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Original Article

Clinicopathological features and risk factors for developing colorectal neoplasia in Hodgkin's lymphoma survivors

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Background: Hodgkin's lymphoma (HL) survivors treated with abdominal radiotherapy and/or procarbazine have an increased risk of developing colorectal neoplasia.

Aims: We evaluated the clinicopathological characteristics and risk factors for developing (advanced) neoplasia (AN) in HL survivors.

Methods: In all, 101 HL survivors (median age 51 years, median age of HL diagnosis 25 years) underwent colonoscopy and 350 neoplasia and 44 AN (classified as advanced adenomas/serrated lesions or colorectal cancer), mostly right-sided, were detected, as published previously. An average-risk asymptomatic cohort who underwent screening colonoscopy were controls (median age 60 years). Clinicopathological characteristics of AN were evaluated in both groups. Mismatch repair (MMR) status was assessed using immunohistochemistry (MLH1/MSH2/MSH6/PMS2). Logistic regression analysis was performed to evaluate the risk factors for AN in HL survivors, including age at HL diagnosis and interval between HL and colonoscopy.

Results: In 101 colonoscopies in HL survivors, AN was primarily classified based on polyp size ≥10 mm, whereas (high-grade) dysplasia was more often seen in AN in controls. An interval between HL diagnosis and colonoscopy >26 years was associated with more AN compared with an interval of <26 years, with an odds ratio for AN of 3.8 (95% confidence interval 1.4–9.1) ($p < 0.01$). All 39 AN that were assessed were MMR proficient.

Conclusions: Colorectal neoplasia in HL survivors differ from average-risk controls; classification AN was primarily based on polyp size (≥10 mm) in HL survivors. Longer follow-up between HL diagnosis and colonoscopy was associated with a higher prevalence of AN in HL survivors.

Key words: cancer survivors, colonoscopy, colorectal neoplasms, DNA mismatch repair, Hodgkin's lymphoma

INTRODUCTION

HODGKIN'S LYMPHOMA (HL) survivors treated with abdominal radiotherapy and/or procarbazine-containing chemotherapy have a two to seven times higher risk of developing colorectal cancer (CRC) compared to the general population.[1–6] This elevated risk for CRC was described 10 years after HL treatment, up to ≥30 years after HL treatment.[6] In a recent prospective study, a higher prevalence of neoplasia and advanced neoplasia (AN) – defined as advanced adenoma, advanced serrated lesion, or CRC – was detected during a first surveillance colonoscopy in HL survivors compared to a general asymptomatic population undergoing primary colonoscopy screening.[7]

Whether the clinicopathological characteristics and risk factors for developing colorectal neoplasia in HL survivors differ from the characteristics and risk factors in the general

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population is still largely unknown. For the general population, several risk factors for developing neoplasia and/or CRC are known, among which are older age, male sex, obesity, smoking, family history of CRC, or inflammatory bowel disease.[8–14] Abdominal radiotherapy and/or procarbazine-containing chemotherapy could influence the neoplasia characteristics and development,[2,4,6] as it has been shown to be a risk factor for AN in HL survivors.[7] A higher prevalence of CRC has been described when HL diagnosis was at a younger age,[2,4,6,15,16] but whether the same occurs for AN is unknown.

Knowledge of the pathogenesis of precursor lesions of CRC in HL survivors is limited. Theories regarding the pathogenesis of second primary cancers induced by prior anticancer treatment involve direct DNA damage, epigenetic changes, and inflammatory processes as a bystander effect in healthy tissues.[17–19] We have previously demonstrated that AN of HL survivors are more often located proximal in the colon and that CRC in HL survivors have a higher frequency of mismatch repair (MMR) deficiency compared with CRC in the general population (24% vs. 11%). The increased frequency of MMR deficiency was due to biallelic somatic inactivation (mutations/loss of heterozygosity) in MMR genes in 7/54 (13%), which occurs less frequently in the general population (8/1111, <0.1%).[20] Knowledge about precursor lesions of both MMR-deficient and MMR-proficient CRC in HL survivors is still sparse. It is also not known whether MMR deficiency due to biallelic somatic MMR gene inactivation arises early or late in the carcinogenesis.

In this study we aimed to evaluate the clinicopathological characteristics of neoplasia in HL survivors in our colonoscopy cohort, including MMR status of the advanced precursor lesions of CRC. Furthermore, we evaluated the role of known risk factors for developing colorectal neoplasia in the HL survivors, including age at HL diagnosis.

METHODS

Patient characteristics

THE STUDY DESIGN and baseline characteristics of our colonoscopy cohort of HL survivors have been previously described.[7,21] In short, patients were invited for a prospective multicenter cohort study in four Dutch study centers (Netherlands Cancer Institute, Amsterdam; Erasmus MC Cancer Institute, Rotterdam; University Medical Center Utrecht, Utrecht; and Radboud University Medical Center, Nijmegen). Inclusion criteria were infradiaphragmatic radiotherapy consisting of at least para-aortic and iliac fields, chemotherapy containing a cumulative procarbazine dose of ≥2.8 g/m^2, or infradiaphragmatic radiotherapy (any field(s)) and chemotherapy (any regimen) and a survival of at least 8 years after the first HL treatment.[7] This study showed that among the 101 HL survivors (median age of 51 years; interquartile range [IQR] 45–57 years) who underwent a colonoscopy between 2015 and 2017, 350 neoplasia and 44 AN were detected (neoplasia detection rate; 72.3% and AN detection rate; 24.8%) (Table 1, Table S1).[7] A Dutch cohort of 1426 asymptomatic individuals aged 50–75 years who underwent a primary screening colonoscopy between 2009 and 2010 were used as the control group. This cohort was screened before implementation of the Dutch national fecal immunochemical test-based screening program, referred to as controls.[7,22]

Table 1 Neoplasia detection rate of colorectal neoplasia detected at first surveillance colonoscopy in Hodgkin's lymphoma (HL) survivors (n = 101) and controls (n = 1426) per neoplastic lesion category

	Number of lesions in HL survivors	Prevalence in HL survivors (%)	Number of lesions in controls	Prevalence in controls (%)	*P*-value	Mean number of neoplasia per HL survivor	Mean number of neoplasia per control	*P*-value
Neoplasia[†]	350	72.3	1531	45.4	<0.01	3.5	1.1	<0.01
Nonadvanced adenoma	135	40.6	614	20.7	<0.01	1.3	0.4	<0.01
Nonadvanced serrated lesion	161	34.7	656	23.4	0.01	1.7	0.5	<0.01
Advanced neoplasia[†]	44	24.8	244	12.0	<0.01	0.4	0.2	<0.01

[†]Duplicated from a previous study.[7]

Study procedures

Study procedures have been described previously.[7] This study provides additional information about the clinicopathological characteristics and risk factors for developing neoplasia developed in HL survivors, which was not yet assessed in the previous publication.[7] In case a colorectal neoplasia (adenoma, serrated lesion) was detected, the location of the polypectomy was classified as right (cecum to transverse colon) or left (splenic flexure to rectum). We evaluated the location for different categories of lesions, i.e. (i) neoplasia (including all nonadvanced and advanced adenomas and serrated lesions), (ii) nonadvanced adenomas, (iii) nonadvanced serrated lesions, and (iv) AN (which was defined as advanced adenomas [high-grade dysplasia, ≥25% villous component, or ≥10 mm diameter] or advanced serrated lesions [hyperplastic polyp or sessile serrated lesion ≥10 mm or sessile serrated lesion with dysplasia], or CRC).[7] A questionnaire was sent to evaluate the known risk factors for CRC, i.e. body mass index (BMI) at colonoscopy, smoking, and family history of CRC.

This study was approved by the Medical Ethics Committee (Dutch Trial Registry – ID NTR4961) and Institutional Review Board (CFMPB717) of the Netherlands Cancer Institute. Collection, storage, and use of patient-derived tissue and data were performed in compliance with the "Human Tissue and Medical Research: Code of conduct for responsible use" Dutch Federation of Dutch Medical Scientific Societies, the Netherlands.

Histopathology and immunohistochemistry

Histopathology of neoplasia detected during colonoscopy was classified by local expert gastrointestinal (GI) pathologists. All AN were reviewed by one expert GI pathologist (P.S.) by evaluating the size, dysplasia, and histopathologic features. The clinicopathological characteristics of neoplasia detected in HL survivors were compared to the neoplasia detected in the control group. Formalin-fixed, paraffin-embedded (FFPE) tissue of AN was obtained for immunohistochemical assessment of MMR protein staining. Immunohistochemistry (IHC) was performed on whole slides for MMR proteins according to standard protocols for Ventana immunostainer (MLH1; Agilent/DAKO, Santa Clara, CA, USA, clone ES05), MSH2 (Roche/Ventana, Oro Valley, AZ, USA, clone G219-1129), MSH6 (Epitomics, Nanterre, France, clone EP49), and PMS2 (Roche/Ventana, clone A16-4)). MMR staining was assessed in both dysplastic and nondysplastic components. AN without intact nuclear staining of one or more MMR proteins was considered MMR-deficient.

Statistical analysis

IBM SPSS Statistics (v. 22, Armonk, NY, USA) was used for statistical analysis and data management. Dichotomous or categorical data between groups was assessed by chi-squared tests or Fisher's exact tests comparing HL survivors to the controls. Analyses that included the controls as a comparison included: (i) neoplasia prevalence, (ii) histopathological features, and (iii) location of neoplasia (right- or left-sided).

To determine the risk factors for the prevalence of neoplasia within the HL group, known risk factors for the prevalence of neoplasia and AN in only HL survivors were tested using univariate and multivariate logistic regression modeling – i.e. age at HL diagnosis (in categories; 15–30 years and 31–48 years), follow-up interval between HL diagnosis and colonoscopy (in categories; 12–25 years and 26–40 years), sex, BMI at colonoscopy (in categories; ≤24, 25–29, and ≥30 kg/m^2), smoking (nonsmoker, past smoker, and current smoker), and family history of CRC (first-degree relative with CRC yes/no, Table S1).[8–14] Variables were included in the multivariable logistic regression analysis when the $P < 0.1$ in a univariate analysis. A $P \leq 0.05$ was considered statistically significant.

RESULTS

Colonoscopy participants

WHEN COMPARING THE 101 HL survivors (56% male and median age of 51 years [IQR 45–57 years]) who underwent a colonoscopy, both (non-) advanced adenomas and (non-)advanced sessile lesions had a significantly higher prevalence compared with controls (Table 1). The baseline characteristics of HL survivors and controls are copied from a previous publication in Table S2.

Clinicopathological characteristics of colorectal neoplasia in HL survivors compared with controls

In HL survivors, the majority of the 44 AN was classified as advanced based on a polyp size of ≥10 mm. In advanced adenomas in HL survivors (n = 19), no high-grade dysplasia was detected, while it was detected in 24% of the 163 advanced adenomas in controls (P = 0.05, Table 2). Among the advanced serrated polyps in HL survivors (n = 25), 88% were sessile serrated lesions and 12% hyperplastic, whereas in the control group only 60% of the advanced serrated lesions was classified as a sessile

Table 2 Histopathological features of advanced neoplasia in Hodgkin's lymphoma (HL) survivors vs. control group

	HL survivors (*n* (%))	Controls (*n* (%))	*P*-value
Advanced adenomas	19 (14.9%)	163 (8.7%)	0.04
Dysplasia			0.05
Low-grade dysplasia	19 (100%)	123 (75.9%)	
High-grade dysplasia	0 (0%)	39 (24.1%)	
Missing	—	1	
Adenoma type			0.41
Tubular adenoma	12 (63.2%)	77 (47.5%)	
Tubulovillous adenoma	7 (35.0%)	83 (51.2%)	
Villous adenoma	0 (0%)	2 (1.2%)	
Missing	—	1	
Size			0.69
<5 mm	1 (5.6%)	16 (9.8%)	
5–9 mm	2 (11.1%)	26 (16.0%)	
>10 mm	15 (83.3%)	121 (74.2%)	
Missing	1	—	
Advanced serrated lesions	25 (11.9%)	72 (3.9%)	<0.01
Dysplasia			0.01
No dysplasia	22 (88.0%)	39 (54.2%)	
Low-grade dysplasia	3 (12.0%)	30 (41.7%)	
High-grade dysplasia	0 (0%)	3 (4.2%)	
Size			<0.01
<5 mm	—	11 (15.3%)	
5–9 mm	1 (4.0%)	17 (23.6%)	
>10 mm	24 (96.0%)	44 (61.1%)	

serrated lesion ($P < 0.01$). Advanced serrated lesions in HL survivors were also mainly classified as advanced based on a size of ≥10 mm. Dysplasia was less often seen in advanced serrated lesions in HL survivors compared with controls (12% vs. 46%, $P < 0.01$, Table 2).

Neoplasia was more often right-sided in HL survivors (73%) compared with controls (40%, $P < 0.01$). This included nonadvanced adenomas, nonadvanced serrated lesions, and AN (Fig. 1). However, for AN this effect was predominately due to right-sided advanced serrated lesions (92% vs. 71%, $P = 0.03$). For advanced adenomas there was no significant difference (45% vs. 29%, $P = 0.10$) for HL survivors and controls, respectively.

MMR-status analysis of AN in HL survivors

Of the 44 AN, MMR status could be assessed in 39 (16 advanced adenomas and 23 advanced serrated lesions) by IHC. Intact IHC nuclear staining of MMR proteins was present in all samples, both in neoplastic and normal adjacent mucosa.

Univariate and multivariate logistic regression analyses for the prevalence of AN in HL survivors and known risk factors for developing colorectal neoplasia

In the univariate analyses, only the interval between HL diagnosis and colonoscopy between 26 and 48 years was significantly associated with the prevalence of both neoplasia and AN (Table 3). Sex, BMI, smoking, alcohol use, and family history (first-degree relative with CRC) were not associated with the prevalence of AN in univariate analysis. The age at HL diagnosis was not significantly associated with the prevalence of AN.

For HL survivors with a longer follow-up period of 26–40 years between HL diagnosis and colonoscopy, the prevalence neoplasia and AN was higher (odds ratio [OR] 3.0, 95% confidence interval [CI] 1.0–8.9 and OR 3.8, 95% CI 1.4–9.1, respectively) than in the interval period of 12–25 years. In multivariate analyses after correcting for sex, the interval between HL diagnosis and colonoscopy and a higher prevalence of AN remained significantly associated.

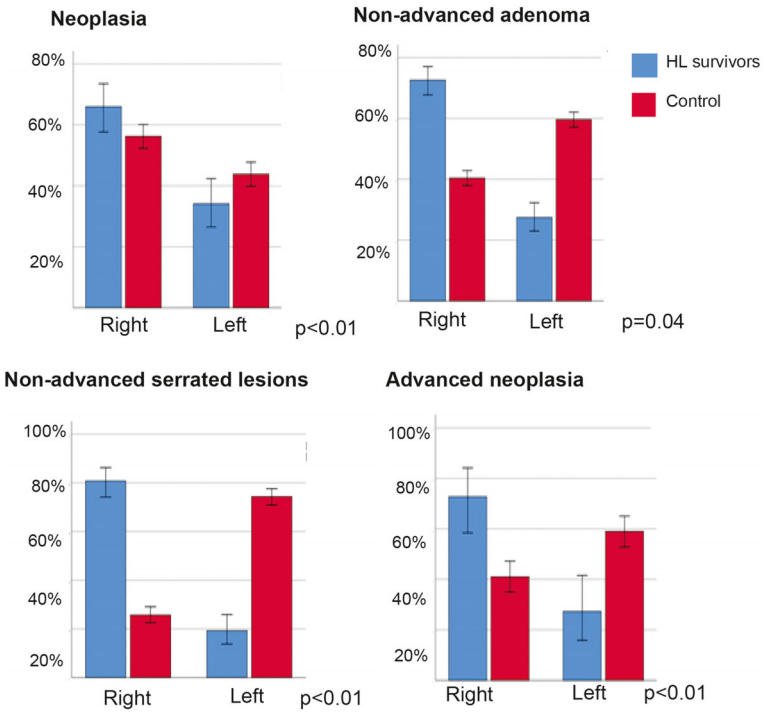

Figure 1 The location of each type of neoplasia – any type of colorectal neoplasia, nonadvanced adenoma, nonadvanced serrated lesion, and advanced neoplasia – in Hodgkin's lymphoma survivors (n = 101) and controls (n = 1426). The location was classified as right (cecum to transverse colon) or left (splenic flexure to rectum) and calculated for every neoplasia detected in percent.

DISCUSSION

IN THIS STUDY we assessed the clinicopathological characteristics of colorectal neoplasia in HL survivors and the presence of risk factors for developing colorectal neoplasia. We show that neoplasia in HL survivors was most often classified as advanced due to size ≥10 mm compared with neoplasia in controls. Among HL survivors, a longer follow-up period between HL diagnosis and colonoscopy was associated with more AN. MMR deficiency was not detected in the advanced precursor lesions of CRC analyzed.

Previously, we have detected a higher prevalence and mean number of AN in HL survivors compared to the general population.[7] In the general population, age, male sex, smoking, obesity, and family history of CRC are all associated with an increased prevalence of neoplasia and/or CRC.[8–14] Our data showed that in univariate and multivariate analysis a longer follow-up period between HL diagnosis and colonoscopy was associated with the prevalence of (advanced) colorectal neoplasia among HL survivors. Correcting for age at colonoscopy in the multivariate analysis was not possible due to correlation with the interval. Our results indicate that a longer time period between HL diagnosis and colonoscopy results in the higher prevalence of AN, and thus, that not solely an older age at colonoscopy was associated with a higher prevalence. We did not find an association with the other aforementioned risk factors in this study. This may be due to small numbers. Furthermore, there was a trend that HL survivors who were diagnosed with HL at a younger age had a higher prevalence of AN. Therefore, we hypothesize that primarily the treatment for HL at a younger age contributes to the increased risk of developing colorectal neoplasia, as previously suggested.[2,4,6,15]

Interestingly, it was shown that anticancer treatment induces mutations and premature aging of colonic mucosa.[18] Whether HL treatment (especially abdominal radiotherapy and/or procarbazine-containing chemotherapy) induces the regular CRC pathways at an earlier age, or whether other pathways are involved, possibly related to single nucleotide polymorphism cancer susceptibility,[23] is unknown. HL treatment may underlie the higher prevalence of colorectal neoplasia among HL survivors.

Compared to the general population, neoplasia in HL survivors was more often located in the right-sided than in the left-sided colon, which has also been shown in other studies.[7,24] Especially infradiaphragmatic radiotherapy exposes the

Table 3 Univariate and multivariate logistic regression model for known risk factors for the prevalence of neoplasia and advanced neoplasia in Hodgkin's lymphoma (HL) survivors

		Univariate		Multivariate	
	Events/total	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Neoplasia in HL survivors					
Sex					
Male	43/57	1.0 (reference)		1.0 (reference)	
Female	30/44	0.7 (0.3–1.7)	0.42	0.7 (0.3–1.6)	0.35
Age at HL diagnosis (categories)					
15–30 years	51/71	1.0 (reference)		NA	
31–48 years	22/30	1.1 (0.4–2.8)	0.88	NA	NA
Interval between HL diagnosis and colonoscopy (categories)					
12–25 years	44/67	1.0 (reference)		1.0 (reference)	
26–40 years	29/34	3.0 (1.0–8.9)	0.04	3.1 (1.1–9.2)	0.04
BMI categories					
<24	29/41	1.0 (reference)		NA	
25–29	24/36	0.8 (0.3–2.2)	0.70	NA	NA
>30	13/16	1.8 (0.4–7.5)	0.42	NA	NA
Smoking					
Nonsmoker[†]	40/60	1.0 (reference)		NA	
Past-smoker	18/21	3.0 (0.8–11.4)	0.11	NA	NA
Current smoker	9/13	1.1 (0.3–4.1)	0.86	NA	NA
Family history of CRC					
No	62/87	1.0 (reference)		NA	
Yes	5/7	1.0 (0.2–5.5)	0.99	NA	NA
Advanced neoplasia in HL survivors					
Sex					
Male	15/57	1.0 (reference)		1.0 (reference)	
Female	10/44	0.8 (0.3–2.1)	0.68	0.8 (0.3–2.0)	0.57
Age at HL diagnosis (categories)					
15–30 years	19/71	1.0 (reference)		NA	
31–48 years	6/30	0.7 (0.2–1.9)	0.47	NA	NA
Interval between HL diagnosis and colonoscopy (categories)					
12–25 years	11/67	1.0 (reference)		1.0 (reference)	
26–40 years	14/34	3.6 (1.4–9.1)	<0.01	3.6 (1.4–9.4)	<0.01
BMI categories					
<24	7/41	1.0 (reference)		NA	
25–29	12/36	2.4 (0.8–7.1)	0.10	NA	NA
>30	5/16	2.2 (0.6–8.4)	0.25	NA	NA
Smoking					
Nonsmoker[†]	14/60	1.0 (reference)		NA	
Past-smoker	7/21	1.6 (0.5–5.7)	0.37	NA	NA
Current smoker	4/13	1.5 (0.4–5.7)	0.57	NA	NA
Family history of CRC					
No	23/87	1.0 (reference)		NA	
Yes	2/7	1.1 (0.2–6.1)	0.90	NA	NA

[†]Nonsmoker includes currently not smoking but past unknown.
BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; OR, odds ratio; NA, not available.

transverse colon (part of the right-sided colon) to radiation.[6] Data from childhood cancer survivors who received pelvic or abdominal radiotherapy showed that 50% of the adenomas and serrated lesions were detected in the radiation field.[24–26] This field-effect is likely also the explanation for the distribution of neoplasia in our cohort of HL survivors.

A recent retrospective study detected a higher prevalence of adenoma after 1 year of HL diagnosis, suggesting the early onset of colorectal adenoma in HL survivors; however, with the highest adenoma detection rate 10 years after HL treatment.[24] In our population, a colonoscopy was offered at least 8 years after HL treatment, with a median interval of 22 years. Therefore, we cannot estimate the risk of neoplasia before that time frame. The optimal time interval for starting surveillance after HL treatment still needs to be determined, but based on current knowledge an 8–10 years interval seems appropriate (i.e. risk of CRC increased 10 years after HL treatment and no CRC detected in our study population). Even though we detected the highest prevalence of AN in the HL survivors with the longest interval between HL diagnosis and colonoscopy, we do suggest that HL survivors benefit from early surveillance, as the risk of developing CRC is increased 10 years after HL diagnosis.[6] When HL is diagnosed at a young age, this interval seems appropriate, with the additional recommendation to start colonoscopy surveillance from an age of 35 years, since the *a priori* chance of CRC is really low before age 35 years.

Dysplasia was less frequently detected in AN in HL survivors than in the controls; however, the cause is unknown. An explanation may be another pathway into carcinoma development. The chance of interobserver variance is low, as in our study all AN were reassessed by the same pathologist, and for the control group all AN were evaluated by one of the two experienced GI pathologists.

Even though we previously revealed an increased prevalence of MMR deficiency in CRC in HL survivors due to biallelic somatic inactivation in MMR genes,[20] we did not detect MMR deficiency in any of the advanced precursor lesions of HL survivors. This can be explained by a low *a priori* chance of detecting MMR deficiency in the precursor lesions. Furthermore, it is unknown whether MMR deficiency is an early or late step in the development of MMR-deficient CRCs, but based on our results we suggest that MMR deficiency is a late step.[27–29] Further research is necessary to gain more insight into the carcinogenesis of CRC and its precursor lesions in HL survivors.

A limitation of our study is that the sample size was small, since only 101 HL survivors underwent a first colonoscopy. The study was stopped based on a significantly higher prevalence of AN compared to the sex- and age-matched control group during a planned interim analyses.[7] Therefore, the number of AN removed during colonoscopy was limited. Our findings should be confirmed in a larger cohort. Furthermore, the colonoscopies in the HL group and control group were performed in different time periods (2015–2017 vs. 2009–2010, respectively). However, this control group is the best comparison, since this is a fecal immunochemical test-naïve average-risk Dutch population who underwent a primary colonoscopy screening. In both studies, expert gastroenterologists performed high-quality colonoscopies with high-definition scopes (predominately with narrow-band imaging). In both studies, participants were excluded if they underwent a colonoscopy in the past 5 years, as previous colonoscopy could influence the detection rate of AN. Additionally, in the logistic regression we corrected for sex; however, not for age, as this was correlated with the variable of interval between HL diagnosis and colonoscopy. Another possible confounder could be the previous treatment of HL, as our group previously detected differences between the different risks between the different HL treatment strategies. We did not include HL treatment in our analysis, as the participants in the study were already classified as a high-risk-group based on the treatment they received. The clinicopathological characteristics of colorectal AN detected in HL survivors differ from those in the general population. Neoplasia is classified as advanced mainly based on polyp size ≥10 mm, while in controls (high grade) dysplasia occurred more often. The prevalence of AN was high and mostly located right-sided compared to the control group. A longer follow-up period between HL diagnosis and colonoscopy was the only risk factor associated with a higher prevalence of AN. Knowledge about the high prevalence of serrated lesions and the different distribution of lesions are important for the endoscopist. Special attention should be given to the recognition of these lesions during colonoscopy.

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CONFLICT OF INTEREST

AUTHORS DECLARE NO conflict of interest for this article.

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SUPPORTING INFORMATION

ADDITIONAL SUPPORTING INFORMATION may be found in the online version of this article at the publisher's web site.

Table S1 Baseline characteristics Hodgkin's lymphoma survivors (n = 101).*

Table S2 Risk factors for neoplasia in Hodgkin lymphoma (HL) survivors and general population controls.