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ARTICLE

Survival of *MUTYH*-Associated Polyposis Patients With Colorectal Cancer and Matched Control Colorectal Cancer Patients

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Background *MUTYH*-associated polyposis is a recessively inherited disorder characterized by a lifetime risk of colorectal cancer that is up to 100%. Because specific histological and molecular genetic features of *MUTYH*-associated polyposis colorectal cancers might influence tumor behavior and patient survival, we compared survival between patients with *MUTYH*-associated polyposis colorectal cancer and matched control patients with colorectal cancer from the general population.

Methods In this retrospective multicenter cohort study from Europe, 147 patients with *MUTYH*-associated polyposis colorectal cancer were compared with 272 population-based control patients with colorectal cancer who were matched for country, age at diagnosis, year of diagnosis, stage, and subsite of colorectal cancer. Kaplan–Meier survival and Cox regression analyses were used to compare survival between patients with *MUTYH*-associated polyposis colorectal cancer and control patients with colorectal cancer. All statistical tests were two-sided.

Results Five-year survival for patients with *MUTYH*-associated polyposis colorectal cancer was 78% (95% confidence interval [CI] = 70% to 84%) and for control patients was 63% (95% CI = 56% to 69%) (log-rank test, $P = .002$). After adjustment for differences in age, stage, sex, subsite, country, and year of diagnosis, survival remained better for *MUTYH*-associated polyposis colorectal cancer patients than for control patients (hazard ratio of death = 0.48, 95% CI = 0.32 to 0.72).

Conclusions In a European study cohort, we found statistically significantly better survival for patients with *MUTYH*-associated polyposis colorectal cancer than for matched control patients with colorectal cancer.

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Worldwide, colorectal cancer accounted for about one million newly diagnosed cancers in 2002, representing approximately 10% of all new cancers (1). Estimated 5-year survival for colorectal cancer is approximately 54% in Western Europe (1). Tumors in patients with inherited cancer syndromes may arise through distinct molecular genetic pathways and show histological features that are different from those in most sporadic tumors. These differences might, at least in part, influence tumor behavior and patient survival. For instance, mismatch repair–deficient tumors (associated with Lynch syndrome or sporadic microsatellite instability) have been reported to have a decreased likelihood of metastasizing, and patients with such tumors have better survival than patients with sporadic colorectal cancer (2–8), although some reports have not confirmed this finding (9–12).

In 2002, the first autosomal recessive inherited form of colorectal cancer, *MUTYH*-associated polyposis (Mendelian Inheritance in Man #608456), was described (13). *MUTYH*-associated polyposis is believed to be responsible for 0.3%–1% of all colorectal cancers (14,15).

The MUTYH protein is a base excision repair glycosylase that is involved in the repair of DNA damage resulting from the oxidation of guanine nucleotides. The oxidation product of guanine, 8-oxo-7,8-dihydro-2′-deoxyguanosine can mispair with adenine, leading to a transversion in which a G:C base pair is replaced with a T:A base pair. The MUTYH protein prevents these transversions by scanning the newly synthesized DNA strand for any mispaired adenines, with guanines or 8-oxo-7,8-dihydro-2′-deoxyguanosines, and excising them.

The risk of colorectal cancer in individuals with biallelic *MUTYH* mutations is high. The penetrance of colorectal cancer in patients with *MUTYH*-associated polyposis at age 60 years was estimated to be 100% in one study (16) and 43% in another (14).

We hypothesized that survival of patients with *MUTYH*-associated polyposis and colorectal cancer might differ from that of colorectal cancer patients from the general population because of the distinct mutational mechanism underlying *MUTYH*-associated polyposis. The purpose of this study was to compare survival between patients with *MUTYH*-associated polyposis colorectal

cancer and matched control patients with colorectal cancer from the general population.

Subjects and Methods

Study Population

This multicenter study was collaboration between three research groups from the Institute of Human Genetics (University of Bonn, Bonn, Germany), the Institute of Medical Genetics (School of Medicine, Cardiff University, Cardiff, United Kingdom), and the Department of Clinical Genetics (Leiden University Medical Center, Leiden, the Netherlands). The study population contained 147 patients with *MUTYH*-associated polyposis colorectal cancer and 272 matched patients with colorectal cancer from the general population. Informed consent was obtained according to protocols approved by the appropriate national and/or local ethic review boards (the Multi-Centre Research Ethics Committee for Wales, ref. 06/MRE09/19; University of Bonn Ethics Review Board No. 063/04; and Leiden University Medical Center Ethics Review Board No. P01.019). The Patients with *MUTYH*-associated polyposis were all biallelic *MUTYH* mutation carriers and included 113 index patients and 34 of their affected siblings. Siblings were selected and tested for *MUTYH* mutations in case they had developed colorectal cancer and/or polyps. Genotyping was performed as described previously (17–19) [see the Leiden Open Variation Database database for all reported *MUTYH* mutations (20)]. The time of diagnoses ranged from June 15, 1967, through August 13, 2001, for Dutch patients; from October 15, 1977, through March 10, 2006, for German patients; and from February 12, 1970, through February 14, 2006 for patients from the United Kingdom.

Colon cancer was defined by use of the code C18 and rectal cancer was defined by use of the codes C19–C20, according to the *International Classification of Diseases for Oncology*, Edition 3 (21). Tumor localization was categorized by the following anatomical subsites: proximal colon (consisting of the cecum, appendix, ascending colon, hepatic flexure, transverse colon, and splenic flexure; C18.0–C18.5), distal colon (consisting of descending colon and sigmoid; C18.6–C18.7), colon not otherwise specified (C18.8–C18.9), and rectum (consisting of rectosigmoid and rectum; C19.9–C20.9). Tumor stage was classified according to pathological TNM stage (22). When the pathological stage was unknown, clinical stage was used. For most patients in this study, treatment information was not known and could, therefore, not be included as a determinant influencing survival. Year of diagnosis was used as a proxy of treatment because treatment changed during the study period. Survival time was defined as the time from the date of diagnosis until death or the end of the study (July 1, 2006). Patients who were still alive at the end of the study were censored on July 1, 2006.

The control patients from the general population were patients who were diagnosed with colorectal cancer and whose data were derived from the Saarland Cancer Registry in Germany, the Eindhoven Cancer Registry in the Netherlands, or the Northern and Yorkshire Cancer Registry and Information Service in the United Kingdom. The Saarland Cancer Registry is the only population-based cancer registry in Germany, and it has provided internationally accepted high-quality data throughout the past 35 years (23). Saarland is a state located in southwestern Germany with a population of approximately 1.1 million or approximately 1.3% of the total German population. The population structure and the health-care system in Saarland are very similar to Germany as a whole. The Eindhoven Cancer Registry is the oldest population-based cancer registry in the Netherlands that collects data from an area of 2.4 million inhabitants in southern Netherlands (24). The Northern and Yorkshire Cancer Registry and Information Service is one of the 11 UK registries and collects data from a population of 6.6 million in the center of the United Kingdom.

We aimed to select two control patients with colorectal cancer for each patient with *MUTYH*-associated polyposis colorectal cancer who were matched for country, stage at diagnosis, age at diagnosis, year of diagnosis, and cancer subsite. The age of diagnosis in the matched German and Dutch control patients was between 7 years younger and 7 years older than that in the case patient. The age of diagnosis in the matched UK control patients was between 4 years younger and 4 years older than that in the case patient. Cancer subsite was defined as either colon or rectum for German and Dutch control patients or as one of the first three characters of *International Classification of Diseases for Oncology* coding—C18, C19, and C20—for UK control patients. Patients with *MUTYH*-associated polyposis colorectal cancer from the United Kingdom were matched by the year of diagnosis for the period from January 1, 1996, through December 31, 2004. For UK patients with *MUTYH*-associated polyposis colorectal cancer

CONTEXT AND CAVEATS

Prior knowledge

Individuals with *MUTYH*-associated polyposis, a recessively inherited disorder, have a lifetime risk for colorectal cancer that approaches 100%. It is not known whether specific histological and molecular genetic features of such cancers influence tumor behavior and patient survival.

Study design

Characteristics and survival of European patients with *MUTYH*-associated polyposis colorectal cancer and matched population-based control patients with colorectal cancer were compared.

Contribution

The survival was statistically significantly better for patients with *MUTYH*-associated polyposis colorectal cancer than for control patients, even after adjustment for differences in age, stage, sex, subsite, country, and year of diagnosis.

Implications

Prospective studies are needed to further investigate this survival difference between *MUTYH*-associated colorectal cancer patients and colorectal cancer patients from the general population and to investigate whether disease-specific interventions, such as timing and type of surgery and chemotherapy, are warranted.

Limitations

Several types of bias are possible, including selection, lead-time, and length-time biases. Treatment was not reported for many patients in this study.

From the Editors

who were diagnosed before 1996 (n = 19), we used control patients who were diagnosed in 1996 because the Northern and Yorkshire Cancer Registry and Information Service did not have data before 1996. Also, no control data were available for patients with *MUTYH*-associated polyposis colorectal cancer who were diagnosed after 2004, and so these patients were matched with control patients from 2004. We selected only control patients without second tumors because otherwise control patients might be included with a possible inheritable form of colorectal cancer that might influence the outcome of the survival analysis.

Statistical Analysis

Differences in patient and tumor characteristics between patients with *MUTYH*-associated polyposis colorectal cancer and control patients were analyzed by use of the χ^2 test. Survival analysis was performed with Kaplan–Meier curves and Cox regression. The Cox model accounted for the clustering effect of sibling pairs. Hazard ratios (HRs) and 95% confidence intervals (CIs) were produced with robust standard errors by comparing patients with *MUTYH*-associated polyposis with control patients. Regression analysis was adjusted for the matching variables (ie, age, period of diagnosis, site of colon tumor, center, and stage). Moreover, all analyses were adjusted for sex. Stratified analyses were performed by adjusting for the same set of variables (ie, age as continuous variable, period of diagnosis [1967–1979, 1980–1989, 1990–1999, or 2000–2006], site of colon tumor [colon or rectum], center [Germany, United Kingdom, or the Netherlands], stage [I, II, III, or IV], and sex [male or female]). We used STATA software, version 10.0 (Stata Corp LP, College Station, TX). The proportional hazard assumption of *MUTYH*-associated polyposis was evaluated by applying Kaplan–Meier curves. The effect of *MUTYH*-associated polyposis over time satisfied the assumption of proportionality because the graphs of the log[−log(survival)] vs log(survival time) resulted in graphs with parallel lines. All statistical tests were two-sided.

Results

Crude survival for patients with *MUTYH*-associated polyposis was statistically significantly better than for control patients with colorectal cancer from the general population (log-rank test 5-year survival, $P = .002$) (Figure 1). Five-year survival was 78% (95% CI = 70% to 84%) for patients with *MUTYH*-associated polyposis colorectal cancer compared with 63% (95% CI = 56% to 69%) for control patients with colorectal cancer.

Perfect matching of all patients with *MUTYH*-associated polyposis and control patients was not feasible. There were some differences between patients with *MUTYH*-associated polyposis and control patients, including the number of positive lymph nodes (N stage), for which 69 (25%) of the 272 control patients had mismatches or missing information; whether metastasis occurred (M stage), in which 81 (30%) had mismatches or missing information; tumor subsite for which 33 (12%) had mismatches; exact year of diagnosis, for which 76 (28%) had mismatches; and sex, for which 128 (47%) had mismatches. Among the 272 control patients, there was a larger proportion of unknown N or M stage (39% or 106 patients) than among the 147 patients with *MUTYH*-associated polyposis (10% or 14 patients). In addition, patients with *MUTYH*-associated polyposis had statistically significantly more tumors located in the proximal colon (52% or 76 patients) than control patients (39% or 107 patients) ($P = .015$) and diagnosis before 1989 (19% or 28 patients vs 16% or 44 patients, respectively) ($P = .046$) (Table 1).

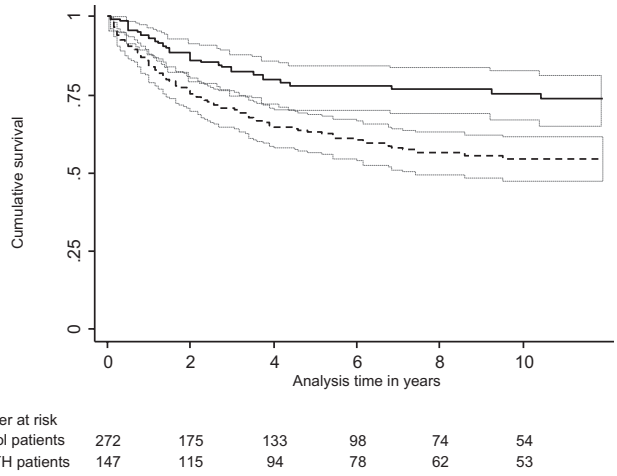

Figure 1. Crude survival of patients with *MUTYH*-associated polyposis colorectal cancer and control patients with colorectal cancer in the United Kingdom, Germany, and the Netherlands (including a total of 419 participants, 147 patients with *MUTYH*-associated polyposis colorectal cancer and 272 control patients). Survival estimates and the corresponding 95% confidence intervals (**gray dotted lines**) for *MUTYH*-associated polyposis patients with colorectal cancer (**black continuous line**) and control patients with colorectal cancer (**black dotted line**). After adjustment for differences in age, stage, sex, subsite, country, and year of diagnosis, survival remained better for *MUTYH*-associated polyposis colorectal cancer patients than for control patients (hazard ratio of death = 0.48, 95% CI = 0.32 to 0.72, $P < .001$).

After adjustment for age, country, period of diagnosis, stage, subsite, and sex, risk of death was statistically significantly lower among patients with *MUTYH*-associated polyposis colorectal cancer than among control patients (HR = 0.48, 95% CI = 0.32 to 0.72, $P < .001$) (Table 2).

When the analysis was stratified by stage, the survival benefit was higher among patients with stage I and II disease (HR = 0.45, 95% CI =0.23 to 0.91) than for stage III and IV disease (HR = 0.64, 95% CI = 0.34 to 1.20) (Table 2). The survival benefit was similar among patients with *MUTYH*-associated polyposis colorectal cancer whose tumor was in the colon (HR = 0.42, 95% CI = 0.26 to 0.67) and among those whose tumor was in the rectum (HR = 0.48 for rectum, 95% CI = 0.22 to 1.02). Increased survival was observed among patients with *MUTYH*-associated polyposis from all three countries (compared with control patients), with that for the German group being the highest. When the analysis was stratified by the period of diagnosis, similar survival benefits were observed for the period 1967–1989 (HR = 0.49, 95% CI = 0.20 to 1.17) and 1990–2006 (HR = 0.51, 95% CI = 0.30 to 0.85).

In this study, colorectal cancer was detected during surveillance in 25 of the 113 index patients with *MUTYH*-associated polyposis and in nine of the 34 siblings with *MUTYH*-associated polyposis. Colon surveillance was initiated in these 25 index patients and nine siblings because of previously identified polyps that caused symptoms, including constipation, diarrhea, or blood in the stool

Table 1. Characteristics of the total study population (n = 419), including 147 patients with *MUTYH*-associated polyposis colorectal cancer (MAP CRC) and 272 control patients with CRC

Characteristic	Patients with MAP CRC	Control CRC patients	Total population
Male, No. (%)	82 (56)	124* (46)†	206 (49)
Index patient, No. (%)	113 (77)	272	385
Siblings, No. (%)	34 (23)	0	34
Method of detection CRC			
Symptomatic, No. (%)	109 (74)	272	381
Surveillance, No. (%)	34 (23)	0	34
Unknown, No. (%)	4 (3)	0	4
Median age (range), y	54.0 (32.1–81.1)	52.1 (28.5–79.1)	53.1 (28.5–81.1)
Location, No. (%)			
Proximal colon	76 (52)	107 (39)‡	183 (44)
Distal colon	21 (14)	73 (27)	94 (22)
Rectum	38 (26)	65 (24)	103 (25)
Colon, not otherwise specified	12 (8)	18 (7)	30 (7)
Unknown	0 (0)	9 (3)	9 (2)
T stage, No. (%)			
0 or in situ	6 (4)	6 (2)	12 (3)
1	15 (10)	33 (12)	48 (12)
2	22 (15)	38 (14)	60 (14)
3	50 (34)	118 (43)	168 (40)
4	8 (5)	18 (7)	26 (6)
Unknown	46 (31)	59(22)	105 (25)
N stage, No. (%)			
0	85 (58)	136 (50)	221 (53)
1	33 (23)	54 (20)	87 (21)
2	15 (10)	29 (10)	44 (11)
Unknown	14 (10)	53 (20)	67(16)
M stage, No. (%)			
0	125 (85)	161 (59)§	286 (68)
1	12 (8)	25 (9)	37 (9)
Unknown	10 (7)	86 (32)	96 (23)
Period of diagnosis, No. (%)			
1967–1979	12 (8)	20 (7)	32 (8)
1980–1989	16 (11)	24 (9)	40 (10)
1990–1999	69 (47)	136 (50)	205 (49)
2000–2006	50 (34)	92 (34)	142 (34)
Country, No. (%)			
Germany	55 (37)	106 (39)	161 (38)
United Kingdom	42 (29)	66 (24)	108 (26)
the Netherlands	50 (34)	100 (37)	150 (36)

* Unknown for six patients.

† $P = .046$. χ^2 test was used. All statistical tests were two-sided.

‡ $P = .015$.

§ $P < .001$.

(n = 16), or because of a family history of colorectal cancer, most often in a parent (n = 18).

In four patients (three index patients and one sibling), the mode of detection of colorectal cancer was not known. When we excluded patients with *MUTYH*-associated polyposis colorectal cancer detected during surveillance from the analysis, we still observed statistically significant better survival among *MUTYH*-associated polyposis patients than among control patients with colorectal cancer (Table 2).

Discussion

In a European cohort, survival of *MUTYH*-associated polyposis patients with colorectal cancer was statistically significantly better than that of control patients with colorectal cancer. This advantage in survival remained statistically significant after adjustments for age, stage, colon site, period of diagnosis, country, and sex. In a stratification analysis for early-stage (ie, stages I and II) vs late stage (ie, stages III and IV) cancers, the survival benefit for patients with *MUTYH*-associated polyposis colorectal cancer compared with control patients with colorectal cancer was slightly higher among patients with early-stage colorectal cancer (HR = 0.45, 95% CI = 0.23 to 0.91) than among those with later stage colorectal cancer (HR = 0.64, 95% CI = 0.34 to 1.20).

To our knowledge, this is the first study to examine survival of *MUTYH*-associated polyposis patients with colorectal cancer compared with that of matched control patients with colorectal cancer from the general population. Patients with *MUTYH*-associated polyposis colorectal cancer were recruited from the largest *MUTYH*-associated polyposis cohort so far assembled.

Table 2. Cox regression analysis for patients with *MUTYH*-associated polyposis (MAP) colorectal cancer (CRC) compared with control CRC patients*

Analysis	Hazard ratio (95% confidence interval) All patients (n = 419)	Hazard ratio (95% confidence interval) Symptomatic patients (n = 381)†
Overall (MAP vs control CRC)	0.48 (0.32 to 0.72)	0.48 (0.32 to 0.73)
Stratified		
Stage		
I or II	0.45 (0.23 to 0.91)	0.47 (0.21 to 1.04)
III or IV	0.64 (0.34 to 1.20)	0.64 (0.33 to 1.22)
Site of diagnosis		
Colon	0.42 (0.26 to 0.67)	0.40 (0.24 to 0.66)
Rectum	0.48 (0.22 to 0.1.02)	0.55 (0.24 to 1.25)
Country		
United Kingdom	0.66 (0.22 to 1.97)	0.76 (0.25 to 2.32)
Germany	0.28 (0.10 to 0.74)	0.28 (0.10 to 0.82)
the Netherlands	0.49 (0.31 to 0.79)	0.45 (0.27 to 0.74)
Calendar period		
1967–1989	0.49 (0.20 to 1.17)	0.40 (0.15 to 1.03)
1990–2006	0.51 (0.30 to 0.85)	0.52 (0.31 to 0.88)

* Data are from the Cox model with robust standard errors. The model was adjusted for the matching variables, age, country, period of diagnosis, stage, and site of colorectal cancer, and also for sex.

† Symptomatic patients are *MUTYH*-associated patients who underwent colon screening because of symptoms (eg, anemia, nausea, diarrhea, or blood in the stool) and had colorectal cancer at presentation. *MUTYH*-associated patients in whom colorectal cancer was detected during surveillance because of a positive family history or previously identified polyps were excluded from this analysis.

Given the retrospective character of the study, there are many possible biases and limitations that might lead to an overestimation or an underestimation of survival benefits (eg, selection, lead-time, and length-time biases). Treatment was not reported for many patients in this study.

Selection Bias

It can be expected that patients from families with several affected members who survived their cancer may be more likely to come to the attention of clinical geneticists than those from families in which all affected members died from their disease. Therefore, cohorts of patients who are recruited through genotyping studies could be biased toward those with better prognosis. This form of bias may have been operating in previous studies of Lynch syndrome–specific survival (9,25). However, a number of observations are counter to this argument. First, Hampel et al. (26) reported that index patients from Lynch syndrome families are younger at diagnosis of colorectal cancer than other mutation-positive patients in their family. Therefore, patients who come to medical attention through genetic testing do not necessarily have a milder phenotype. Second, although patients who die young or shortly after their diagnosis of colorectal cancer might not come to the immediate attention of clinical geneticists, the nonaffected members of their family may be referred for genetic counseling. *MUTYH* genotyping can be done on DNA isolated from archived formaldehyde-fixed tumor tissue (27) of a deceased patient or in the DNA isolated from blood of parents and/or siblings who are still alive. Third, patients with *MUTYH*-associated polyposis who have a relatively mild phenotype (eg, nonaggressive colorectal cancer at a later age) are likely be underrepresented in our cohort of patients with *MUTYH*-associated polyposis because the likelihood that they could have inherited a predisposition toward colorectal cancer may be lower.

Another selection bias might be that patients with *MUTYH*-associated polyposis who have no polyps or only a few polyps (eg, 0–10 polyps) are likely to be underrepresented in our cohort, particularly when there is no family history of colorectal cancer in a sibling. *MUTYH* mutation screening in population-based colorectal cancer patients has shown that one-third of biallelic mutation carriers with colorectal cancer have no or only few polyps (eg, 0–10 polyps) (15,28). Such patients are less frequently referred for molecular genetic analysis than patients with more florid forms of polyposis (eg, more than 10 polyps, numerous or multiple polyps). It is not known whether prognosis of patients with no or only few polyps (eg, 0–10 polyps) differs from that of patients with *MUTYH*-associated polyposis with colorectal cancer and polyposis.

Finally, for UK patients with *MUTYH*-associated polyposis colorectal cancer who were diagnosed before 1996 (n = 19), we used control patients who were diagnosed in 1996 because the Cancer Registry did not have data before 1996. This procedure could have lead to better survival in control patients because treatment of cancer is expected to have improved between 1970 and 1996, the period in which the 19 UK case patients were diagnosed with colorectal cancer. However, after adjustment for date period in the multivariable Cox regression analysis, results remained unchanged.

Lead-Time and Length-Time Bias

Heightened awareness among and surveillance of high-risk patients lead to diagnoses at an earlier stage of disease (lead-time bias) and might account for an apparent survival advantage. Length-time bias is also a consideration if screening tests lead to detection of asymptomatic indolent tumors. Patients with *MUTYH*-associated polyposis who are enrolled in surveillance programs could gain a survival benefit by early detection.

As expected, there are differences in stage between patients whose disease was detected by surveillance and those whose disease was detected symptomatically; stage I disease was diagnosed in 14 (41%) of the 34 patients during surveillance and in 21 (19%) of the 109 patients diagnosed symptomatically. It should be noted that, after adjustment for other factors including stage, exclusion of patients with *MUTYH*-associated polyposis diagnosed during surveillance, survival benefit (ie, hazard ratio) did not change (Table 2, second column).

Other Possible Biases

Another explanation of the better survival of patients with *MUTYH*-associated polyposis compared with that of control patients might be that patients with *MUTYH*-associated polyposis receive more extensive surgery because they usually have more polyps. However, the overall survival of patients with *MUTYH*-associated polyposis might actually be worse because they are

prone to develop multiple cancers. Indeed, 46 (31%) of the 147 patients with *MUTYH*-associated polyposis in this study actually had two or more colorectal cancers at the time of diagnosis or developed a second colorectal cancer later on in life.

Immune Response Differences and Survival Advantage

An active immune response (represented by a high number of tumor-infiltrating lymphocytes) is strongly associated with better survival rates in control patients with colorectal cancer (29–31). It has been proposed that the immune system of patients with high microsatellite instability and mismatch repair–deficient tumors might be more active than that of colorectal cancer patients in the general population, which would lead to better survival (32,33). Because of a defect in the DNA repair, more mutant proteins are expected in the mismatch repair–deficient tumors than in sporadic colon tumors. As a result, more peptide fragments of mutant proteins might be presented at the cell surface of the mismatch repair–deficient cancer cells, which activate the immune system. Furthermore, the enhanced mutation rate in these tumors may also induce a mutation burden that is not compatible with tumor cell survival.

We have previously shown (34) that *MUTYH*-associated polyposis colorectal cancers share similar characteristics with mismatch repair–deficient cancers, including a preferential proximal location, a high rate of mucinous morphology, and an increased level of tumor-infiltrating lymphocytes. The disruption of MUTYH protein function in *MUTYH*-associated polyposis carcinoma cells might lead to more oxidative DNA damage and generation of mutant peptides that could be presented to cytotoxic T cells through the expression of HLA class I receptors. It has, indeed, been shown that loss of expression of HLA class I receptors has been frequently identified in *MUTYH*-associated polyposis colorectal cancers and in mismatch repair–deficient colorectal tumors (35,36,37), indicating that these tumors may be subject to strong selective pressure that favors outgrowth of cancer cells that acquire an immune-evasive phenotype (37).

In conclusion, in this study, patients with *MUTYH*-associated polyposis colorectal cancer had statistically significantly better survival than matched control patients. The reasons for this difference remain unknown, but a compromised base excision repair system could render *MUTYH*-associated polyposis colorectal cancers more immunogenic than sporadic colorectal cancers, which are characterized predominantly by chromosomal instability. This survival difference may have implications for clinical decision making in relation to the timing and type of interventions required, such as surgery and chemotherapy. Future prospective studies are needed to confirm this survival difference between *MUTYH*-associated colorectal cancer patients and colorectal cancer patients from the general population.

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Notes

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