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Increased Risk of Colorectal Cancer Development Among Patients With Serrated Polyps

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BACKGROUND & AIMS: Sessile serrated adenomas/polyps (SSA/Ps) and traditional serrated adenomas (TSAs) are now distinguished from hyperplastic polyps and recognized as precursors to colorectal cancer (CRC). We studied CRC risks associated with serrated polyps. **METHODS:** By using Danish databases (1977–2009), we conducted a nationwide population-based, case-control study nested within individuals who had received colonoscopies (n = 272,342), and identified 2045 CRC cases and 8105 CRC-free individuals (controls). For each case and control, we identified the first colorectal polyp(s) that underwent a biopsy or were excised during or after the initial colonoscopy, and obtained tissue blocks for hyperplastic lesions. Four expert pathologists reviewed these lesions using current terminology for serrated polyps. We used logistic regression to compute odds ratios (ORs) to associate the risk of CRC with polyp type and estimated the absolute risks by multiplying the risk in patients with no polyps by these ORs. **RESULTS:** Seventy-nine cases and 142 controls had SSA/Ps (OR, 3.07; 95% confidence interval [CI], 2.30–4.10). SSA/Ps with cytology markers of dysplasia were associated with a particularly high OR (4.76; 95% CI, 2.59–8.73). Women with SSA/P had a higher risk for CRC than men with SSA/P (OR for women, 5.05; 95% CI, 3.05–8.37 vs OR for men, 2.18; 95% CI, 1.24–3.82); patients with SSA/P proximal to the splenic flexure had the highest risk for CRC (OR, 12.42; 95% CI, 4.88–31.58). The OR for CRC was 4.84 in the 14 cases vs 17 controls with TSAs (95% CI, 2.36–9.93), 2.51 in the 757 cases vs 1698 controls with conventional adenomas (95% CI, 2.25–2.80), and 1.30 in the 55 cases vs 235 controls with hyperplastic polyps (95% CI, 0.96–1.77). The 10-year risk for CRC was 4.4% for patients with SSA/P with dysplasia, 4.5% for patients with TSAs, and 2.3% for patients with conventional adenomas. **CONCLUSION:** Patients with SSA/P or TSA are at increased risk for CRC; their level of risk is similar to or higher than that of patients with conventional adenomas.

Keywords: Tumor; Colorectal Neoplasm; Risk Factor; Early Detection.

Most colorectal cancers (CRCs) develop via the well-known adenoma-carcinoma sequence, but approximately one-third now are thought to arise through the more recently recognized, and less well-characterized, alternative serrated pathway.[1] Evidence for the malignant potential of serrated lesions comes in part from cross-sectional studies showing dysplasia and adenocarcinoma arising in serrated precursor lesions such as the sessile serrated adenoma/polyp (SSA/P) (as termed by the World Health Organization [WHO][2]), which comprise 3%–22% of all serrated lesions.[3] In addition, these lesions share molecular characteristics with sporadic microsatellite-unstable CRCs and CpG island methylator phenotype–positive microsatellite-stable CRCs.[4–8] The 2 other serrated polyp types are the hyperplastic polyp (HP) and the traditional serrated adenoma (TSA), the latter also thought to have an increased risk of progression to CRC.[9,10] Available longitudinal studies of serrated polyps included few CRCs, with some limited further by short-term or incomplete follow-up evaluation. Thus, evidence regarding the long-term clinical course of patients with these lesions is sparse.[11–18]

Before the mid-2000s, most lesions now recognized as serrated polyps were diagnosed as HPs and received minimal intervention and little follow-up evaluation after excision or biopsy. In Denmark, the availability of nationwide databases and permanent storage of paraffin blocks from diagnostic pathology specimens make it possible to study the association of serrated polyps with subsequent CRC. We investigated CRC risk in patients with a history of serrated polyps in a nationwide population-based setting.

Materials and Methods

This nationwide population-based, case-control study was conducted within the entire Danish population, cumulatively comprising approximately 8.2 million individuals over the study period. Individual-level data were linked using the unique 10-digit personal identifier assigned at birth or immigration to all Danish residents by the Danish Civil Registration

Abbreviations used in this paper: **AD, conventional adenomas; CI, confidence interval; CRC, colorectal cancer; HP, hyperplastic polyp; OR, odds ratio; SSA/P, sessile serrated polyp/adenoma; TSA, traditional serrated adenoma; WHO, World Health Organization.**

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System.[19] This study was approved by the Danish Data Protection Agency (J. 2008-41-2405) and the Committee on Health Research Ethics (M-20090204).

Study Base

Our case-control study was nested within the study base of all patients recorded in the Danish National Patient Registry as having had one or more colonoscopies during 1977–2009 (N = 272,342), corresponding to the period for which we had available data at the time of study initiation. This registry has recorded all nonpsychiatric hospitalizations in Denmark since 1977 and all hospital outpatient visits (including essentially all specialist care) since 1995.[20] It records admission and discharge dates, procedure and surgery codes, and up to 20 discharge diagnoses, coded by physicians according to the International Classification of Diseases, 8th revision until the end of 1993, and the 10th revision thereafter. Virtually all colonoscopies in Denmark are performed by surgeons and gastroenterologists either at public hospitals or specialist clinics and are recorded in the Danish National Patient Registry. The quality of the coding of colonoscopy procedures in this registry is well documented, even before 1995 (Supplementary Appendix).[21] Patients with a diagnosis of CRC either before or within 6 months after their initial colonoscopy were excluded. We also omitted patients with a recorded diagnosis of inflammatory bowel disease before or on the colonoscopy date (Supplementary Table 1 lists the codes). Of note, general CRC screening was not established in Denmark during the study period.

Colorectal Cancer Cases and Controls

Cases were patients identified from the study base with an incident CRC diagnosis recorded in the Danish Cancer Registry during 1977–2006 (Supplementary Table 1), the period for which we had available data.[22] This registry has recorded incident malignancies in Denmark since 1943. Its database includes International Classification of Diseases, 10 revision, coded diagnoses, month and year of diagnosis (exact date since 2004), tumor location (proximal to the splenic flexure, distal colorectum, unknown, or multifocal), and stage at diagnosis (localized/regional, metastatic, or unknown).

For each case, we used risk-set sampling to select from the study base 4 controls, matched to cases on sex and year of birth within 1 year, who were free of CRC for at least the same duration of follow-up evaluation after the initial colonoscopy as the corresponding matched case. The mean follow-up period was 5.90 years. We defined the index date for controls as the diagnosis date of the matched case.

Polyp History

For cases and controls, we used records from the Danish Pathology Data Bank to obtain information on all colorectal specimens removed on or after the date of the initial colonoscopy and before the CRC diagnosis/index date. The Data Bank, updated daily, is used in routine clinical practice to manage all diagnostic tissue specimens. It contains data from the 1970s to the present, and is considered complete on a nationwide scale from 1997.[23] Its data include pathology diagnoses recorded according to a Danish modification of the Systematized Nomenclature of Medicine coding system, specimen sampling date, and geographic location of stored specimen paraffin blocks.

We used the Pathology Data Bank to categorize lesions found during the first endoscopy that yielded polyps as HPs, conventional adenomas (ADs), or synchronous HP/ADs (Supplementary Table 1). For these earliest recorded lesions, we sought to review the pathology of lesions originally diagnosed as HPs and to reclassify them according to modern serrated polyp criteria.[2] We did not review lesions that had been diagnosed as ADs because confusion between polyps from the serrated and adenoma pathways is uncommon. We collected original HP specimens from the archives of the 19 Pathology Departments in Denmark,[23] which routinely store paraffin blocks permanently. Thus, nearly all blocks were available (Figure 1). From each block, one new H&E-stained section was scanned using a Nanozoomer digital scanner (Hamamatsu Photonics KK, Hamamatsu City, Japan). We did not collect specimens for other polyp types or for metachronous polyps (ie, polyps recorded after the first/earliest polyps).

The scanned virtual slides were reviewed independently by 4 study pathologists using the 2010 WHO diagnostic criteria for serrated lesions (Supplementary Table 2).[2] The pathologists had no access to each other's classifications or to any patient characteristics including case/control status and polyp anatomic location. Polyps were classified initially into 14 groups derived from WHO terminology,[2] and these detailed groups then were collapsed for analysis purposes, according to majority opinion, as follows: HP, SSA/P (with/without cytologic dysplasia), TSA, AD, and uncertain/equivocal (Supplementary Table 2). In the 105 (7.3%) slides for which initial review did not yield agreement on classification by a majority of study pathologies, a consensus diagnosis was assigned after discussion.

After rediagnosis of the polyps initially classified as HPs, the pathology reports were reviewed to ascertain anatomic location. It was not possible to obtain information on polyp size.

Statistical Analysis

By using conditional logistic regression, we computed odds ratios (ORs) and 95% confidence intervals (CIs) of CRC for each of the polyp types (after reclassification of the HPs by the pathologists). Patients with no polyps served as the referent. We adjusted for age at, and calendar year of, CRC diagnosis/index. Because we used risk-set sampling to select controls, the ORs provided estimates of incidence rate ratios. ORs also were calculated after stratification by sex, time between initial colonoscopy and CRC diagnosis/index date, time period of colonoscopy (1977–1996, 1997–2009), and the anatomic location of lesions. We also computed ORs associating polyp types with CRC stage and location. This required dissolving the matching and using polytomous logistic regression with stage and location as the dependent variables, and adjusting for age, sex, and year of CRC diagnosis/index. We used Wald statistics to calculate *P* values for interactions and to test for trends.

In a subsequent analysis, we computed ORs after stratifying patients by the types of metachronous polyps diagnosed after the first biopsy/excision and before the CRC diagnosis/index date. Because we did not review the pathology for any of these metachronous lesions, they could be classified only as reported ADs, HPs, or a mix of the 2 polyp types. After obtaining causes of death through the Causes of Death