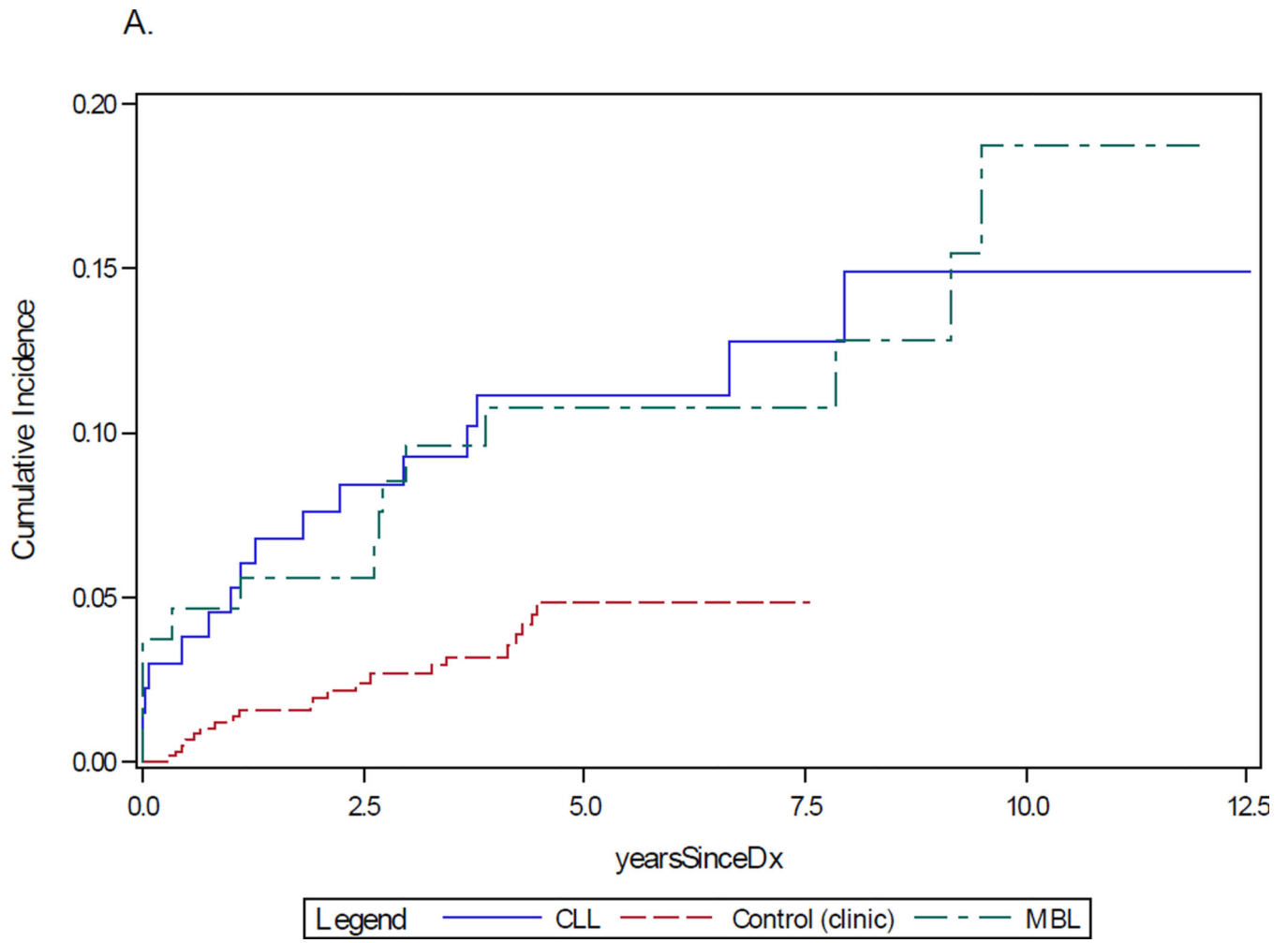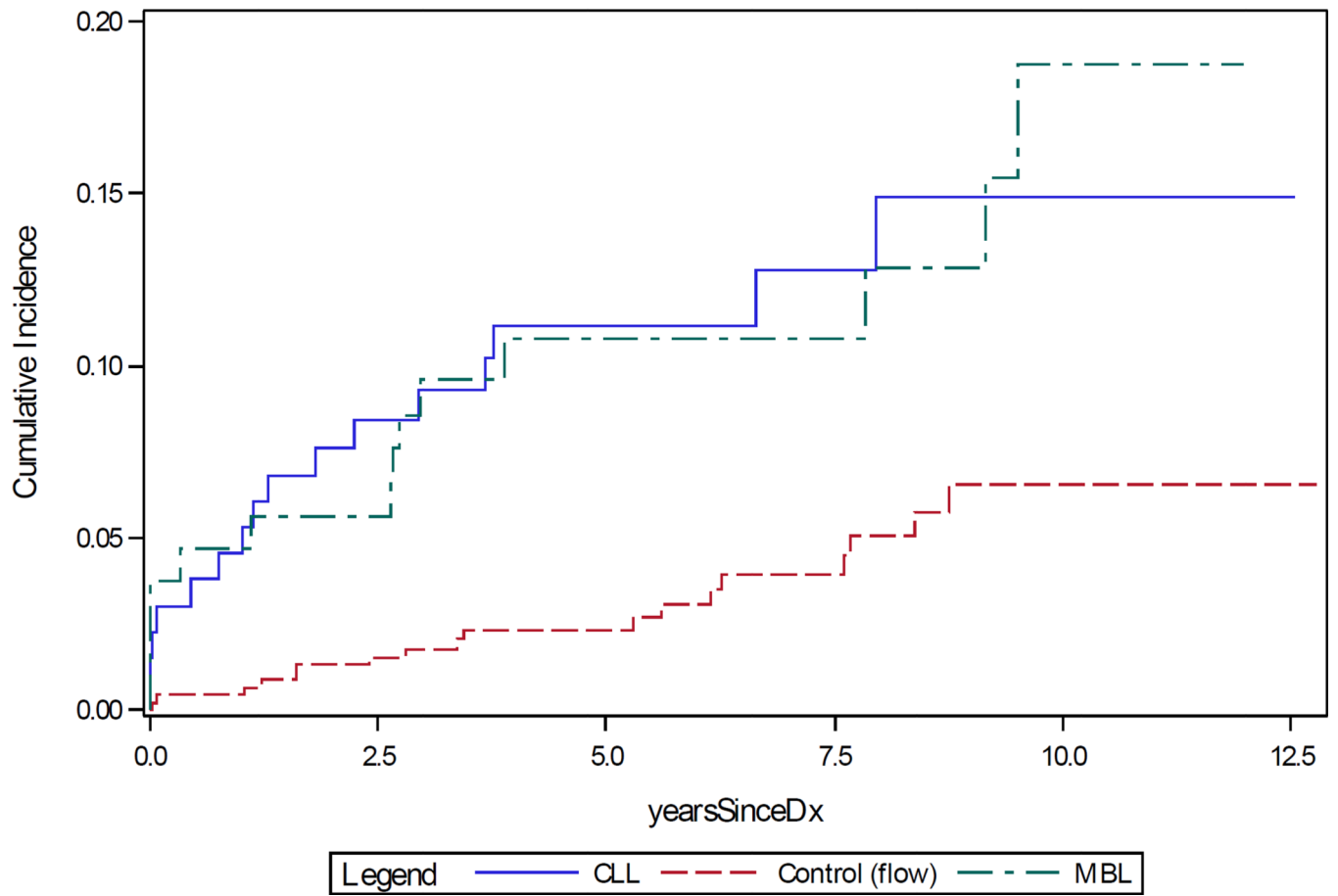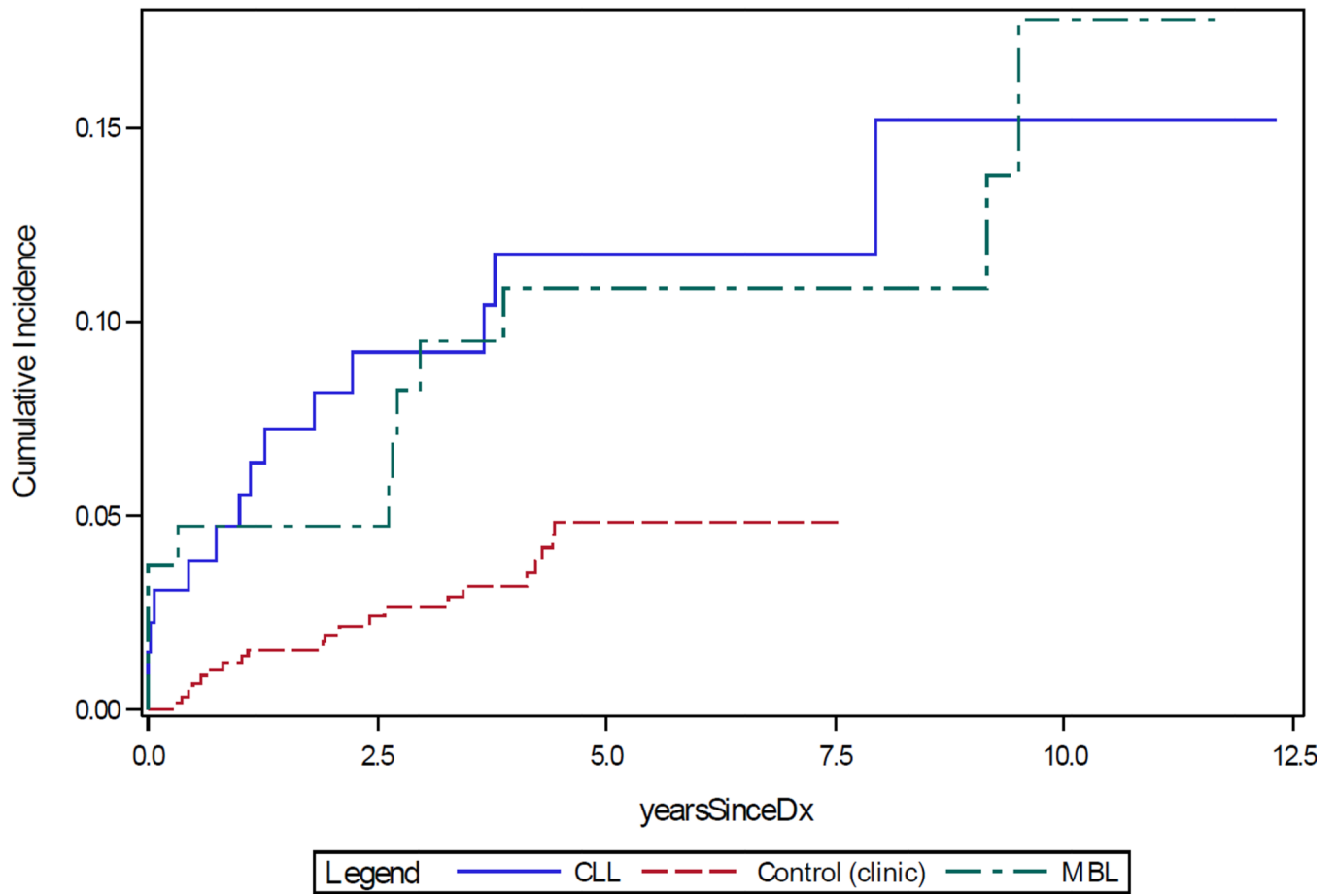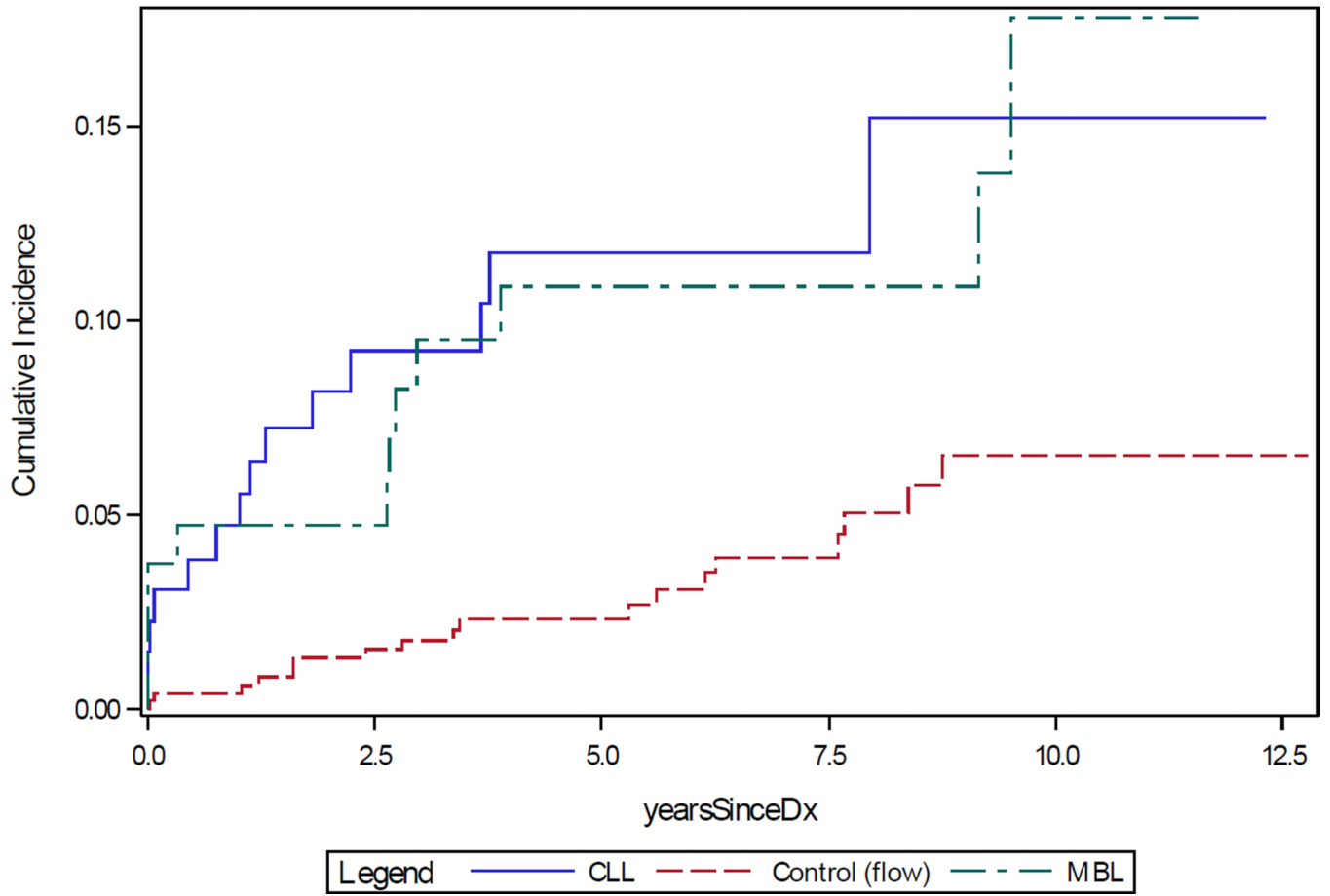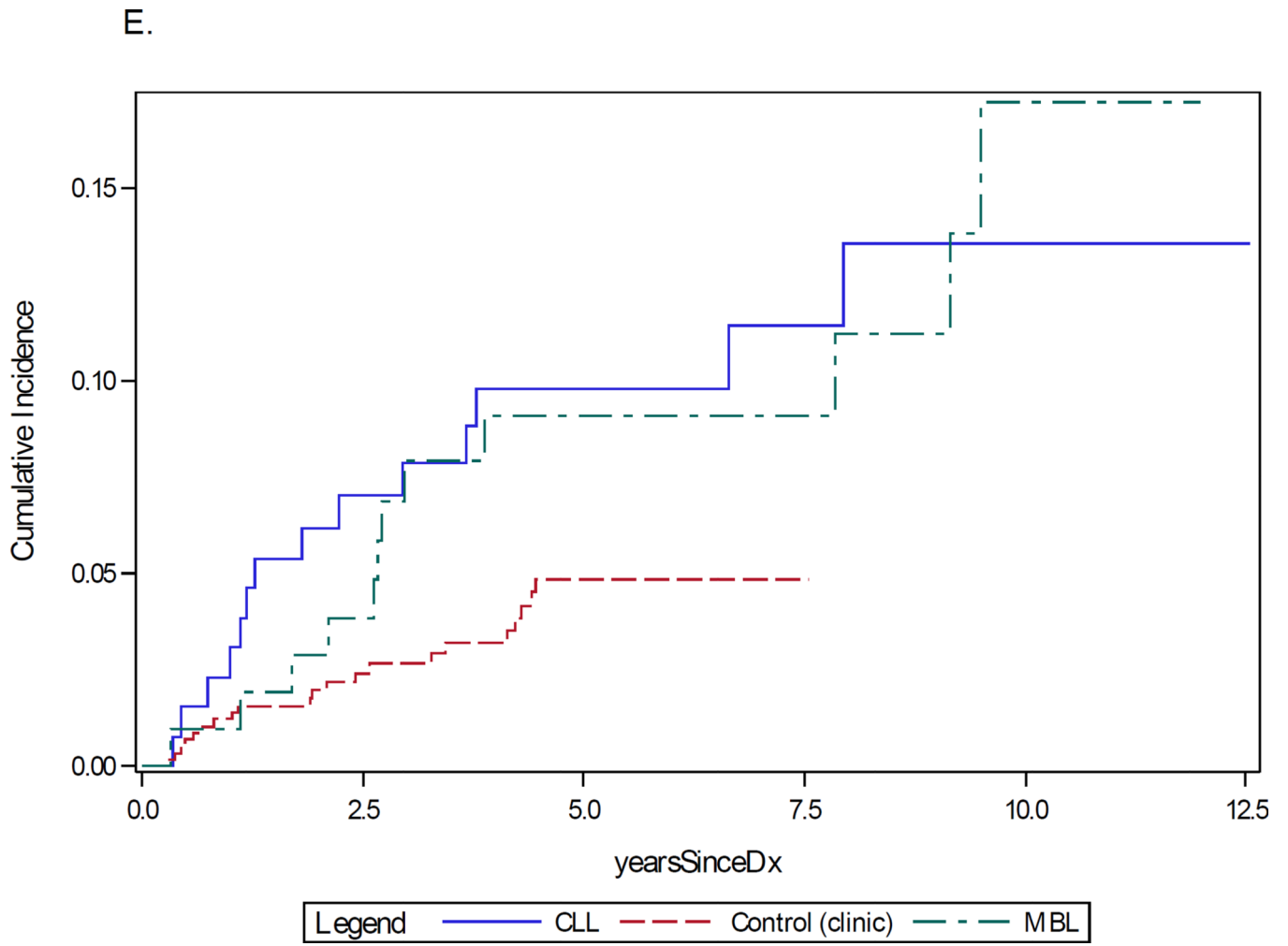
A.

Figure 1a

B.

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Figure 1b

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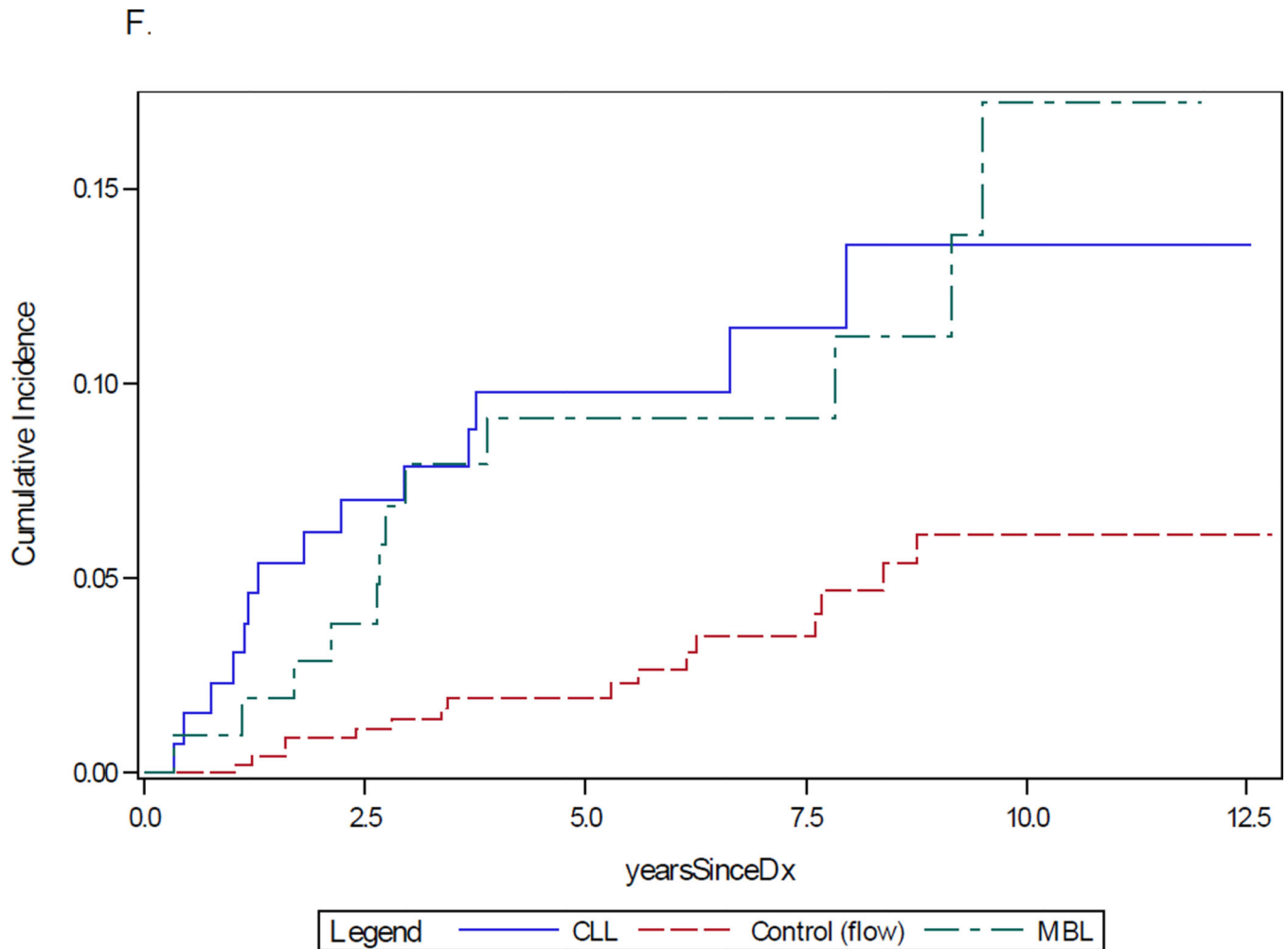
Figure 1f

Figure 1.

Time to Diagnosis non-hematologic cancer

A. Time from diagnosis to non-hematologic cancer, clinic control (Gray's test p-value=0.003)

B. Time from diagnosis to non-hematologic cancer, flow control (Gray's test p-value =0.0001)

C. Time from diagnosis to non-hematologic cancer, censored at treatment, clinic control (Gray's test p-value=0.002)

D. Time from diagnosis to non-hematologic cancer, censored at treatment, flow control (Gray's test p-value=0.0002)

E. Time from diagnosis to non-hematologic cancer, clinic control, exclude concurrent cancers (Gray's test p-value=0.03)

F. Time from diagnosis to non-hematologic cancer, flow control, exclude concurrent cancers (Gray's test p-value =0.0006)

Table 1

Patient Characteristics

Variable	CLL n=132	MBL n=107	Clinic controls n=589	Flow cytometry controls n=482
	n (%)	n (%)	n (%)	n (%)
Age				
Median (range)	68 (27–97)	69 (45–94)	58 (19–87)	51 (18–94)
Age 65 (n (%))	79 (60)	71 (66)	214 (36)	132 (27)
p-value [*]			**<0.0001**	**<0.0001**
Sex				
Female	44 (33)	43 (40)	316 (54)	298 (62)
Male	88 (67)	64 (60)	273 (46)	184 (38)
p-value [*]			**<0.0001**	**<0.0001**
Comorbidities (any major)	56 (42%)	51 (48%)	182 (31%)	215 (45%)
p-value [*]			**0.001**	0.72

[*] p-values based on the chi-square or Kruskal-Wallis tests are testing differences between MBL, CLL, and the specific control group characteristics

Table 2

Non-hematologic cancer in individuals with CLL and MBL compared to Clinic Controls

Cancer	CLL n=132	MBL n=107	Clinic controls n=589	p-value[1]
	n (%)	n (%)	n (%)	
Any cancer	16 (12)[2]	14 (13)[3]	21 (4)	**<0.0001**
Breast	0/44 (0)	3/43 (7)	1/316 (0.3)	**0.0002**
Lung	4 (3)	4 (4)	3 (0.5)	**0.005**
Gastro-intestinal	5 (4)	2 (2)	2 (0.3)	**0.002**
Pancreas	0 (0)	0 (0)	0 (0)	
Colorectal	4 (3)	1 (1)	0 (0)	
Liver	1 (1)	1 (1)	0 (0)	
Stomach	0 (0)	0 (0)	1 (0.2)	
Esophagus	0 (0)	0 (0)	1 (0.2)	
Genitourinary	2 (2)	1 (1)	1 (0.2)	0.1
Bladder	1 (1)	0 (0)	0 (0)	
Kidney	1 (1)	1 (1)	0 (0)	
Ureter	0 (0)	0 (0)	1 (0.2)	
Prostate	2/88 (2)	3/64 (5)	5/273 (2)	0.4
Gynecologic	1/44 (2)	1/43 (2)	2/316 (1)	0.38
Endometrial	1/44 (2)	1/43 (2)	1/316 (0.3)	
Ovarian	0/44 (0)	0/43 (0)	1/316 (0.3)	
Peritoneum	0/44 (0)	0/43 (0)	1/316 (0.3)	
Nervous System	1 (1)	2 (2)	0 (0)	**0.001**
Brain	0 (0)	1 (1)	0 (0)	
Peripheral Nerve (Acoustic)	1 (1)	0 (0)	0 (0)	
Meningioma	0 (0)	1 (1)	0 (0)	
Head and Neck	1 (1)	0 (0)	1 (0.2)	0.4
Tongue	1 (1)	0 (0)	0 (0)	
Tonsil	0 (0)	0 (0)	1 (0.2)	
Neck	0 (0)	0 (0)	0 (0)	
Melanoma	3 (2)	1 (1)	5 (1)	0.36
Thyroid	0 (0)	1 (1)	1 (0.2)	0.28

[1] p-values based on chi-square or Fisher's exact test are testing differences between MBL, CLL, and clinic controls

[2] Includes 2 concurrently diagnosed malignancies (e.g. identified +/−2 months of CLL diagnosis): 1 patient with melanoma, 1 patient with prostate cancer.

*3*Includes 2 concurrently diagnosed malignancies (e.g. identified +/−2 months of MBL diagnosis): 1 patient with breast cancer, 1 patient with both prostate and thyroid cancers)

Table 3

Non-hematologic cancer in Individuals with CLL and MBL compared to Flow Cytometry Controls

Cancer	CLL n=132	MBL n=107	Flow controls n=482	p-value[1]
	n (%)	n (%)	n (%)	
Any cancer	16 (12)[2]	14 (13)[3]	18 (4)[4]	**<0.0001**
Breast	0/44 (0)	3/43 (7)	3/298 (1)	**0.01**
Lung	4 (3)	4 (4)	1 (0.2)	**0.002**
Gastro-intestinal	5 (4)	2 (2)	4 (1)	**0.046**
Pancreas	0 (0)	0 (0)	0 (0)	
Colorectal	4 (3)	1 (1)	2 (0.4)	
Liver	1 (1)	1 (1)	2 (0.4)	
Stomach	0 (0)	0 (0)	0 (0)	
Esophagus	0 (0)	0 (0)	0 (0)	
Genitourinary	2 (2)	1 (1)	3 (1)	0.6
Bladder	1 (1)	0 (0)	3 (1)	
Kidney	1 (1)	1 (1)	0 (0)	
Ureter	0 (0)	0 (0)	0 (0)	
Prostate	2/88 (2)	3/64 (5)	3/184 (2)	0.38
Gynecologic	1/44 (2)	1/43 (2)	0/298 (0)	**0.03**
Endometrial	1/44 (2)	1/43 (2)	0/298 (0)	
Ovarian	0/44 (0)	0/43 (0)	0/298 (0)	
Peritoneum	0/44 (0)	0/43 (0)	0/298 (0)	
Nervous System	1 (1)	2 (2)	1 (0.2)	0.11
Brain	0 (0)	1 (1)	1 (0.2)	
Peripheral Nerve (Acoustic)	1 (1)	0 (0)	0 (0)	
Meningioma	0 (0)	1 (1)	0 (0)	
Head and Neck	1 (1)	0 (0)	1 (0.2)	0.48
Tongue	1 (1)	0 (0)	0 (0)	
Tonsil	0 (0)	0 (0)	0 (0)	
Neck	0 (0)	0 (0)	1 (0.2)	
Melanoma	3 (2)	1 (1)	2 (0.4)	0.11
Thyroid	0 (0)	1 (1)	0 (0)	0.06

[1] p-values based on chi-square or Fisher's exact tests are testing differences between MBL, CLL, and flow cytometry controls

[2] Includes 2 concurrently diagnosed malignancies (e.g. identified +/–2 months of CLL diagnosis): 1 patient with melanoma, 1 patient with prostate cancer.

[3] Includes 2 concurrently diagnosed malignancies (e.g. identified +/−2 months of MBL diagnosis): 1 patient with breast cancer, 1 patient with both prostate and thyroid cancers

[4] Includes 2 concurrently diagnosed malignancies (e.g. identified up to 2 months after negative flow cytometry date): 1 patient with brain cancer, 1 patient with hepatocellular cancer

Table 4

Multivariable Cox Regression Analysis, Time to Non-hematologic Cancer diagnosis

Comparison Group	Factor	Hazard Ratio	95% Confidence interval	p-value
Clinic Controls	Age	1.02	1.003–1.04	**0.02**
	Sex (male)	1.40	0.72–2.53	0.35
	CLL vs clinic controls	1.93	0.91–4.09	0.09
	MBL vs clinic controls	2.00	0.94–4.24	0.07
	Comorbidities (any major)	1.43	0.78–2.64	0.25
Flow Controls	Age	1.03	1.01–1.05	**0.004**
	Sex (male)	1.21	0.65–2.27	0.55
	CLL vs flow controls	2.25	1.01–5.01	**0.047**
	MBL vs flow controls	2.36	1.05–5.34	**0.04**
	Comorbidities (any major)	1.23	0.64–2.37	0.53