REGION KRONOBERG

Large sessile and flat colorectal lesions

- Analysis of risk factors

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Abstract

Background: Colorectal lesions ≥ 20 mm in size occur in about 1% of patients in a screening population and are mostly sessile or flat and to a large extent dysplastic. At the same time, patients with these large polyps often have synchronous, smaller polyps. Various features of large sessile and flat polyps are associated with an increased risk of high-grade intraepithelial neoplasia in synchronous polyps.

Lifestyle changes could prevent a large proportion of colon cancer cases. The known risk factors for colon cancer and precursor lesions are associated with polyps of different histology or with advanced versus non-advanced adenomas to different degrees. It can be assumed that there also are specific risk factors for large sessile and flat polyps.

Aim: In the first part of this work the aim was to characterize clinicopathological features of large flat colonic polyps and their impact on occurrence and characteristics of synchronous polyps. In the second part, the aim was to identify modifiable, behavioral risk factors for the progression of polyps to these large lesions ≥ 20 mm.

Method: A total of 802 patients that underwent endoscopic mucosal resection (EMR) of flat colonic polyps ≥ 20 mm from 2003 to 2014 in an academic endoscopy unit were retrospectively analyzed for size, location and histology of large polyps and synchronous polyps. Behavioral factors were retrospectively analyzed in these patients and controls with at most one diminutive polyp. Information on lifestyle factors, comorbidities, and demographic parameters were determined by a structured, self-administered questionnaire.

Results: Increase in polyp size, advanced age and location in the distal colon were associated with presence of HGD/ adenocarcinoma in large polyps, as identified by multivariate analysis. Synchronous polyps were detected in 67.2% of patients undergoing complete colonoscopy during EMR. Presence of HGD/adenocarcinoma in the large polyp (odds ratio: 3.33; 95% confidence interval: 1.77-6.35; p-value: 0.0002), localization of any synchronous polyp in the rectosigmoid colon and occurrence of multiple synchronous polyps were associated with presence of HGD/adenocarcinoma in synchronous polyps.

The study group in the second part of the analysis consisted of 350 patients; 489 patients were included in the control group. Multivariate analysis showed that frequent cigarette smoking, consumption of red meat and frequent bowel movements (OR 1.62, CI 1.13–2.33, p = 0.0093) were associated with the occurrence of large, sessile and flat polyps and that the consumption of full grain products was a possible protective factor.

Conclusion: This study found a frequent co-occurrence of high-grade dysplasia in large, sessile and flat colonic polyps and synchronous polyps. This underlines the importance of a complete colonoscopy prior to endoscopic removal and during follow-up of patients with large colonic polyps. Multiple behavioral factors modulate the risk for developing these large polyps. A hypothetical causal relationship between patients with large polyps and frequent bowel movements could be inflammatory processes triggered by intestinal bacteria associated with adenomas and therefore occurring more frequently in these patients. This knowledge can be used to improve prevention of colorectal cancer.

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Introduction

The main route of colorectal cancer development is through a progression from adenoma with low to high-grade dysplasia to adenocarcinoma [1]. The risk of dysplasia in adenomas increases with the presence of villous components and with the size of the adenomas [2]. Large colorectal lesions – most frequently defined by diameter ≥ 20 mm – occur in about 1% of people in a screening population and are mostly sessile or flat and to a large extent dysplastic [3,4].

Large polyps are associated with an increased risk for detection of other advanced adenomas upon follow-up colonoscopy, so called metachronous polyps [5]. However, it is known that even advanced adenomas - especially those with a flat morphology and localization in the proximal colon - are often overlooked during colonoscopy [6] and it can therefore be assumed that some of these metachronous dysplastic adenomas in fact are synchronous lesions, thus already present at initial examination. These synchronous, i.e., simultaneously occurring, smaller polyps, are common in patients with large colonic polyps. Various features of the large sessile and flat polyps are associated with an increased risk of high-grade intraepithelial neoplasia in synchronous polyps. Some studies find that it is the increasing size of the large lesions [7] that is a risk factor for synchronous highly dysplastic lesions, while others find an association with their location in the colon [8].

In the first part of this study localization and histopathology of sessile and flat colonic lesions ≥ 20 mm in a large single center cohort were determined with the goal to identify associations between histology and location of large polyps with prevalence and characteristics of synchronous polyps.
Colorectal cancer is the third most common form of cancer worldwide and at the same time the one with the second highest mortality [9], albeit increasing efforts are made by detection and removal of precursor lesions in screening colonoscopies, which is effective in reducing colorectal cancer associated death rates [10,11]. Important reasons for this discrepancy include low acceptance of screening endoscopy and participation rates in nationwide screening programs [12]. Good knowledge of risk factors for colorectal cancer and its precursor lesions is necessary for improvement of screening procedures, as well as to individually increase the motivation for participation in preventive programs. A crucial factor for the individual´s motivation to participate in a colorectal cancer screening program is awareness of the topic, which is strengthened, among other things, by publicly available information and recommendations from the family doctor [13].

Between one third to half of all CRC cases is thought to be avoidable by adopting a healthier lifestyle or by changing eating habits [14,15]. It can be assumed that there are distinct risk and protective factors for the development of colonic polyps and those for the progression of these polyps to more advanced lesions. Physical activity and the consumption of dietary supplements containing calcium are for example more strongly associated with a reduced incidence of advanced, large adenomas than of non-advanced adenomas [16,17].

The question arises how patients with large sessile and flat polyps can be identified, respectively which of the known or theoretical risk factors for colonic lesions present a strong association especially with large polyps. Since polyps are common in the general population and only a small proportion of patients with polyps develop colon cancer, it is particularly relevant to identify risk factors for the progression of polyps into large and dysplastic lesions. Patients with these large polyps can benefit from primary prevention, as most non-cancerous polyps can still be removed safely by endoscopic resection. Hence, identifying those patients can enhance prevention of colorectal cancer.

Therefore, in the second part of this analysis modifiable risk factors for large sessile and flat lesions ≥ 20 mm were determined using a self-administered exploratory questionnaire.

Methods

Data collection

The electronic database of the Central Interdisciplinary Endoscopy Unit of Mannheim University Hospital, Heidelberg University, was reviewed for all patients who underwent endoscopic mucosal resection (EMR) from January 2003 to January 2014. All patients with colonic polyps ≥ 20 mm in maximal dimension were included in the preliminary review. EMRs of the large colonic polyp by both sigmoidoscopy and colonoscopy were included. Only patients with flat and sessile polyps (Paris classification 0–Is, 0–IIa, 0–IIb, 0–IIc) were included, those with pedunculated polyps were excluded. Localization of large colonic polyps was extracted from the endoscopy report. The area proximal of the splenic flexure was defined as the proximal colon and the descending colon, sigmoid and rectum were defined as the distal colon. Histopathology reports provided by the central pathology department were reviewed for histological subtype and grade of dysplasia. Histological findings were assigned into major groups according to Vienna Classification: adenoma with low-grade dysplasia (LGD), adenoma with high-grade dysplasia (HGD) and adenocarcinoma. Serrated polyps include hyperplastic polyps, traditional serrated adenomas and sessile serrated adenomas/polyps. When evaluating the characteristics of synchronous polyps in patients with large polyps, we included only patients who underwent a complete colonoscopy during endoscopic removal of the large polyp. In some cases, a stepwise removal of multiple synchronous polyps in consecutive endoscopic procedures was described. To obtain a comprehensive data set on detected synchronous polyps, we collected available reports of colonoscopies performed up to 6 weeks prior and 6 months after EMR of the large polyp. The total number of detected synchronous polyps and their characteristics were then summarized for each patient.

To obtain information on behavioral risk factors, structured, self-administered questionnaires were consecutively sent to all identified patients. The study group was derived from the patients with large sessile and flat polyps as stated above. For the control cohort, the electronic databases of following sources were reviewed: the Central Interdisciplinary Endoscopy Unit of Mannheim University Hospital, the Heilig Geist Hospital Bensheim (secondary medical center), and two ambulatory gastroenterological practices. Patients who underwent screening or diagnostic

colonoscopy from January 2004 to March 2015 were included in the initial evaluation. Only patients without polyps or with one diminutive polyp (≤5 mm) were selected for subsequent analysis.
We retrieved information on the following items: biometric parameters, comorbidities, incidence of colorectal cancer among first- and second-degree relatives, history of previous endoscopic examinations, smoking status, alcohol consumption, intake of selected dietary components, frequency of bowel movements, and physical activity. Information on following co-morbidities was inquired: history of colorectal cancer and other cancers, inflammatory bowel disease, viral hepatitis B/C, hypertension, type 2 diabetes, lactose intolerance, and celiac disease. Smoking status was classified into the following categories: never, light (<20 pack years), and heavy (≥20 pack years) smokers. Alcohol consumption was classified into regular or never drinkers, with past or present regular consumption of at least one alcoholic beverage per week considered as regular drinking. Dietary habits were determined for the following food components: milk/dairy products, rare meat, red meat (pork, beef, mutton), fish, vegetables, fruits, and full grain products/cereals. Frequency of consumption was classified into daily, 1–3×/week, <1/week, or never. Frequency of bowel movements was classified into >3× per day, 2–3× per day, once per day, or once/less than once every 2 days. Frequency of physical activity was determined for light physical activity such as walking or cycling (categories—several hours per day, 60 min per day, 30 min per day, or few times per week) and physical training (categories—yes or no, type of physical training, frequency of physical training).

Statistical analysis

Continuous variables were summarized using mean ± standard deviation (SD). Frequencies (%) were used for categorical variables.

Non-parametric Mann–Whitney-Wilcoxon/Kruskal-Wallis test were used to compare continuous parameters between two/multiple groups. Jonckheere-Terpstra test was used to test for trends across groups. Fisher's exact test was used to assess independence between categorical parameters. Odds ratios including 95% confidence intervals from logistic regression models were used to assess the impact of independent factors/predictors - biometric patient data, histology, the number and location of the (synchronous) polyps, or lifestyle risk factors recorded in the questionnaire – on the dependent variables - advanced dysplasia of the polyps in the first part or occurrence of large polyps in the second part. In the analysis of the questionnaires, all results were adjusted for age and gender to consider the unequal distribution of these factors in the study and comparison groups.

All tests were two-sided. P values below 0.05 were considered statistically significant. R v 3.1 and 3.2.4 was used for all analyses.

Ethical approval

This study is approved by the local board of ethics (Medizinische Ethikkommission II, Heidelberg University, identifier 2013-557N-MA.

Results

A total of 802 patients (481 men and 321 women, mean age 65.4 ± 10.5) with 802 colonic polyps ≥ 20 mm were included in the analysis. Large flat and sessile polyps were removed in 582 cases by complete colonoscopy, in 119 cases by incomplete colonoscopy and in 101 cases by sigmoidoscopy (Figure 1). Mean size of all large polyps was 34.1 mm (range 20–150 mm, standard deviation 16.1 mm).

The most frequent histological subtypes were adenoma with low-grade intraepithelial dysplasia (LGD) with n = 421 (52.5%), followed by high-grade intraepithelial dysplasia (HGD) with n = 214 (26.7%), adenocarcinoma with n = 90 (11.2%) and serrated polyps (SP) with n = 77 (9.6%). The majority of serrated polyps were hyperplastic polyps or sessile serrated adenomas/polyps with no or low-grade dysplasia. Nonserrated adenomas included 254 tubular, 372 tubulovillous and 9 villous adenomas. Large flat polyps were localized in 60.7% (n = 487) in the proximal colon and in 39.3% (n = 315) in the distal colon.

We found no difference in distribution of histological subtypes ($p = 0.97$) between different sex. Large polyps containing SP were on average smaller than polyps with other histological subtypes ($p < 0.0001$). In addition, there was a trend towards HGD/adenocarcinoma with increase of polyp size in non-serrated adenomas. The mean age of patients with SP was lower compared to patients with other histology (59.4 vs 66.1, $p < 0.0001$). We observed a distinct anatomic distribution for polyps with specific histological subtypes. Serrated polyps were predominantly found in the proximal colon (80.5% of all SP) while adenocarcinomas were preferentially localized in the distal colon (72.2% of all adenocarcinomas). For LGD or HGD, there was no preference for a specific location within the colon. However, villous adenomas were mainly detected in the distal colon (67% of all villous adenomas) and tubular adenomas in the proximal colon (74% of all tubular adenomas). Localization of polyps also influenced mean size of polyps, with the highest average polyp size in the rectum compared to other sites (44.2 mm vs. 31.2 mm, $p < 0.0001$) (see Figure 2).

Data from complete colonoscopies was available from 582 patients, allowing for a characterization of synchronous polyps. Synchronous polyps were detected in 391 patients undergoing complete colonoscopies (67.2%). The mean number of polyps of patients with synchronous polyps was 3.8

(range 1–40). The mean number of polyps was slightly, but significantly higher for male than female (mean 2.0 vs. 2.9, $p = 0.0029$). The total proportion of male patients with at least one synchronous polyp was also higher (71% vs 61%, $p = 0.01$). Most of the patients were found to have synchronous polyps at multiple sites within the colon (222 of 378 cases) and there was a general trend towards occurrence in the proximal colon. Adenocarcinoma was found in 6%, HGD in 13.8%, LGD in 85.4% and SP in 28.2% of all patients with histologically assessed synchronous polyps. The histology of synchronous polyps was associated with overall polyp load, as patients with HGD in any synchronous polyp had a higher average number of polyps (SP: 2.5 vs. HGD: 6.8, $p < 0.0001$).

Based on this data, we sought to identify factors that were associated with the occurrence of adenoma with HGD/adenocarcinoma, for both large flat polyps and synchronous polyps. By multivariate logistic regression analysis based on all patients with synchronous polyps, it was found that increase in polyp size (OR 1.29, 95% CI 1.09–1.55, per 10 mm increase, $p = 0.0041$), location of the large polyp in the rectosigmoid colon (OR 3.89, 95% CI 2.26–6.79, $p < 0.0001$) and increase in age (OR 1.13, 95% CI 1.00 1.29, per 5 year increase, $p = 0.0471$) were independently associated with presence of HGD/adenocarcinoma in large polyps. In contrast, gender, the location and number of synchronous polyps had no significant effect on histology of the large polyp.

In the last step, parameters potentially associated with occurrence of HGD/adenocarcinoma in synchronous polyps were analyzed. Location of any synchronous polyp in the rectosigmoid colon (OR 2.65, 95% CI 1.44–5.0, $p = 0.002$) and a high number of synchronous polyps (OR 1.16, 95% CI 1.09–1.24, $p<0.001$) were independently associated with HGD/adenocarcinoma. Interestingly, presence of HGD/adenocarcinoma in the large polyp (OR 3.33, 95% CI 1.77–6.35, $p = 0.0002$) was also associated with occurrence of HGD/adenocarcinoma in synchronous polyps. In contrast, location of the large polyp in the rectosigmoid colon was not associated with the occurrence of HGD/adenocarcinoma in our multivariate analysis.

In the second part of this study, we received correctly filled in questionnaires from 367 patients with large flat and sessile colorectal polyps (response rate 44.6%) and 709 control patients (response rate 33.2%). Questionnaires of 350 patients with large, flat colorectal polyps (217 males and 133 females) and 489 controls patients (234 males and 255 females) were included in the final analysis (Figure 3). The mean age of patients at the time of endoscopic examination/intervention was 64.8 years (range 41–91 years, SD 9.96 years) for the case cohort and 56.2 years (range 20–97 years, SD

11.22 years) for the control cohort. In the control cohort, 20 patients had one diminutive hyperplastic polyp in their endoscopic examination while all other patients were free of polyps. Mean BMI in the case group was 26.41 (range 18.4–45.1, SD 4.14) and 25.77 in the control group (range 17.2–66.6, SD 4.58). A trend towards association with large polyps was observed for obese patients (BMI >30) compared to patients with normal weight (BMI <25) (OR 1.53, CI 0.99–2.38, p = 0.06). For co-morbidities, only hypertension was associated with an increased risk for large colorectal polyps (OR 1.50, CI 1.09–2.06, p = 0.01).

Nicotine consumption was strongly associated with the presence of large, sessile and flat polyps (≥20 pack years, OR 2.35, CI 1.46–3.80, p = 0.00044). Regular consumption of alcoholic beverages was reported by 78–84.7% of all participants (mean daily dose of over 10 g) but was not associated with the occurrence of large colorectal polyps (OR 0.72, CI 0.43–1.20, p = 0.20).

Most participants reported unchanged dietary habits for >5 years (19.8%) or >10 years (74.4%). In univariate analysis, daily intake of fruits and frequent intake of cereals/full grain products were associated with a lower risk for large colonic lesions (fruits—OR 0.59, CI 0.42–0.81, p = 0.0014; cereals—OR 0.52, CI 0.38–0.71, p < 0.0001). In contrast, daily intake of red meat resulted in an increased risk, compared to participants who did not at all consume red meat (OR 5.95, CI 1.88–23.16, p = 0.0045). Interestingly, the data also showed that a high frequency of bowel movements (>1× per day) was strongly associated with large colorectal polyps (OR 1.62, CI 1.15–2.29, p = 0.006). No association was found for light physical activity, but regular physical training was associated with a lower risk for large colorectal polyps (OR 0.64, CI 0.46–0.88, p = 0.0057).

Since many behavioral patterns are interlinked and strongly dependent on sex and age, multivariate analysis was performed on a panel of parameters. The analysis was conducted using multiple imputations for missing values since most questions were not answered by all participants. Multiple factors were identified to be independently associated with the occurrence of large colorectal polyps. Increase in patient age (per 1 year—OR 1.09, CI 1.07–1.11, p < 0.0001), frequent cigarette smoking (OR 2.04, CI 1.25–3.32, p = 0.0041), daily consumption of red meat (OR 3.61, CI 1.00–12.96, p = 0.0492), and frequent bowel movements (OR 1.62, CI 1.13–2.33, p = 0.0093) were associated with an increased risk for large, flat colorectal polyps. In contrast, only frequent intake of cereals (OR 0.62, CI 0.44–0.88, p = 0.0074) was associated with a reduced risk. For all other factors, no independent association could be found in multivariate analysis.

Discussion

This evaluation presents an overview of the characteristics of very large colonic lesions, which, with their average size of 34.1 mm, preferably are removed by EMR in specialized tertiary centers. Adenomas account with 79.2% for most of these lesions, followed by invasive adenocarcinomas and serrated lesions with approximately the same frequency. With 60.7%, large flat and sessile polyps preferably occurred in the proximal colon as shown by others [18].

The proportion of adenomas with high-grade dysplasia (26.7% of all 802 polyps) was within the reported range in other studies [19,20]. The proportion of invasive adenocarcinomas in lesions ≥ 20 mm is very variable in the literature and differs significantly in European and Asian studies. For example, authors from Japan found the prevalence of invasive adenocarcinomas in laterally spreading lesions ≥ 20 mm to be between 13-42% [21], while authors from Italy and Great Britain found a prevalence of 2.5-3, 4% [22,23].

The rate of SSA/P was shown to be around 1.2% in patients undergoing screening colonoscopy [30], while we found a much higher rate of SL in our cohort (9,6%). A higher prevalence of SL in large polyps is also found by others [24,25].

The correlation between histology and location of large colonic polyps showed that large adenomas with HGD and adenocarcinomas are predominantly located in the rectosigmoid colon, which is in line with previous observations [26,27]. While small hyperplastic polyps are mostly left sided, sessile serrated adenomas/polyps are located predominantly in the proximal colon [28]. Indeed, the majority of SP in this cohort were sessile serrated adenomas/polyps and we found a preference towards a right-sided location.

Independent risk factors for the occurrence of high-grade dysplasia or adenocarcinoma in the large polyps were their size, as well as the age of the patients. These also traditionally represent the primary risk factors for the occurrence of dysplasia in smaller polyps (< 20 mm) [19,29].

In screening examinations synchronous polyps can be found in up to 30% of all patients [30] and in 36-48% of patients with colorectal cancer [31,32]. The rate of synchronous polyps was much

higher in our cohort (67.4%) than in these older studies. It has previously been shown that patients with synchronous polyps have an increased risk for metachronous adenomas and carcinomas [33,34]. It can therefore be argued that special emphasis must be placed on surveillance colonoscopies in patients with large and highly dysplastic polyps – as in our own study group – to avoid metachronous neoplasms or to detect them early.

Our study demonstrates that the presence of HGD in the large polyp is strongly associated with co-occurrence of synchronous polyps with the same histology. This underlines the necessity for a full colonoscopy in patients with large polyps and that the examination should not be limited to the location of the large polyp. The association of large dysplastic polyps with synchronous, smaller and also dysplastic polyps provides further clinical evidence for the theory of field carcinogenesis, which implies that the environmental milieu that leads to carcinogenesis is not a local event but affects larger parts of the colon [35].

When evaluation behavioral risk factors for large colonic lesions, our results demonstrate that previously described risk factors for colorectal cancer also are associated with an increased risk for large sessile and flat colorectal polyps. Those include smoking, advanced age and frequent consumption of red meat. A known protective factor that has been confirmed by our own data is the consumption of full grain products.

On the contrary, our own study did not show significant associations for some risk factors for colonic lesions which present strong or at least relatively convincing evidence in common literature. These include obesity [36,37], alcohol [38] or NSAID intake [39], for which no significant associations could be shown as well as physical activity [40] and hypertension [41], which showed a significant association only in univariate analysis.

Beyond the established risk factors, our own data demonstrates an association between frequent bowel movements and the occurrence of large sessile and flat polyps. Rather than frequent bowel movements, constipation was previously seen as a risk factor for colorectal cancer, especially in case-control studies [42]. However, prospective studies fail to show such a connection [43, 44] and it is assumed that a lack of data adjustment for confounding factors is a reason for this discrepancy [45]. Nevertheless, to our knowledge, there are no epidemiological studies that show a connection between frequent bowel movements or diarrhea with colorectal adenomas or carcinomas. Changes in the intestinal flora, which are known to occur in patients with colon cancer, might present a

causal relationship between colon adenomas and frequent bowel movements. In these patients' intestinal flora, a dominance of certain bacteria is seen, which is suspected of building a milieu in which neoplastic colonic lesions can thrive. For example, Fusobacterium nucleatum and Enterotoxigenic Bacteroides fragilis – both common in patients with colon cancer – trigger chronic inflammatory processes in the mucosa, which are thought to play a role in the development of dysplastic lesions [46]. That inflammatory processes in the mucosa can cause frequent bowel movements is well-known in patients with inflammatory bowel disease or for example microscopic colitis.

Due to the retrospective approach this study has several limitations. Behavioral risk factors were not systematically recorded at the time of polyp removal, and all questionnaires were self-reported. Therefore, the information obtained is most likely influenced by recall bias. The median time intervals between endoscopic examination and completion of the questionnaires were 3 years for the control cohort and 4 years for the case cohort. While the impact of behavioral factors such as nutrition, which we showed to be constant over a long time, may not be severely biased, other factors such as weight, doses of nicotine consumption, or frequency of physical exercise are likely imprecisely recorded. Another drawback is the unequal distribution of age and sex between case and control group. This "control group bias" may lead to confounding variables being overlooked and associations being overestimated [47,48].

Conclusion

In summary, this retrospective analysis shows that the prevalence of synchronous polyps is high in patients with large polyps and that occurrence of large polyps with HGD/adenocarcinoma significantly correlates with presence of synchronous polyps containing high-grade dysplasia and adenocarcinoma. These findings underline the importance of a complete colonoscopy prior to endoscopic removal and during follow-up of patients with large colonic polyps. Furthermore, our study provides an exploratory analysis of risk and protective factors for the development of large flat and sessile colorectal polyps. Independent risk factors included age, smoking, consumption of red meat, and frequent bowel movements, while intake of cereals/full grain products was protective. Our data can help to identify patients who benefit from endoscopic surveillance and polyp removal prior to development of invasive colorectal cancer. To specify the contribution of each factor, prospective studies are needed.

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Figures and tables

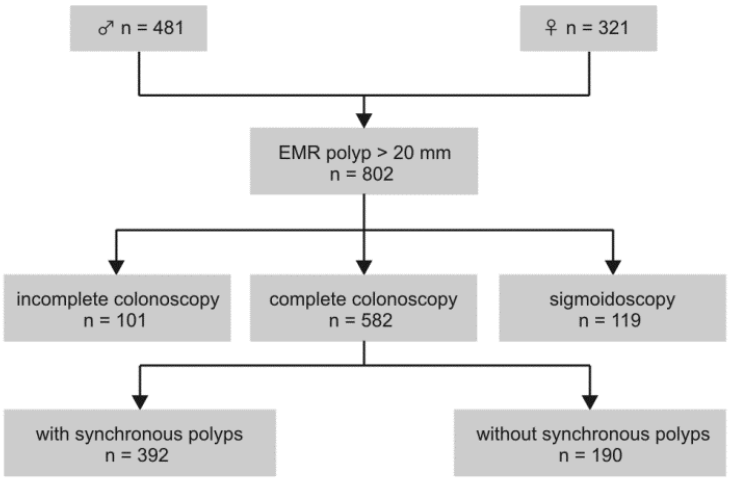

Figure 1. Flow chart showing basic distribution of patients and endoscopic procedures.

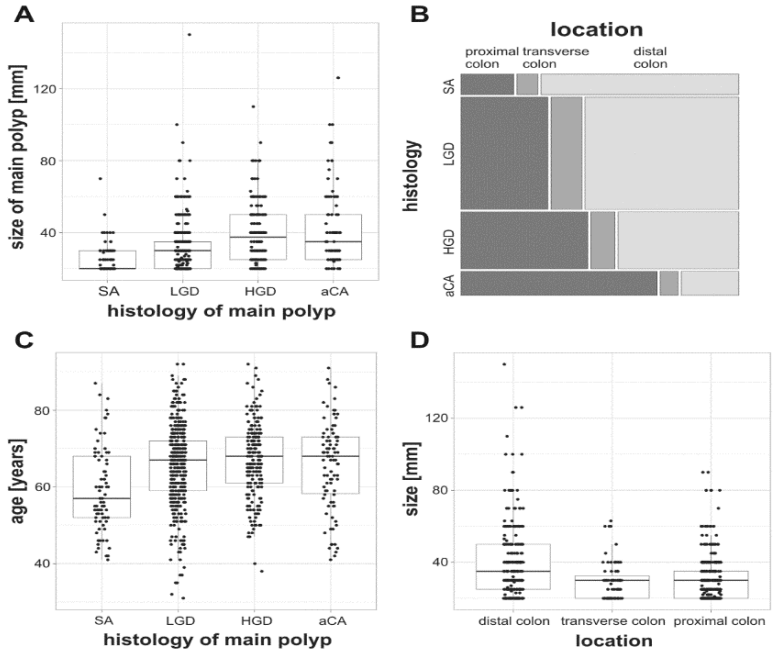

Figure 2. Correlations of size, histology and anatomic distribution of large polyps. A-B) Box plot shows distribution of size (A) and age (B) for different histological subtypes. C) Mosaic plot showing distribution of location versus histology. D) Box plot showing size of polyps relative to anatomic location.

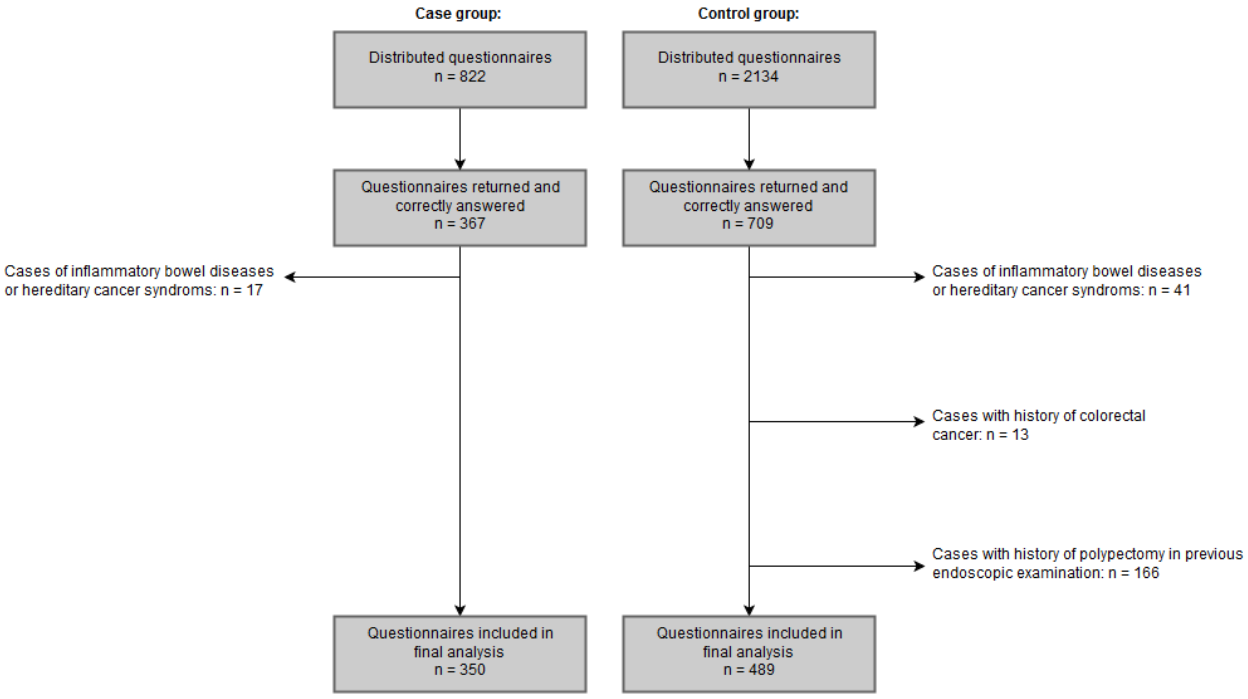

Figure 3. Flow chart showing patient selection for case and control group for the evaluation of the questionnaires.