Gastrointestinal malignancies in high-risk populations = Gastro-intestinale maligniteiten in hoog-risico populaties

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4 CLINICOPATHOLOGICAL FEATURES AND RISK FACTORS FOR DEVELOPING COLORECTAL NEOPLASIA IN HODGKIN LYMPHOMA SURVIVORS

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ABSTRACT

Background

Hodgkin lymphoma (HL) survivors treated with abdominal radiotherapy and/or procarbazine have an increased risk of developing colorectal neoplasia. We evaluated clinicopathological characteristics and risk factors for developing (advanced) neoplasia (AN) in HL survivors.

Methods

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 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 (advanced) neoplasia compared with interval of <26 years, with an odds ratio for advanced neoplasia 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 (advanced) neoplasia in HL survivors.

Clinical trial registration number: Dutch Trial Registry (ID NTR4961)

INTRODUCTION

Hodgkin 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 population is still largely unknown. For the general population, several risk factors for developing neoplasia and/or CRC are known, among which older age, male gender, obesity, smoking, family history of CRC and 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 a risk factor for (advanced) neoplasia 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 (advanced) neoplasia 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.

MATERIALS AND 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 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 first HL treatment.[7] This studied 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 advanced neoplasia detection rate; 24.8%) (Table 1, Supplementary Table 1).[7] A Dutch cohort of 1426 asymptomatic individuals aged 50 to 75 years who underwent a primary screening colonoscopy between 2009 and 2010 were used as control group. This cohort was screened before implementation of the Dutch national fecal immunochemical test-based screening program, referred to as controls.[7,22]

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 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, (1) neoplasia (including all non-advanced and advanced adenomas and serrated lesions), (2) non-advanced adenomas, (3) non-advanced serrated lesions and (4) 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 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 pa-

tient-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 GI-pathologists. All AN were reviewed by one expert GI pathologist (PS) 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, clone ES05), MSH2 (Roche/Ventana, clone G219-1129), MSH6 (Epitomics, clone EP49) and PMS2 (Roche/Ventana, clone A16-4)). MMR staining was assessed in both dysplastic and non-dysplastic components. AN without intact nuclear staining of one or more MMR proteins, was considered MMR deficient.

Statistical analysis

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

To determine risk factors for 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 modelling – 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 (non-smoker, past smoker and current smoker) and family history of CRC (first degree relative with CRC yes/no, Supplementary Table 1).[8-14] Variables were included in the multivariable logistic regression analysis when the p-value was <0.1 in a univariate analysis. A p-value of ≤0.05 was considered statistically significant.

RESULTS

Colonoscopy participants

When comparing the 101 HL survivors (56% male and median age of 51 years (interquartile range (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 previous publication in Supplementary Table 2.

Clinicopathological characteristics of colorectal neoplasia in Hodgkin lymphoma 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 serrated lesion (p<0.01). Advanced serrated lesions in HL survivors were also mainly classified as advanced based on 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 non-advanced adenomas, non-advanced serrated lesions and AN (Figure 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 advanced neoplasia in Hodgkin lymphoma 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.

Table 1 | Neoplasia detection rate of colorectal neoplasia detected at first surveillance colonoscopy in Hodgkin lymphoma 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
Non-advanced adenoma	135	40.6%	614	20.7%	<0.01	1.3	0.4	<0.01
Non-advanced 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 previous study.[7]

Table 2 | Histopathological features of advanced neoplasia in Hodgkin lymphoma (HL) survivors versus control group.

	HL survivors (n, (%))	Controls (n, (%))	p-value
Advanced adenomas	n = 19 (14.9%)	n = 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	n = 25 (11.9%)	n = 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%)	

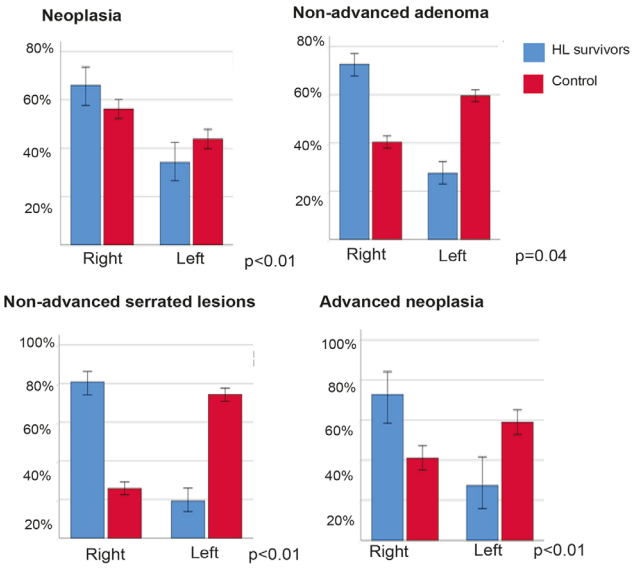

Figure 1 | The location of each type of neoplasia – any type of colorectal neoplasia, non-advanced adenoma, non-advanced serrated lesion and advanced neoplasia - in Hodgkin lymphoma survivors (n = 101) and controls (n = 1426). The location was classified as right (cecum to transverse colon) or left (splenic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

Univariate and multivariate logistic regression analyses for prevalence of (advanced) neoplasia in Hodgkin lymphoma 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 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 (advanced) neoplasia in univariate analysis. The age at HL diagnosis was not significantly associated with the prevalence of (advanced) neoplasia.

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 (OR 3.0 (95% 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 a multivariate analyses after correcting for sex, interval between HL diagnosis and colonoscopy and a higher prevalence of (advanced) neoplasia remained significantly associated.

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

		Univariate		**Multivariate**	
	Events/total	OR (95% CI)	p-value	OR (95% CI)	p-value
Neoplasia in HL survivors					
Sex					0.35
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)	
Age at HL diagnosis (categories)					
15-30 years	51/71	1.0 (reference)			
31-48 years	22/30	1.1 (0.4-2.8)	0.88		
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)			
25-29	24/36	0.8 (0.3-2.2)	0.70		
>30	13/16	1.8 (0.4-7.5)	0.42		
Smoking					
Non-smoker*	40/60	1.0 (reference)			
Past-smoker	18/21	3.0 (0.8-11.4)	0.11		
Current smoker	9/13	1.1 (0.3-4.1)	0.86		
Family history of CRC					

No	62/87	1.0 (reference)			
Yes	5/7	1.0 (0.2-5.5)	0.99		
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)			
31-48 years	6/30	0.7 (0.2-1.9)	0.47		
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)			
25-29	12/36	2.4 (0.8-7.1)	0.10		
>30	5/16	2.2 (0.6-8.4)	0.25		
Smoking					
Non-smoker*	14/60	1.0 (reference)			
Past-smoker	7/21	1.6 (0.5-5.7)	0.37		
Current smoker	4/13	1.5 (0.4-5.7)	0.57		

Family history of CRC			
No	23/87	1.0 (reference)	
Yes	2/7	1.1 (0.2-6.1)	0.90

OR = odds ratio, 95% CI =95% confidence interval * Non-smoker includes currently not smoking but past unknown.

DISCUSSION

In this study, we assessed the clinicopathological characteristics of colorectal neoplasia in HL survivors and its 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 (advanced) neoplasia. MMR deficiency was not detected in the advanced precursor lesions of CRC analyzed.
Previously we have detected a higher prevalence and mean number of (advanced) neoplasia in HL survivors compared to the general population.[7] In the general population, age, male gender, smoking, obesity and family history of CRC are all associated with an increased prevalence of neoplasia and/or CRC.[8-14] Our data did show that in univariate and multivariate analysis 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 (advanced) neoplasia, and thus that not solely only 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 anti-cancer treatment induces mutations and premature ageing 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 been also shown in other studies.[7,24] Especially infradiaphragmatic radiotherapy exposes the transverse colon (part of 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 already after one 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 eight 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 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 (advanced) neoplasia 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 the 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 gastrointestinal 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.
The 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 five years, as previous colonoscopy could influence the detection rate of (advanced) neoplasia. Additionally, in the logistic regression we did correct 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.

CONCLUSIONS

The clinicopathological characteristics of colorectal (advanced) neoplasia 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. Prevalence of (advanced) neoplasia is 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 factors associated with a higher prevalence of (advanced) neoplasia. Knowledge about the high prevalence of serrated lesions and the different distribution of lesions are important for endoscopist; Special attention should be given to the recognition of these lesions during colonoscopy.

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SUPPLEMENTARY INFORMATION

Supplementary Table 1 | Baseline characteristics Hodgkin lymphoma survivors (n = 101)*.

Characteristic	Value
Age at HL treatment, median (IQR), y	25 (20-32)
Age at HL treatment, %	
16 – 25 y	51
26 – 35 y	36
36 – 48 y	13
Time between HL treatment and colonoscopy, %	
12 – 19 y	29
20 – 29 y	55
30 – 40 y	17
Year of HL treatment, %	
1975 – 1984	15
1985 – 1994	50
1995 – 2004	35
HL stage, %	
I	11
II	50
III	21
IV	17
Unknown	2
HL treatment category, %	
Abdominal RT + procarbazine	35
Procarbazine	50
Abdominal RT	15

* With permission duplicated from previous study[7]

Supplementary Table 2 | Risk factors for neoplasia in Hodgkin lymphoma (HL) survivors and general population controls.

	HL survivors (*n*=101) %	**Controls (*n*=1426) %**	***P* value**
Age, median (IQR), y	51 (45-57)	60 (55-65)	<0.001
Male sex	56	51	0.28
Family history			
1st degree relative(s) with CRC	7	13	0.12
No 1st degree relative(s) with CRC	86	87	
Missing	7	0	
Smoking status			
Current smoker	13	13	0.70
Non-smoker	80	73	
Former smoker	21	41	
Never smoker	47	31	
Non-smoker, history unknown	13	0	
Missing	7	14	
BMI in kg/m^2			
<25	41	32	0.07
25-30	42	53	
>30	10	14	
Missing	8	<1	
Alcohol in units/week			
<15	89	72	0.004
≥15	3	11	
Missing	8	18	

Abbreviations: IQR: interquartile range; HL, CRC, colorectal cancer; BMI, body mass index.