Published in final edited form as:
Int J Cancer. 2009 June 1; 124(11): 2737–2743. doi:10.1002/ijc.24248.

Reproductive factors, exogenous hormone use, and risk of lymphoid neoplasms among women in the National Institutes of Health-AARP Diet and Health Study cohort

Lindsay M. Morton[1], **Sophia S. Wang**[1], **Douglas A. Richesson**[1], **Arthur Schatzkin**[1], **Albert R. Hollenbeck**[2], and **James V. Lacey Jr.**[1]

[1] Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, DHHS, Rockville, MD

[2] AARP, Washington, DC

Abstract

Reasons for higher incidence of lymphoid neoplasms among men than women are unknown. Because female sex hormones have immunomodulatory effects, reproductive factors and exogenous hormone use may affect risk for lymphoid malignancies. Previous epidemiologic studies on this topic have yielded conflicting results. Within the National Institutes of Health-AARP Diet and Health Study cohort, we prospectively analyzed detailed, questionnaire-derived information on menstrual and reproductive factors and use of oral contraceptives and menopausal hormone therapy among 134,074 US women. Using multivariable proportional hazards regression models, we estimated relative risks (RRs) for 85 plasma cell neoplasms and 417 non-Hodgkin lymphomas (NHLs) identified during follow-up from 1996-2002. We observed no statistically significant associations between plasma cell neoplasms, NHL, or the three most common NHL subtypes and age at menarche, parity, age at first birth, oral contraceptive use, or menopausal status at baseline. For menopausal hormone therapy use, overall associations between NHL and unopposed estrogen and estrogen plus progestin were null, with the potential exception of an inverse association (RR=0.49, 95% CI, 0.25-0.96) between use of unopposed estrogen and diffuse large B-cell lymphoma (DLBCL), the most common NHL subtype, among women with a hysterectomy. These data do not support an important role for reproductive factors or exogenous hormones in modulating lymphomagenesis.

INTRODUCTION

Lymphoid neoplasms, including non-Hodgkin lymphomas (NHL), Hodgkin lymphomas, and plasma cell neoplasms, are the sixth most commonly diagnosed group of cancers worldwide.1 Severe disruption of immune function is a well-established, strong risk factor for lymphomas, but much of lymphoid-neoplasm etiology remains unknown. The potential effects of modest immune perturbation on lymphomagenesis are not well understood.

In humans and animals, menses, pregnancy, and exogenous hormone use affect immune function.[as reviewed in 2, 3] This raises the possibility that reproductive factors and exogenous hormones modulate lymphomagenesis in women, which could help explain the lower incidence of almost all lymphoid neoplasm subtypes among women compared with men. Overall, associations between these factors and lymphoma risk are conflicting.[4-26]

* Address correspondence or requests for reprints to: Lindsay M. Morton, PhD; Division of Cancer Epidemiology and Genetics; National Cancer Institute, NIH, DHHS; 6120 Executive Blvd., EPS 7040, MSC#7238; Rockville, MD 20852; Phone: 301-435-3972; Fax: 301-402-0207; Email: mortonli@mail.nih.gov.

Recent studies reported strong, statistically significant inverse associations between menopausal hormone therapy (MHT) and lymphoid neoplasms.[20, 26] Odds ratios (ORs) of 0.6—40% risk reductions compared with never-use—for diffuse large B-cell lymphoma (DLBCL),[20, 26] Hodgkin lymphoma,[18] and all NHL combined[13] could, if true, reveal etiologic or prevention clues. However, the validity of these findings is unclear. The types of available MHT and patterns of use have substantially changed since the 1960s,[27] so associations with broadly defined "MHT" (especially from older studies) may reflect exposures that are not comparable across studies conducted during different time periods. Associations with specific subtypes of NHL are biologically plausible[28, 29] but warrant cautious interpretation because they could be due to chance and often are difficult to replicate.[30] Large, prospective studies with detailed data on use of specific MHT formulations and regimens have helped identify replicable associations between MHT and other cancers. We therefore evaluated MHT and other reproductive exposures as risk factors for lymphoid neoplasms and specific lymphoid neoplasm subtypes in the National Institutes of Health (NIH)-AARP Diet and Health Study.

MATERIAL AND METHODS

Study design/population

This study began in 1995-1996, when 3.5 million AARP members, male and female, ages 50-71, residing in six states (CA, FL, LA, NJ, NC, and PA) and two metropolitan areas (Atlanta, GA and Detroit, MI) received a mailed questionnaire.[31] The 567,169 AARP members (16.2%) who satisfactorily completed it received a second questionnaire, which collected detailed data on menstrual and reproductive factors and use of oral contraceptives and MHT, as well as other risk factors, in 1996-1997. A total of 334,908 AARP members (59.1%) completed that questionnaire. Overall, participants in the study were more likely to be non-Hispanic Caucasian, were slightly better educated, and had a slightly lower rate of current smoking compared with the general population.[31] Participants are followed annually for change of address and linked to state cancer registries and the National Death Index (NDI).

To focus on the detailed MHT data from the second questionnaire, we excluded 188,117 men, 10,383 proxy respondents, and 1550 women who reported a personal history of cancer on either questionnaire (including 119 lymphoid neoplasms), and 784 women for whom all MHT data were missing. Analysis therefore included 134,074 women.

Exposure ascertainment

The baseline questionnaire ascertained gynecologic surgeries, demographics, reproductive history, oral contraceptive use, menopausal status, smoking, family history of cancer, and basic information (ever-never, recency, and duration) about MHT use. The second questionnaire collected detailed MHT data. With those data, we used self-reported type, dates, and duration of MHT use to classify exposure according to formulation (i.e., unopposed estrogen vs. estrogen plus progestin), regimen [sequential (fewer than 15 days of progestin per cycle) or continuous (at least 15 days of progestin per cycle), for use of estrogen plus progestin], duration, and recency, as previously described.[32] Exposure categories included women who reported use of only one MHT formulation (~95% of MHT users); the ~5% of women who reported multiple formulations were classified separately.

Cancer ascertainment

Probabilistic linkage to state cancer registries in the study states,[33] plus three states to which relocation is common (AZ, NV, and TX) identified incident cancers among participants. Linkage to NDI provided date and cause of death for fatal cancers.

Lymphoma classification

We defined incident lymphoid neoplasms using International Classification of Diseases for Oncology, Second and Third Edition (ICD-O-2 and ICD-O-3)34, 35 histology codes provided by the cancer registries. According to the World Health Organization classification36 and the International Lymphoma Epidemiology Consortium (InterLymph) guidelines,37 we grouped 634 total lymphoid neoplasm cases into plasma cell neoplasms (ICD-O-3 codes 9731-4; N=85), Hodgkin lymphoma (9650-55, 9659, 9661-9667; N=16), NHL (9591, 9670-1, 9673, 9675, 9678-80, 9684, 9687, 9689-91, 9695, 9698-9702, 9705, 9708-9, 9714, 9716-9, 9727-9, 9760-4, 9823, 9826-7, 9831-37, 9940; N=417), and lymphoid neoplasms NOS (9590, 9822; N=116). We also evaluated the three most common NHL subtypes: diffuse large B-cell lymphoma (DLBCL; 9678-80, 9684; N=96), follicular lymphoma (9690-1, 9695, 9698; N=105), and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL; 9670, 9823; N=84).

Statistical analysis

Cox proportional hazards regression, with age as the time scale and ties handled by complete enumeration,38 generated hazard ratios to estimate relative risks (RRs). Tests of proportional hazards revealed no departures. Follow-up began when the second questionnaire was received and scanned. Follow-up ended at the earliest of the following dates: diagnosis of lymphoid neoplasm (N=634), movement out of a registry catchment area (N=5219), death (N=4496), diagnosis of a non-lymphoid hematopoietic neoplasm (ICD-O-3 codes 9740-58, 9800-5, 9840-9931, 9945-64, 9975-9989; N=75), or June 30, 2002 (N=123,650). We truncated follow-up in 2002 because we did not update MHT use during follow-up and millions of women changed or stopped their MHT use after the July 2002 publication of Women's Health Initiative study results.39

Models included adjustment for age at baseline, race, education, menopausal status, and use of oral contraceptives. Additional adjustment for calendar time or other potential confounders had little influence of RRs, so these factors were dropped from statistical models. For each exposure, we evaluated potential associations with five outcomes: plasma cell neoplasms, NHL, and the three most common NHL subtypes: DLBCL, follicular lymphoma, and CLL/SLL. We excluded Hodgkin lymphoma from further analysis due to too few cases (N=16). In addition, for MHT, we investigated formulations (i.e., unopposed estrogen vs. estrogen plus progestin) two ways: first, among the entire cohort, and second, after stratifying on hysterectomy status at baseline. For the latter, unopposed estrogen was evaluated only among women with hysterectomy and estrogen plus progestin was evaluated only among women with an intact uterus, to reflect the predominant prescribing patterns over the last 15 years.

RESULTS

The 134,074 women in the NIH-AARP Diet and Health Study accrued 719,035 total person-years during follow-up. The mean age at study entry was 63 years (range 51 to 72 years), and 91% of women were Caucasian. The 417 NHLs diagnosed during follow-up were similar to the number expected among US women of comparable age (based on 12 SEER registries, standardized incidence ratio (SIR) 1.05, 95% CI 0.95-1.16), whereas the 85 plasma cell neoplasms diagnosed during follow-up were fewer than expected (SIR 0.76, 95% CI 0.61-0.94), likely because our study population includes proportionally fewer non-white women than the SEER areas.

We observed no statistically significant associations between any of the outcomes and age at menarche, parity, age at first birth, oral contraceptive use, hysterectomy, or menopausal

status at baseline (Table 1). No clear patterns of association emerged for age at first birth or parity when analyses were restricted to parous women (data not shown). Use of MHT, regardless of formulation, was also not significantly associated with plasma cell neoplasms, NHL overall, or NHL subtypes (Table 2). Risk estimates were unchanged after adjustment for race, menopausal status, oral contraceptive use, education, and smoking.

We evaluated associations with MHT formulations after stratifying on hysterectomy status (Tables 3 and 4). We observed no statistically significant associations with plasma cell neoplasms, NHL overall, follicular lymphoma, or CLL/SLL. Ever-use and current use of unopposed estrogen were statistically significantly associated with DLBCL (RR=0.49, 95% CI, 0.25-0.96 and RR=0.47, 95% CI, 0.22-0.98, respectively). For estrogen plus progestin, ever-use, duration of use, recency of use, and regimen used generated null associations with plasma cell neoplasms, NHL overall, and NHL subtypes.

DISCUSSION

This large cohort of US women with detailed exposure information revealed null associations between lymphoid neoplasms and most reproductive factors, including menarche, parity, oral contraceptives, and menopausal status. Substantial changes in the types of available MHT and patterns of use over the last several decades27 complicate the comparisons with older studies of MHT and lymphoid neoplasm risk. Almost all MHT use consisted of unopposed estrogen therapy until the 1970s, when the discovery of increased endometrial cancer risks among women taking estrogen therapy led to sharp declines in MHT use.27 The combined estrogen-plus-progestin formulations emerged in the 1980s, and use of unopposed estrogen (among women with hysterectomy) and estrogen plus progestin (among women with an intact uterus) steadily increased until the early 2000s, when clinical trial data documented unfavorable risk-benefit profiles for MHT use among postmenopausal women.27 Few previous studies have considered MHT formulation or accounted for hysterectomy status, a strong predictor of unopposed estrogen use.13¯21, 23, 26

Although our overall findings for MHT use were null, our risk estimates were generally less than one for all lymphoid neoplasm types, which is consistent with most of the previous literature on this topic. In analyses restricted to women with hysterectomy, we observed inverse associations between unopposed estrogen and NHL (RR=0.63, 95% CI, 0.29-1.37) and DLBCL (RR=0.49, 95% CI, 0.25-0.96). These results are most comparable with four previous studies that evaluated risk by MHT formulation20 or collected data when essentially all reported MHT use was unopposed estrogen (i.e., 1980s through the early 1990s).13, 15, 26 Of those studies, three also reported inverse associations with NHL,13, 20, 26 and the two that considered NHL subtypes also found significant associations for DLBCL.20, 26 In contrast, we and others did not observe the positive association between unopposed estrogen use and follicular lymphoma that was reported by Cerhan *et al*.15 Although some previous studies have observed somewhat stronger associations with current or long-duration use,15, 16, 18, 20, 21, 24 the absence of consistent statistical significance and dose-response by duration or recency argue against a true association or a simple, uncomplicated relationship between MHT and lymphoma. Nevertheless, the potential inverse association between unopposed estrogen use and DLBCL—which could also be due to chance—warrants further study. Our data on unopposed estrogen and the other main subtypes, plasma cell neoplasms, CLL/SLL, and Hodgkin's lymphoma, were too imprecise to draw firm conclusions about these potential associations.

In contrast to the unopposed estrogen data, our analysis of estrogen plus progestin use revealed null associations with plasma cell neoplasms, NHL overall, and specific NHL subtypes. These findings could be due to low statistical power, especially for the NHL

subtypes. For the entire cohort of 134,074 women and the outcome of NHL overall, we had approximately 86% statistical power to detect a RR=0.7 for ever-use of unopposed estrogen and 57% power to detect a RR=0.7 for ever-use of estrogen plus progestin. For women with hysterectomy and NHL overall as the outcome, we had 56% power to detect a RR=0.7 for ever-use of unopposed estrogen. For women with an intact uterus and NHL overall as the outcome, we had 51% power to detect a RR=0.7 for ever-use of estrogen plus progestin. If our null associations with estrogen plus progestin are confirmed in future studies—to date, none of the other studies of NHL and MHT have reported data on estrogen plus progestin use among women with an intact uterus—then the potential contrast between inverse associations with unopposed estrogen and null associations with estrogen plus progestin would suggest possible distinct roles for estrogen and progestin in lymphomagenesis. This suggestion is particularly intriguing in light of evidence suggesting that estrogen, but not progestin, influences B-cell development and antibody production.[2, 40]

Previous data on menstrual and reproductive factors and risk of lymphoid neoplasms are inconsistent.[4, 10, 11, 13, 14, 21, 22, 24, 25] Study design, participant demographics, and exposure ascertainment do not appear to explain the inconsistencies, as both significant and null associations have been reported in older and newer studies, among younger and older women, and in case-control and cohort designs. Although decreased risk of Hodgkin lymphoma has been associated somewhat more consistently with reproductive factors such as higher parity and earlier age at first birth,[5-9, 11, 12, 18] we did not have a sufficient number of Hodgkin lymphoma cases in this older adult cohort for analysis. The inverse association we observed between DLBCL and increasing duration of oral contraceptive use might not be real because it was based on small numbers and not statistically significant. Nonetheless, the potential for two different exogenous hormones (i.e., oral contraceptives and ET) to decrease risk of DLBCL warrants further study.

Our study's strengths—e.g., large sample size, prospective design, and subtype-specific analyses—increase the validity of these results. Detailed data on specific formulations and regimens minimized misclassification of exogenous hormone use and allowed us to evaluate contemporary MHT use in detail, instead of relying on broad exposure categories that capture diverse patterns of MHT use over time. We lacked follow-up data on hormone therapy use after baseline, but we assume that many current users in 1996-1997 continued their use at least through mid-2002.[32] Selection bias might particularly affect analyses of reproductive factors and lymphoma in previous case-control studies.[41] Low response to our mailed questionnaires could theoretically produce similar bias, but this seems unlikely because response was not associated with reproductive factors.[32] Some other limitations, such as small numbers of some NHL subtypes, affect most single studies of NHL.

Our primarily null associations between menstrual and reproductive factors, use of oral contraceptives, and specific detailed measures of MHT and precise NHL subtypes add substantial weight to the previous suggestions from other studies that reproductive factors and exogenous hormones are not generally strong risk factors for lymphoid neoplasms. Before the observed inverse associations between exogenous hormones and DLBCL can be considered indicative of hormonal exposures reducing risk for some lymphoid neoplasms, they should be replicated in sufficient detail—both for specific MHT exposures and NHL subtypes—across diverse study designs or in pooled analyses. Other hormone-related risk factors that might contribute to the observed sex differences in susceptibility to lymphoid neoplasms warrant continued consideration.

Acknowledgments

Cancer incidence data from the Atlanta metropolitan area were collected by the Georgia Center for Cancer Statistics, Department of Epidemiology, Rollins School of Public Health, Emory University. Cancer incidence data from California were collected by the California Department of Health Services, Cancer Surveillance Section. Cancer incidence data from the Detroit metropolitan area were collected by the Michigan Cancer Surveillance Program, Community Health Administration, State of Michigan. The Florida cancer incidence data used in this report were collected by the Florida Cancer Data System under contract to the Department of Health (DOH). The views expressed herein are solely those of the authors and do not necessarily reflect those of the contractor or DOH. Cancer incidence data from Louisiana were collected by the Louisiana Tumor Registry, Louisiana State University Medical Center in New Orleans. Cancer incidence data from New Jersey were collected by the New Jersey State Cancer Registry, Cancer Epidemiology Services, New Jersey State Department of Health and Senior Services. Cancer incidence data from North Carolina were collected by the North Carolina Central Cancer Registry. Cancer incidence data from Pennsylvania were supplied by the Division of Health Statistics and Research, Pennsylvania Department of Health, Harrisburg, Pennsylvania. The Pennsylvania Department of Health specifically disclaims responsibility for any analyses, interpretations or conclusions.

Supported by the Intramural Research Program of the National Cancer Institute, NIH, DHHS.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global Cancer Statistics, 2002. CA Cancer J Clin. 2005; 55(2):74–108. [PubMed: 15761078]
2. Bouman A, Heineman MJ, Faas MM. Sex hormones and the immune response in humans. Human Reprod Update. 2005; 11(4):411–23.
3. Straub RH. The complex role of estrogens in inflammation. Endocr Rev. 2007; 28(5):521–74. [PubMed: 17640948]
4. Olsson H, Olsson M, Ranstam J. Late age at first full-term pregnancy as a risk factor for women with malignant lymphoma. Neoplasma. 1990; 37(2):185–90. [PubMed: 2342631]
5. Kravdal O, Hansen S. Hogkin's disease: the protective effect of childbearing. Int J Cancer. 1993; 55(6):909–14. [PubMed: 8253527]
6. Glaser SL. Reproductive factors in Hodgkin's disease in women: A review. Am J Epidemiol. 1994; 139(3):237–46. [PubMed: 8116598]
7. Zahm S, Hoover R, Fraumeni J Jr. Hodgkin's disease and parity. Int J Cancer. 1995; 62(3):362–3. [PubMed: 7628880]
8. Kravdal O, Hansen S. The importance of childbearing for Hodgkin's disease: new evidence from incidence and mortality models. Int J Epidemiol. 1996; 25(4):737–43. [PubMed: 8921450]
9. Zwitter M, Zakelj M, Kosmelj K. A case-control study of Hodgkin's disease and pregnancy. Br J Cancer. 1996; 73(2):246–51. [PubMed: 8546914]
10. Adami H-O, Tsaih S, Lambe M, Hsieh C, Adami J, Trichopolous D, Melbye M, Glimelius B. Pregnancy and risk of non-Hodgkin's lymphoma: a prospective study. Int J Cancer. 1997; 70:155–8. erratum appears in Int J Cancer 1997, 71(4):705. [PubMed: 9009153]
11. Tavani A, Pregnolato A, La Vecchia C, Franceschi S. A case-control study of reproductive factors and risk of lymphomas and myelomas. Leuk Res. 1997; 21:885–8. [PubMed: 9393604]
12. Lambe M, Hsieh CC, Tsaih SW, Adami J, Glimelius B, Adami HO. Childbearing and the risk of Hodgkin's disease. Cancer Epidemiol Biomarkers Prev. 1998; 7(9):831–4. [PubMed: 9752994]
13. Nelson R, Levine A, Bernstein L. Reproductive factors and risk of intermediate- or high-grade B-cell non-Hodgkin's lymphoma in women. J Clin Oncol. 2001; 19:1381–7. [PubMed: 11230482]
14. Cerhan JR, Habermann TM, Vachon C, Putnam S, Zheng W, Potter JD, Folsom AR. Menstrual and reproductive factors and risk of non-Hodgkin lymphoma: the Iowa women's health study (United States). Cancer Causes Control. 2002; 13:131–6. [PubMed: 11936819]
15. Cerhan JR, Vachon C, Habermann TM, Ansell S, Witzig T, Kurtin P, Janney C, Zheng W, Potter JD, Sellers TA, Folsom AR. Hormone replacement therapy and risk of non-Hodgkin lymphoma and chronic lymphocytic leukemia. Cancer Epidemiol Biomarkers Prev. 2002; 11:1466–71. [PubMed: 12433728]

16. Beiderbeck A, Holly EA, Sturkenboom M, Coebergh J, Stricker B, Leufkens H. No increased risk of non-Hodgkin's lymphoma with steroids, estrogens and psychotropics (Netherlands). Cancer Causes Control. 2003; 14:639–44. [PubMed: 14575361]

17. Fernandez E, Gallus S, Bosetti C, Franceschi S, Negri E, LaVecchia C. Hormone replacement therapy and cancer risk: a systematic analysis from a network of case-control studies. Int J Cancer. 2003; 105(3):408–12. [PubMed: 12704678]

18. Glaser SL, Clarke CA, Nugent RA, Stearns CB, Dorfman RF. Reproductive factors in Hodgkin's disease in women. Am J Epidemiol. 2003; 158(6):553–63. [PubMed: 12965881]

19. Altieri A, Gallus S, Franceschi S, Fernandez E, Talamini R, La Vecchia C. Hormone replacement therapy and risk of lymphomas and myelomas. Eur J Cancer Prev. 2004; 13(4):349–51. [PubMed: 15554564]

20. Zhang Y, Holford TR, Leaderer B, Zahm SH, Boyle P, Morton LM, Zhang B, Zou K, Flynn S, Tallini G, Owens PH, Zheng T. Prior medical conditions and medication use and risk of non-Hodgkin lymphoma in Connecticut United States women. Cancer Causes Control. 2004; 15(4): 419. [PubMed: 15141141]

21. Zhang Y, Holford TR, Leaderer B, Boyle P, Zahm SH, Zhang B, Zou K, Morton LM, Owens PH, Flynn S, Tallini G, Zheng T. Menstrual and reproductive factors and risk of non-Hodgkin's lymphoma among Connecticut women. Am J Epidemiol. 2004; 160(8):766–73. [PubMed: 15466499]

22. Frisch M, Pedersen B, Wohlfahrt J, Hjalgrim H, Biggar R. Reproductive patterns and non-Hodgkin lymphoma risk in Danish women and men. Eur J Epidemiol. 2006; 21(9):673–9. [PubMed: 17048087]

23. Norgaard M, Poulsen A, Pedersen L, Gregersen H, Friis S, Ewertz M, Johnsen H, Sorensen H. Use of postmenopausal hormone replacement therapy and risk of non-Hodgkin's lymphoma: a Danish population-based cohort study. Br J Cancer. 2006; 94(9):1339–41. [PubMed: 16670705]

24. Lee J, Bracci PM, Holly EA. Reproductive factors and hormone use in non-Hodgkin lymphoma (abstract #356). Am J Epidemiol. 2007; 165(Suppl):S89.

25. Prescott J, Sullivan-Halley J, Clarke C, Cozen W, Bernstein L. Reproductive factors, body size, and risk of non-Hodgkin lymphoma subtypes in the California Teachers Study. AACR Meeting Abstracts. 2007:B114.

26. Lee JS, Bracci PM, Holly EA. Non-Hodgkin lymphoma in women: reproductive factors and exogenous hormone use. Am J Epidemiol. 2008:10. June Epub ahead of print.

27. Stefanick ML. Estrogens and progestins: background and history, trends in use, and guidelines and regimens approved by the US Food and Drug Administration. Am J Med. 2005; 118(12, Supplement 2):64–73. [PubMed: 16414329]

28. Rothman N, Skibola CF, Wang SS, Morgan G, Lan Q, Smith MT, Spinelli JJ, Willett E, de Sanjose S, Cocco P, Berndt S, Brennan P, et al. Genetic variation in TNF and IL10 and risk of non-Hodgkin lymphoma: a report from the InterLymph Consortium. Lancet Oncol. 2006; 7(1):27–38. [PubMed: 16389181]

29. Smedby KE, Vajdic CM, Falster M, Engels EA, Martinez-Maza O, Turner J, Hjalgrim H, Vineis P, Seniori Costantini A, Bracci PM, Holly EA, Willett E, et al. Autoimmune disorders and risk of non-Hodgkin lymphoma subtypes: a pooled analysis within the InterLymph Consortium. Blood. 2008 Epub ahead of print, 8 Feb.

30. Weiss NS. Subgroup-specific associations in the face of overall null results: should we rush in or fear to tread? Cancer Epidemiol Biomarkers Prev. 2008; 17(6):1297–9. [PubMed: 18559544]

31. Schatzkin A, Subar AF, Thompson FE, Harlan LC, Tangrea J, Hollenbeck AR, Hurwitz PE, Coyle L, Schussler N, Michaud DS, Freedman LS, Brown CC, et al. Design and serendipity in establishing a large cohort with wide dietary intake distributions: The National Institutes of Health-American Association of Retired Persons Diet and Health Study. Am J Epidemiol. 2001; 154(12):1119–25. [PubMed: 11744517]

32. Lacey JV Jr. Brinton LA, Leitzmann MF, Mouw T, Hollenbeck A, Schatzkin A, Hartge P. Menopausal hormone therapy and ovarian cancer risk in the National Institutes of Health-AARP Diet and Health Study cohort. J Natl Cancer Inst. 2006; 98(19):1397–405. [PubMed: 17018786]

33. Michaud DS, Midthune D, Hermansen S, Leitzmann MF, Harlan LC, Kipnis V, Schatzkin A. Comparison of cancer registry case ascertainment with SEER estimates and self-reporting in a subset of the NIH-AARP Diet and Health Study. J Regist Manag. 2005; 32(2):70–5.
34. Percy, C.; Van Holten, V.; Muir, C., editors. International Classification of Diseases for Oncology. 2nd edition. World Health Organization; Geneva: 1990.
35. Fritz, A.; Percy, C.; Jack, A.; Shanmugaratnam, K.; Sobin, L.; Parkin, D., et al., editors. International Classification of Diseases for Oncology. 3rd edition. World Health Organization; Geneva: 2000.
36. Kleihues, P.; Sobin, LH. World Health Organization Classification of Tumours. In: Jaffe, E.; Harris, N.; Stein, H.; Vardiman, J., editors. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. IARC Press; Lyon: 2001. p. 352
37. Morton LM, Turner JJ, Cerhan JR, Linet MS, Treseler PA, Clarke CA, Jack A, Cozen W, Maynadie M, Spinelli J, Seniori Costantini A, Rudiger T, et al. Proposed classification of lymphoid neoplasms for epidemiologic research from the International Lymphoma Epidemiology Consortium (InterLymph). Blood. 2007; 110(2):695–708. [PubMed: 17389762]
38. Gail M, Lubin JH, Rubinstein L. Likelihood calculations for matched case-control studies and survival studies with tied death times. Biometrika. 1981; 68:703–7.
39. Rossouw J, Anderson G, Prentice R, LaCroix A, Kooperberg C, Stefanick ML, Jackson R, Beresford S, Howard B, Johnson KC, Kotchen J, Ockene J, et al. Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results From the Women's Health Initiative Randomized Controlled Trial. JAMA. 2002; 288(3):321–33. [PubMed: 12117397]
40. Medina KL, Strasser A, Kincade PW. Estrogen influences the differentiation, proliferation, and survival of early B-lineage precursors. Blood. 2000; 95(6):2059–67. [PubMed: 10706875]
41. Glaser SL, Clarke CA, Keegan THM, Gomez SL, Nugent RA, Topol B, Stearns CB, Stewart SL. Attenuation of social class and reproductive risk factor associations for Hodgkin lymphoma due to selection bias in controls. Cancer Causes Control. 2004; 15(7):731–9. [PubMed: 15280631]

Table 1

Selected demographic characteristics and reproductive factors, and relative risk of lymphoid neoplasms, by type, among 134,074 women in the NIH-AARP Diet and Health Study

	Plasma cell neoplasms (N=85)				Non-Hodgkin lymphoma (N=417)				Diffuse large B-cell lymphoma (N=96)				Follicular lymphoma (N=105)				CLL/SLL (N=84)			
	No. cancers*	Person-years	RR**	95% CI	No. cancers*	Person-years	RR**	95% CI	No. cancers*	Person-years	RR**	95% CI	No. cancers*	Person-years	RR**	95% CI	No. cancers*	Person-years	RR**	95% CI
Age at study entry (years)																				
<57	4	136,100		-	50	136,234		-	5	136,097		-	21	136,149		-	8	136,113		-
57-60	12	138,442		-	77	138,653		-	15	138,467		-	18	138,466		-	19	138,465		-
61-64	24	163,598		-	92	163,781		-	22	163,596		-	19	163,585		-	17	163,570		-
65-68	26	185,148		-	133	185,470		-	32	185,183		-	32	185,159		-	26	185,159		-
≥69	19	94,150		-	65	94,292		-	22	94,162		-	15	94,140		-	14	94,123		-
Race, ethnicity																				
Caucasian	72	653,095	1.00	Ref.	395	654,046	1.00	Ref.	92	653,178	1.00	Ref.	101	653,180	1.00	Ref.	77	653,099	1.00	Ref.
Other/unknown	13	64,343	1.92	1.06 - 3.46	22	64,384	0.58	0.38 - 0.89	4	64,327	0.46	0.17 - 1.26	4	64,319	0.41	0.15 - 1.10	7	64,331	0.94	0.43 - 2.03
Education																				
Less than High School	7	37,236	1.00	Ref.	24	37,294	1.00	Ref.	9	37,257	1.00	Ref.	7	37,233	1.00	Ref.	2	37,226	1.00	Ref.
High School Grad	21	174,813	0.68	0.29 - 1.60	112	175,055	1.02	0.66 - 1.59	22	174,815	0.55	0.26 - 1.20	22	174,793	0.68	0.29 - 1.59	28	174,798	3.07	0.73 - 12.88
Some College	29	256,922	0.69	0.30 - 1.57	128	257,256	0.82	0.53 - 1.27	35	256,960	0.64	0.31 - 1.33	28	256,938	0.59	0.26 - 1.36	26	256,930	2.00	0.48 - 8.45
College Grad or Higher	24	228,228	0.68	0.29 - 1.58	139	228,570	1.03	0.67 - 1.60	27	228,245	0.59	0.28 - 1.26	43	228,298	1.03	0.46 - 2.30	28	228,253	2.50	0.59 - 10.50
Current Smoking Status																				
Never	40	318,115	1.00	Ref.	204	318,630	1.00	Ref.	39	318,134	1.00	Ref.	62	318,173	1.00	Ref.	44	318,130	1.00	Ref.
Former	33	282,390	0.94	0.59 - 1.49	154	282,738	0.86	0.70 - 1.06	42	282,431	1.23	0.80 - 1.90	28	282,388	0.51	0.33 - 0.80	31	282,388	0.80	0.50 - 1.26
Current	10	94,684	0.93	0.47 - 1.87	45	94,778	0.78	0.56 - 1.07	9	94,685	0.86	0.42 - 1.77	13	94,689	0.71	0.39 - 1.30	8	94,666	0.64	0.30 - 1.36
Age at menarche (years)																				
<13	34	349,736	1.00	Ref.	207	350,266	1.00	Ref.	48	349,807	1.00	Ref.	56	349,806	1.00	Ref.	41	349,769	1.00	Ref.
13-14	40	297,501	1.32	0.84 - 2.09	172	297,886	0.96	0.78 - 1.17	37	297,497	0.87	0.57 - 1.33	42	297,503	0.88	0.59 - 1.31	35	297,472	0.98	0.63 - 1.55
≥15	10	64,211	1.51	0.75 - 3.06	34	64,285	0.87	0.61 - 1.25	9	64,212	0.96	0.47 - 1.97	6	64,203	0.58	0.25 - 1.35	8	64,202	1.04	0.49 - 2.21
Parity																				
Nulliparous	11	105,090	1.00	Ref.	53	105,225	1.00	Ref.	10	105,098	1.00	Ref.	13	105,109	1.00	Ref.	14	105,095	1.00	Ref.

	Plasma cell neoplasms (N=85)				Non-Hodgkin lymphoma (N=417)				Diffuse large B-cell lymphoma (N=96)				Follicular lymphoma (N=105)				CLL/SLL (N=84)			
	No. cancers*	Person-years	RR**	95% CI	No. cancers*	Person-years	RR**	95% CI	No. cancers*	Person-years	RR**	95% CI	No. cancers*	Person-years	RR**	95% CI	No. cancers*	Person-years	RR**	95% CI
1	12	73,297	1.56	0.69 - 3.52	28	73,352	0.76	0.48 - 1.20	8	73,285	1.14	0.45 - 2.90	7	73,280	0.77	0.31 - 1.93	4	73,273	0.41	0.14 - 1.24
2	23	185,548	1.15	0.56 - 2.36	114	185,814	1.21	0.87 - 1.67	29	185,573	1.61	0.78 - 3.29	31	185,562	1.35	0.70 - 2.57	19	185,536	0.76	0.38 - 1.51
≥3	34	341,125	0.82	0.42 - 1.62	212	341,640	1.16	0.86 - 1.57	44	341,171	1.18	0.59 - 2.35	54	341,185	1.28	0.69 - 2.35	46	341,159	0.95	0.52 - 1.73
Age at first birth (years)																				
Nulliparous	11	105,090	1.00	Ref.	53	105,225	1.00	Ref.	10	105,098	1.00	Ref.	13	105,109	1.00	Ref.	14	105,095	1.00	Ref.
≤20	14	119,444	1.12	0.51 - 2.46	64	119,583	1.06	0.74 - 1.53	16	119,459	1.42	0.64 - 3.12	18	119,443	1.23	0.60 - 2.52	12	119,435	0.74	0.34 - 1.61
20-24	35	310,544	0.97	0.49 - 1.90	193	311,014	1.18	0.87 - 1.59	46	310,590	1.41	0.71 - 2.79	47	310,584	1.22	0.66 - 2.26	34	310,549	0.78	0.42 - 1.46
25-29	17	129,423	1.10	0.51 - 2.35	77	129,602	1.12	0.79 - 1.59	15	129,422	1.08	0.48 - 2.40	21	129,437	1.29	0.65 - 2.59	21	129,435	1.15	0.59 - 2.27
≥30	5	42,305	0.99	0.34 - 2.85	20	42,348	0.89	0.53 - 1.49	4	42,299	0.88	0.28 - 2.81	5	42,304	0.94	0.33 - 2.63	2	42,290	0.34	0.08 - 1.49
Hysterectomy																				
No	47	408,247	1.00	Ref.	228	408,804	1.00	Ref.	52	408,279	1.00	Ref.	62	408,293	1.00	Ref.	50	408,252	1.00	Ref.
Yes	37	301,253	1.03	0.67 - 1.58	184	301,683	1.08	0.89 - 1.31	42	301,291	1.06	0.70 - 1.59	43	301,273	0.94	0.64 - 1.39	34	301,245	0.90	0.58 - 1.40
Menopausal status at baseline																				
Pre-menopausal	2	26,208	1.43	0.33 - 6.26	8	26,230	0.67	0.32 - 1.40	3	26,210	2.05	0.58 - 7.32	3	26,215	0.83	0.24 - 2.84	1	26,204	0.36	0.05 - 2.75
Natural menopause, ≤45 years	4	45,954	0.61	0.21 - 1.76	26	46,024	0.92	0.60 - 1.41	2	45,950	0.33	0.08 - 1.39	11	45,975	1.71	0.85 - 3.45	8	45,969	1.18	0.54 - 2.59
Natural menopause, 45-49 years	14	108,562	0.97	0.51 - 1.86	56	108,691	0.86	0.63 - 1.19	20	108,585	1.49	0.82 - 2.70	15	108,569	0.99	0.53 - 1.86	6	108,545	0.39	0.16 - 0.93
Natural menopause, 50-54 years	26	193,612	1.00	Ref.	116	193,868	1.00	Ref.	24	193,613	1.00	Ref.	27	193,615	1.00	Ref.	28	193,606	1.00	Ref.
Natural menopause, ≥55 years	6	43,371	0.93	0.38 - 2.26	23	43,435	0.84	0.54 - 1.31	5	43,374	0.83	0.32 - 2.16	5	43,368	0.83	0.32 - 2.17	8	43,378	1.23	0.56 - 2.69
Surgical menopause	32	278,049	0.88	0.53 - 1.48	176	278,470	1.07	0.84 - 1.35	37	278,080	1.10	0.66 - 1.84	43	278,075	1.12	0.69 - 1.81	30	278,040	0.76	0.45 - 1.26
Natural menopause, age unknown	0	1,273	-	-	1	1,277	1.26	0.18 - 8.99	1	1,277	5.74	0.78 - 42.46	0	1,273	-	-	0	1,273	-	-
Oral contraceptive use																				
Never	55	427,602	1.00	Ref.	268	428,271	1.00	Ref.	68	427,675	1.00	Ref.	63	427,629	1.00	Ref.	56	427,590	1.00	Ref.
< 5 years	10	122,927	0.90	0.46 - 1.80	59	123,055	0.89	0.66 - 1.18	13	122,941	0.91	0.50 - 1.67	15	122,943	0.86	0.48 - 1.54	11	122,931	0.77	0.40 - 1.51
5 - 9 years	8	88,133	1.01	0.48 - 2.15	45	88,242	0.94	0.68 - 1.30	8	88,137	0.78	0.37 - 1.65	15	88,155	1.20	0.67 - 2.15	7	88,143	0.69	0.31 - 1.53
10+ years	11	69,775	1.66	0.86 - 3.20	41	69,858	1.06	0.76 - 1.48	5	69,755	0.59	0.24 - 1.47	11	69,773	1.11	0.58 - 2.14	10	69,770	1.21	0.61 - 2.41

Abbreviations: chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); relative risk (RR).

* No. cancers may not sum to total due to missing values for some variables.

** RRs adjusted for age (continuous).

Table 2

Menopausal hormone therapy use and relative risk of lymphoid neoplasms, by type, among 134,074 women in the NIH-AARP Diet and Health Study

Hormone therapy	No. cancers	Person-years	RR*	95% CI	RR**	95% CI
	Plasma cell neoplasms (N=85)					
No hormone therapy use	38	276,678	1.00	Ref.	1.00	Ref.
Estrogen only	21	203,356	0.78	0.46 - 1.33	0.79	0.43 - 1.45
Estrogen and estrogen plus progestin	2	30,147	0.49	0.12 2.04	0.49	0.12 - 2.04
Estrogen plus progestin only	12	123,896	0.91	0.47 - 1.77	0.92	0.46 - 1.81
	Non-Hodgkin lymphoma (N=417)					
No hormone therapy use	171	277,099	1.00	Ref.	1.00	Ref.
Estrogen only	128	203,673	1.04	0.82 - 1.30	0.95	0.73 - 1.24
Estrogen and estrogen plus progestin	14	30,184	0.76	0.44 - 1.30	0.73	0.42 - 1.26
Estrogen plus progestin only	57	124,027	0.83	0.61 - 1.12	0.83	0.61 - 1.13
	Diffuse large B-cell lymphoma (N=96)					
No hormone therapy use	43	276,707	1.00	Ref.	1.00	Ref.
Estrogen only	25	203,389	0.82	0.50 - 1.35	0.80	0.46 - 1.41
Estrogen and estrogen plus progestin	3	30,153	0.65	0.20 2.10	0.65	0.20 - 2.10
Estrogen plus progestin only	11	123,900	0.73	0.37 - 1.43	0.72	0.36 - 1.44
	Follicular lymphoma (N=105)					
No hormone therapy use	43	276,695	1.00	Ref.	1.00	Ref.
Estrogen only	31	203,388	0.99	0.62 - 1.57	0.90	0.52 - 1.55
Estrogen and estrogen plus progestin	4	30,152	0.86	0.31 - 2.40	0.79	0.28 - 2.23
Estrogen plus progestin only	16	123,909	0.85	0.48 - 1.53	0.81	0.44 - 1.47
	CLL/SLL (N=84)					
No hormone therapy use	34	276,665	1.00	Ref.	1.00	Ref.
Estrogen only	24	203,360	0.97	0.57 - 1.63	1.10	0.59 - 2.02
Estrogen and estrogen plus progestin	4	30,151	1.08	0.38 3.05	1.12	0.39 - 3.18
Estrogen plus progestin only	13	123,907	0.93	0.49 - 1.78	0.92	0.47 - 1.79

Abbreviations: chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); relative risk (RR).

Not shown: use of other or unknown hormone therapy types (N=12 plasma cell neoplasms. RR= 1.15, 95% CI, 0-59-2.25; N=47 NHL, RR=0.91, 95% CI, 0.65-1.27; N=14 Diffuse large B-cell lymphoma, RR=1.18, 95% CI, 0.63-2.20; N=11 follicular lymphoma, RR=0.81, 95% CI, 0.41-1.60; N=9 CLL/SLL, RR=0.98. 95% CI, 0.46-2.08).

* RRs adjusted for age (continuous).

** RRs adjusted for age (continuous), race, menopausal status, oral contraceptive use, education, smoking status, and other hormone therapy formulations.

Table 3

Estrogen only menopausal hormone therapy use and relative risk of lymphoid neoplasms, by type, among women with hysterectomy in the NIH-AARP Diet and Health Study

Hormone therapy	No. cancers*	Person-years	RR**	95% CI	RR†	95% CI
	Plasma cell neoplasms (N=37)					
No hormone therapy use	11	63203.18	1.00	Ref.	1.00	Ref.
Estrogen only	18	172352.83	0.64	0.30 - 1.36	0.63	0.29 - 1.37
Recency of use						
Former	5	37043.49	0.85	0.30 - 2.41	0.84	0.30 - 2.41
Current	13	133756.23	0.65	0.29 - 1.42	0.65	0.29 - 1.46
Duration of use						
<10 years	5	75122.6	0.48	0.17- 1.36	0.48	0.17 - 1.39
>10 years	12	94678.38	0.78	0.35 - 1.74	0.79	0.35 - 1.78
	Non-Hodgkin lymphoma (N=184)					
No hormone therapy use	42	63304.16	1.00	Ref.	1.00	Ref.
Estrogen only	106	172616.45	0.94	0.66 - 1.35	0.91	0.64 - 1.32
Recency of use						
Former	27	37119.44	1.16	0.72 - 1.86	1.14	0.71 - 1.84
Current	77	133939.05	0.93	0.64 - 1.34	0.90	0.62 - 1.30
Duration of use						
<10 years	49	75256.33	1.07	0.71 - 1.60	1.06	0.71 - 1.60
>10 years	56	94806.71	0.94	0.64 - 1.39	0.90	0.61 - 1.33
	Diffuse large B-cell lymphoma (N=42)					
No hormone therapy use	16	63226.79	1.00	Ref.	1.00	Ref.
Estrogen only	21	172380.25	0.51	0.26 - 0.98	0.49	0.25 - 0.96
Recency of use						
Former	7	37059.87	0.89	0.37 - 2.16	0.89	0.37 - 2.18
Current	13	133763.51	0.48	0.23 - 1.00	0.47	0.22 - 0.98
Duration of use						
<10 years	9	75145.08	0.64	0.28 - 1.45	0.63	0.28 - 1.44
>10 years	12	94683.54	0.59	0.28 - 1.24	0.58	0.27 - 1.23

Hormone therapy	No. cancers*	Person-years	RR**	95% CI	RR†	95% CI
	Follicular lymphoma (N=43)					
No hormone therapy use	8	63196.18	1.00	Ref.	1.00	Ref.
Estrogen only	25	172371.25	1.14	0.51 - 2.54	1.02	0.45 - 2.29
Recency of use						
Former	3	37042.14	0.54	0.15 - 1.95	0.52	0.14- 1.86
Current	22	133776	1.11	0.54 - 2.30	0.98	0.47 - 2.05
Duration of use						
<10 years	12	75147.8	1.03	0.45 - 2.38	0.97	0.42 - 2.25
>10 years	13	94671.81	0.95	0.43 - 2.13	0.82	0.37 - 1.86
	CLL/SLL (N=34)					
No hormone therapy use	7	63198.46	1.00	Ref.	1.00	Ref.
Estrogen only	19	172354.33	1.02	0.43 - 2.43	1.10	0.45 - 2.64
Recency of use						
Former	2	37043.74	0.58	0.12 - 2.77	0.61	0.13 - 2.95
Current	16	133756.4	1.31	0.54 - 3.19	1.41	0.57 - 3.46
Duration of use						
<10 years	10	75140.74	1.49	0.56 - 3.96	1.58	0.59 - 4.21
>10 years	9	94661.97	1.02	0.38 - 2.73	1.09	0.40 - 2.95

Abbreviations: chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); relative risk (RR).

*No. cancers may not sum to total due to use of other hormone therapy formulations or missing data.

**RRs adjusted for age (continuous).

†RRs adjusted for age (continuous), race, menopausal status, oral contraceptive use, education, smoking status, and other hormone therapy formulations.

Table 4

Estrogen plus progestin only menopausal hormone therapy use and relative risk of lymphoid neoplasms, by type, among women with intact uteri in the NIH-AARP Diet and Health Study

Hormone therapy	No. cancers*	Person-years	RR**	95% CI	RR†	95% CI
	Plasma cell neoplasms (N=47)					
No hormone therapy use	26	209,746	1.00	Ref.	1.00	Ref.
Estrogen plus progestin only	12	115,221	1.16	0.58 - 2.35	1.24	0.60 - 2.58
Recency of use						
Former	1	20,159	0.51	0.07 - 3.76	0.55	0.08 - 4.11
Current	11	94,219	1.34	0.65 - 2.76	1.44	0.67 - 3.07
Duration of use						
<10 years	11	86,532	1.61	0.78 - 3.35	1.72	0.81 - 3.63
>10 years	1	28,154	0.30	0.04 - 2.25	0.31	0.04 - 2.32
Regimen of estrogen plus progestin						
Sequential (<15 days)	4	41,503	1.16	0.40 - 3.37	1.21	0.39 - 3.76
Continuous	4	22,529	1.97	0.68 - 5.70	2.13	0.72 - 6.27
	Non-Hodgkin lymphoma (N=228)					
No hormone therapy use	128	210,069	1.00	Ref.	1.00	Ref.
Estrogen plus progestin only	52	115,345	0.86	0.62 - 1.20	0.84	0.60 - 1.17
Recency of use						
Former	9	20,179	0.81	0.41 - 1.61	0.80	0.41 - 1.59
Current	43	94,322	0.88	0.62 - 1.25	0.85	0.59 - 1.23
Duration of use						
<10 years	36	86,606	0.84	0.57 - 1.23	0.82	0.56 - 1.21
>10 years	16	28,204	0.93	0.55 - 1.56	0.89	0.52 - 1.52
Regimen of estrogen plus progestin						
Sequential (<15 days)	14	41,538	0.67	0.38 - 1.16	0.64	0.36 - 1.13
Continuous	15	22,558	1.26	0.74 - 2.17	1.23	0.72 - 2.13
	Diffuse large B-cell lymphoma (N=52)					
No hormone therapy use	26	209,754	1.00	Ref.	1.00	Ref.
Estrogen plus progestin only	11	115,226	1.07	0.52 - 2.20	1.08	0.52 - 2.27

Hormone therapy	No. cancers*	Person-years	RR**	95% CI	RR†	95% CI
Recency of use						
Former	2	20,164	1.02	0.24 - 4.30	1.06	0.25 - 4.48
Current	9	94,219	1.10	0.51 - 2.37	1.10	0.49 - 2.45
Duration of use						
<10 years	7	86,527	1.02	0.43 - 2.40	1.04	0.44 - 2.48
>10 years	4	28,164	1.19	0.41 - 3.43	1.18	0.39 - 3.51
Regimen of estrogen plus progestin						
Sequential (<15 days)	3	41,505	0.87	0.26 - 2.91	0.76	0.22 - 2.70
Continuous	3	22,530	1.48	0.44 - 4.92	1.63	0.49 - 5.48
	Follicular lymphoma (N=62)					
No hormone therapy use	35	209,775	1.00	Ref.	1.00	Ref.
Estrogen plus progestin only	15	115,234	0.82	0.44 - 1.52	0.77	0.41 - 1.46
Recency of use						
Former	3	20,163	0.92	0.28 - 3.01	0.89	0.27 - 2.93
Current	12	94,227	0.80	0.41 - 1.57	0.75	0.38 - 1.50
Duration of use						
<10 years	12	86,539	0.90	0.46 - 1.78	0.85	0.43 - 1.68
>10 years	3	28,160	0.62	0.19 - 2.03	0.59	0.18 - 1.95
Regimen of estrogen plus progestin						
Sequential (<15 days)	4	41,509	0.61	0.22 - 1.74	0.58	0.20 - 1.68
Continuous	3	22,528	0.84	0.26 - 2.73	0.78	0.24 - 2.57
	CLL/SLL (N=50)					
No hormone therapy use	27	209,743	1.00	Ref.	1.00	Ref.
Estrogen plus progestin only	12	115,232	0.89	0.45 - 1.80	0.86	0.42 - 1.75
Recency of use						
Former	1	20,160	0.41	0.06 - 3.00	0.40	0.05 - 2.96
Current	11	94,229	1.02	0.50 - 2.09	0.97	0.46 - 2.04
Duration of use						
<10 years	8	86,528	0.83	0.37 - 1.87	0.80	0.35 - 1.83
>10 years	4	28,169	1.07	0.37 - 3.06	1.01	0.34 - 2.97

Int J Cancer. Author manuscript; available in PMC 2010 June 1.

Hormone therapy	No. cancers*	Person-years	RR**	95% CI	RR†	95% CI
Regimen of estrogen plus progestin						
Sequential (<15 days)	2	41,506	0.43	0.10 - 1.81	0.41	0.09 - 1.78
Continuous	4	22,530	1.51	0.52 - 4.35	1.41	0.48 - 4.14

Abbreviations: chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); relative risk (RR).

*No. cancers may not sum to total due to use of other hormone therapy formulations or missing data.

**RRs adjusted for age (continuous) and other hormone therapy formulations.

†RRs adjusted for age (continuous), race, menopausal status, oral contraceptive use, education, smoking status, and other hormone therapy formulations.