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Association of small versus diminutive adenomas and the risk for metachronous advanced adenomas: Data from the New Hampshire Colonoscopy Registry

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Abstract

Background and Aims—Limited data are available to investigate the impact of index adenoma size on the risk of metachronous advanced adenomas. Our goal was to examine the impact of having small (5–9 mm) versus diminutive (<5 mm) adenomas on the future risk of advanced adenomas within the categories for polyps <1cm currently used in the United States: 1 to 2 and 3 or more tubular adenomas.

Methods—We included data from individuals participating in the statewide, population-based New Hampshire Colonoscopy Registry (NHCR). Groups were based on index findings: (1) 1 to 2 adenomas <5 mm (both diminutive), (2) 1 to 2 adenomas <1 cm (one or both small), (3) 3 to 10 adenomas <5 mm (all diminutive), (4) 3 to 10 adenomas <1 cm (one or more small), and (5) advanced adenomas (AA). AAs were defined as adenomas >1cm or those with villous elements or high-grade dysplasia and colorectal cancer (CRC). Outcomes were the absolute and adjusted risk of meta chronous advanced adenomas. Covariates included age, sex, body mass index, family history of CRC, lifestyle factors, presence of serrated polyps, and time since the index examination.

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Results—After adjusting for the covariates, we observed that having 1 to 2 adenomas with at least one 5 to 9 mm adenoma (adjusted odds ratio [AOR], 1.54; 95% CI, 1.12–2.11), 3 to 10 diminutive adenomas (AOR, 1.75; 95% CI, 1.03–2.95), 3 to 10 adenomas <1 cm (1 or more small) (AOR, 2.14; 95% CI, 1.39–3.29) or advanced adenomas (AOR, 2.77; 95% CI, 2.05–3.74) were associated with an increased risk for metachronous AA as compared with having 1 to 2 diminutive adenomas. A further stratification of Group 2 observed that those with exactly 2 small adenomas had an absolute risk of future AA of 7.6% (11/144) (95% CI, 4.3%–13.2%), higher than the absolute risk in the 1 to 2 diminutive polyp group, and similar to the risk for 3 to 10 adenomas 8.2 (95% CI, 5.4–11.9).

Conclusions—For individuals with 1 to 2 adenomas <1 cm, having at least 1 small adenoma increased the metachronous risk of AA compared to having only diminutive adenomas. Furthermore, the subset with 2 small adenomas had a risk of future AA similar to the risk for 3 to 10 adenomas. These data suggest that individuals with at least 1 small adenoma may be at higher risk for future advanced adenomas and thus require closer follow-up than those with only diminutive adenomas. These data may be valuable to guideline committees for the creation of future surveillance recommendations.

Background

Colorectal cancer (CRC) is the second most common cause of death from cancer in the United States[1], despite being a preventable disease. The key to prevention lies in delivery of appropriate and timely screening and surveillance colonoscopies, and development of appropriate guideline recommendations for prevention requires evidence to inform those guidelines. Colonoscopy is the most common form of CRC screening in the United States, and surveillance colonoscopies, which are follow-up colonoscopies in individuals found to have potentially precancerous polyps or CRC, account for about 3 million examinations annually in the United States[2, 3]. Therefore, evidence to support surveillance guidelines is essential to effective CRC prevention and early detection.

The current US guideline recommendation for surveillance intervals for individuals with only 1 to 2 diminutive and small (ie, <1 cm) tubular adenomas is to have a repeat colonoscopy in 5 to 10 years[4, 5]. Small and diminutive (<1 cm) tubular adenomas are a common finding on colonoscopy, and there has been a debate regarding the appropriate surveillance intervals for individuals with these polyps. A few long-term studies suggest that individuals with 1 to 2 tubular adenomas <1 cm are at a low risk for CRC,[6–8] and thus these lesions are referred to as low-risk adenomas (LRA). However, long-term studies may be limited by low numbers of CRC as well as the analytic challenge of accounting for the impact of surveillance examinations when comparing the risk for individuals with low-risk adenomas with those with no adenomas[6, 7]. Although preventing CRC is the primary aim of CRC screening and surveillance through colonoscopy, evidence to inform guidelines is often based on the risk of metachronous advanced adenomas, which are more commonly detected and are often used as a surrogate outcome for CRC[9–12]. Thus, data examining metachronous risk for advanced adenomas are useful in investigating clinical management issues for individuals with index adenomas ≤1 cm.

One issue that should be addressed is whether recommendations for adults with only diminutive tubular adenomas detected at colonoscopy should parallel recommendations for individuals with small tubular adenomas. For example, it is unclear whether 1 to 2 diminutive (<5 mm) adenomas are associated with the same level of risk posed by having 1 to 2 small (6–9 mm) adenomas, and evidence to illuminate this question is lacking. Since index adenoma size has been shown to be an important predictor for metachronous advanced adenomas, it has been postulated that further risk stratification of individuals with index diminutive and small adenomas may improve CRC surveillance[11, 13]. The size of small adenomas has been shown to be an important predictor of future neoplasia for individuals with non advanced[11] and advanced adenomas[12]. Current U.S. Multi-Society on Colorectal Cancer surveillance guidelines recommend that individuals with 1 to 2 adenomas <1 cm return for surveillance colonoscopy in 5 to 10 years; and that individuals with >3 adenomas, or at least one adenoma >1cm, considered to be at higher risk, have a surveillance examination in 3 years[4]. Further stratifying the current risk category of 1 to 2 adenomas <1 cm into those with small versus diminutive index adenomas may help identify individuals currently considered low risk who may actually be at higher risk for metachronous advanced adenomas.

Our goal in the current analysis was to determine whether diminutive and small adenomas are associated with equivalent levels of risk. Specifically, we investigated the metachronous risk of advanced adenomas for individuals having at least 1 small (5–9 mm) tubular adenoma compared with those having all diminutive (<5 mm) tubular adenomas within the categories for polyps <1cm currently used in the United States: 1 to 2 and 3 or more small tubular adenomas.

Methods

Population

The New Hampshire Colonoscopy Registry (NHCR), described in detail elsewhere, was founded in 2004 as a population-based, statewide registry collecting data from endoscopy sites throughout New Hampshire (NH)[14–16]. Prior to colonoscopy, consenting patients complete a self-administered patient questionnaire which collects data on demographic factors (e.g. age, sex, marital status, education), health behaviors (e.g.smoking, alcohol intake, aspirin use and exercise), and detailed family and personal history of polyps and CRC.

Endoscopists complete the NHCR procedure form immediately after the exam has been completed. The endoscopist may personally complete form or communicate information to the endoscopy nurse assisting with the colonoscopy. Data collected include detailed indication for the exam, findings (location, size and specific treatment of polyps, cancer, or other findings), type and quality of bowel preparation, sedation medication, anatomical location reached during the procedure, withdrawal time, follow-up recommendations, and immediate complications. Size is recorded as per the endoscopist's measurement and is categorized as < 5 mm, 5–9 mm and > 10 mm.

The NHCR requests pathology reports for all colonoscopies with findings directly from the pathology laboratory used by each participating endoscopy facility. Trained NHCR staff abstract and enter these pathology findings, including location, size, and histology of each polyp, into the NHCR database, matching individual polyp level pathology data to information from the colonoscopy procedure form.[16] All data collection and study procedures were approved by the Committee for the Protection of Human Subjects at Dartmouth College (study # 00015834), as well as by other relevant human subjects reviewing bodies at participating sites.

Cohort—We included individuals with index adenomas and a follow up colonoscopy at least one year after index exam in the NHCR. Exams with poor bowel preparation or incomplete exams and individuals with familial syndromes or IBD were excluded.

Covariates—The covariates examined were patient age, sex, body mass index (BMI), family history of CRC (defined as at least one first-degree relative with CRC), previous colorectal neoplasia, aspirin use (none versus at least once per week), educational level (high school or more), exercise (never versus at least once per week), and alcohol intake (≥5 versus <5 servings per week). Presence at index colonoscopy of clinically significant serrated polyps (CSSPs, including all SSA/Ps, TSAs, HPs ≥1 cm anywhere in the colon or any HP > 5mm in the proximal colon) was also a covariate. Endoscopist Adenoma Detection Rate (ADR) was assessed at both index and surveillance colonoscopy. All variables were considered categorical except for age, BMI, ADR, and months since index exam, which were continuous variables.

Exposure variable—Individuals were divided into 5 groups based on index findings: Group 1) 1–2 diminutive tubular adenomas (< 5 mm), Group 2) 1–2 tubular adenomas < 1cm (one or both small (5–9 mm), Group 3) 3–10 diminutive tubular adenomas (< 5 mm), Group 4) 3–10 tubular adenomas (< 1 cm) (one or more small) and Group 5) advanced adenomas (AA). AAs were defined as adenomas ≥1cm or those with villous elements, high-grade dysplasia, or CRC.

Statistical approach—Outcomes were the absolute and adjusted risk of metachronous AAs. Covariates in the multivariable analysis included age (continuous), sex, BMI (continuous), family history of CRC, smoking (never, past or current), alcohol intake, education, exercise, presence of CSSPs, months (continuous) since index exam as well as co-variates listed above.

Results

There were 6876 adults in the NHCR database with two exams at least one year apart with at least one adenoma at index exam. After excluding both index and follow-up exams which were incomplete (n=199), or had poor bowel preparation (n=456), and patients with IBD (n=77) or familial colorectal cancer syndromes (n=61), 6083 individuals remained in the sample. These patients were stratified by index findings into: Group 1) 1–2 diminutive adenomas (n=2568), Group 2) 1–2 tubular adenomas (at least one small) (n=1294), Group 3) 3–10 diminutive adenomas (n=293), Group 4) 3–10 tubular adenomas (one or more small)

(n=425) and Group 5) advanced adenomas (n= 1503). Characteristics for these groups including age, sex, BMI, lifestyle factors, synchronous serrated polyps and months to follow up are shown in Table 1.

The absolute risks for metachronous advanced adenomas are shown in Table 2. After adjusting for the covariates, we observed that having 1–2 adenomas at least one of which was small (5–9 mm) was associated with an increased risk for metachronous AA as compared to having 1–2 *diminutive* adenomas (Table 2). However, the metachronous risk for individuals with 3–10 adenomas that were all diminutive was similar to those with 3–10 adenomas < 1cm, at least one of which was small. A further stratification of Group 2 observed that those with *exactly 2* small adenomas had an absolute risk of future AA of 7.6% (11/144) (95% CI; 4.3–13.2%), higher than the absolute risk in the 1–2 diminutive polyp group, and similar to the risk for 3–10 adenomas 8.2 (95%: 5.4–11.9). The risks associated with each co-variate are shown in Table 3.

To examine the impact of time between index and surveillance colonoscopy on risk of metachronous findings at subsequent colonoscopy, we performed a sensitivity analysis in which we restricted the cohort to those with surveillance colonoscopy at least 3 years after index exam. The results were similar and are shown in Table 4.

Discussion

Our analysis showed that all adenomas < 1 cm may not be associated with equal risks; rather, the specific size of index tubular adenomas <1cm was important and positively modified the risk for metachronous advanced adenomas in adults with “low risk” adenomas. Specifically, we observed that individuals with 1–2 adenomas < 1 cm, at least one of which was small (5–9 mm), had an increased metachronous risk of advanced adenomas as compared to those with 1–2 diminutive (< 5 mm) adenomas. Furthermore, a subset of Group 2 with 2 adenomas, both of which were small, had a risk of future advanced adenomas similar to that in patients with 3–10 adenomas <1 cm. In adults with 3–10 adenomas < 1cm, there was no increased risk observed with having at least one small versus having all diminutive adenomas.

A 2014 meta-analysis demonstrated that individuals with low risk adenomas (1–2 small tubular adenomas) had a higher rate of metachronous adenomas than those with no adenomas on index exam[17]. However, the absolute risk for metachronous adenoma was low in both groups: 1.6% for the no adenoma group and 3.6% for the low risk adenoma group. Some studies have attempted to use index adenoma size to stratify adults with small adenomas into those at high and low risk for metachronous advanced adenoma. One such study from South Korea showed that adults with 3–10 diminutive tubular adenomas did not have an increased risk for metachronous advanced colorectal neoplasia as compared to the reference group, having 1–2 small adenomas on index colonoscopy[10]. Conversely those with advanced adenoma or 3–10 adenomas and at least 3 small tubular adenomas had an increased risk. In our analysis, adults with 3–10 adenomas < 1cm, there was no increased risk observed with having at least one small versus having all diminutive adenomas.

A more recent study from South Korea divided individuals with index adenomas into 4 groups, those with: 1–2 non-advanced adenomas;≥3 non-advanced, diminutive (1 to 5 mm) adenomas; ≥3 non-advanced, small (6–9 mm) adenomas; and advanced adenomas[9]. They observed that those with ≥ 3 non-advanced diminutive adenomas had a borderline increased risk of metachronous advanced adenomas compared with patients with 1–2 small tubular adenomas, suggesting that size (small versus diminutive) may be an important modifier for multiple adenomas. One limitation of this study is that the median follow up for the low risk adenoma group (38 months) was shorter than the recommended interval of 5–10 years. One possible consequence, as suggested by an accompanying editorial, was that metachronous risk may have been underestimated in the low risk group[18]. The follow up time between index and surveillance colonoscopy for our study was more consistent with current guidelines. For example, the mean follow up for those with 1–2 adenomas was close to 60 months (5 years) while that for patients with ≥3 advanced adenomas was closer to 36 months (3 years). In addition, we performed a sensitivity analysis excluding those with the shortest follow-up intervals (1–3 years) and observed similar results.

The data presented here support the recommendation that individuals with 1–2 *diminutive* adenomas are at low risk for metachronous advanced adenomas, and current surveillance guideline recommendations of 5–10 year follow up are appropriate. We also observed a statistically significant increased risk for metachronous advanced adenomas for those individuals with ≥3 adenomas, regardless of size, and for those with advanced adenomas. These data support the close follow up suggested in the guidelines. Our analyses also demonstrated a statistically significant increase for metachronous advanced adenomas in those individuals with 1–2 adenomas, at least one of which is small, as compared to those with 1–2 *diminutive* adenomas. Thus, our data suggest that shorter surveillance intervals may be appropriate for adults with 1–2 adenomas <1 cm, at least one of which is small, as compared to our reference group with 1–2 diminutive adenomas. Furthermore, a subgroup with 2 adenomas, *both* of which were small, had a higher risk of metachronous advanced adenomas that was similar to the risk for those with ≥3 adenomas, supporting the suggestion that individuals in this group may require closer follow up than those with diminutive adenomas only.

Strengths of this analysis included the incorporation of several known CRC risk factors as covariates, including BMI, family history, smoking and other lifestyle factors such as alcohol intake. A recent editorial suggested that endoscopists routinely adjust for these important factors when measuring their own adenoma detection rates for quality purposes[18]. Our analysis also adjusted for the impact of clinically significant serrated polyps detected at index colonoscopy. In addition, we accounted for follow up time, which did not impact our results. Finally, since much of the data regarding impact of size is published from Korea, our data provide novel information using a different population, in addition to analysis of different multiplicity and size categories.

One limitation of this study is that the cohort lacks racial diversity and is predominantly white, which limits generalizability. Although New Hampshire does not have significant racial diversity, there is considerable ethnic, urban/rural and socioeconomic diversity in the population that is captured within the NHCR[19]. However, the results should be confirmed in

other patient populations. Another limitation is that the polyp sizes were based on the endoscopist's visual estimate. While it is well known that endoscopic estimates of polyp size may be inaccurate and can vary in both directions (too large and too small),[20, 21] this is currently the most widely utilized form of assessment and the method that guidelines assume endoscopists use to measure polyp size . Therefore, we used the endoscopist's measurement of polyp size for our analyses. Furthermore, the specified ranges for size categories used on NHCR data collection forms for size categories used on NHCR data collection forms may help to ensure appropriate distinctions between diminutive, small, and large polyps. It should be acknowledged that the prospective cohort design as compared to a controlled trial may be limited with regard to possible confounding factors. However, our analysis is similar to that used in the studies cited above[9, 10] as well as other studies examining metachronous risk[22, 23]. Furthermore, we adjusted for many known CRC risk factors, decreasing the potential that confounding factors may have influenced the results.

In summary, NHCR participants with 1–2 diminutive adenomas had a low risk for metachronous advanced adenomas, and these individuals may not require closer surveillance than currently recommended; extending to ten years may be an appropriate follow-up interval for this group. However, patients with 1–2 adenomas including at least one small adenoma appear to be at increased risk for future advanced adenomas compared to the group with only diminutive adenomas. These data can inform future surveillance guidelines.

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Abbreviations and Acronyms

ADR
Adenoma detection rate

SDR
Serrated polyp detection rate

SSA/P
Sessile serrated adenomas/polyps

TSA
Traditional serrated adenomas

HP
Hyperplastic polyps

NHCR
New Hampshire Colonoscopy Registry

ACG

American College of Gastroenterology

ASGE
American Society for Gastrointestinal Endoscopy

CRC
Colorectal Cancer

BMI
Body Mass Index

IBD
Inflammatory bowel disease

LRA
Low risk adenoma

HRA
High risk adenoma

US Multi Society Task Force

CSSPs
Clinically significant serrated polyps

HGD
High grade dysplasia

HS
High school

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Table 1.

Patient and exam characteristics, stratified by index findings

Factors	Index Colonoscopy Findings				
	Group 1 1–2 diminutive* adenomas	**Group 2 1–2 adenomas < 1 cm, one or more small****	**Group 3 3–10 diminutive* adenomas**	**Group 4 3–10 adenomas < 1 cm, one or more small****	**Group 5 Advanced adenoma*****
N	2568	1294	293	425	1503
Age (mean + S.D.)	59.1 ± 8.9	58.7 ± 9.5	62.5 ± 8.9	62.5 ± 9.1	60.0 ± 9.7
Sex (% male)	1387 (54.0%)	744 (57.5%)	204 (69.6%)	309 (72.7%)	890 (59.2%)
BMI	28.5 ± 5.9	28.6 ± 6.1	29.7 ± 6.7	29.9 ± 5.8	29.2 ± 6.1
Family history of CRC (first degree relative)	617 (24.0%)	305 (23.6%)	68 (23.2%)	92 (21.6%)	313 (20.8%)
Current smokers	239 (9.9%)	135 (10.17%)	39 (13.5%)	46 (11.2%)	211 (14.5%)
Aspirin use (regular)	995 (38.7%)	536 (41.4%)	115 (39.2%)	217 (51.1%)	556 (37.0%)
Alcohol (at least 5 drinks per week)	804 (31.3%)	384 (29.7%)	104 (35.5%)	129 (30.4%)	448 (29.8%)
Education (HS or more)	2383 (92.8%)	1207 (93.3%)	272 (92.8%)	389 (91.5%)	1379 (91.7%)
Regular exercise (at least 1/week)	1444 (56.2%)	699 (54.0%)	145 (49.5%)	217 (51.1%)	742 (49.4%)
Previous adenomas	795 (31.5)	388 (30.6%)	135 (48.0%)	197 (47.7%)	397 (27.0%)
Clinically significant serrated polyps**** at index exam	190 (7.5%)	138 (10.8%)	22 (7.6%)	42 (9.9%)	149 (11.3%)
Months to surveillance exam	57.9 ± 19.2	56.7 ± 12.1	42.5 ± 15.1	40.6 ± 16.0	38.6 ± 23.0

* Diminutive = <5 mm;

** Small = 5–9 mm;

*** Advanced adenomas: adenomas ≥1cm or those with villous elements, high-grade dysplasia, or CRC.

**** Clinically Significant serrated polyps: all SSA/Ps, TSAs, HPs >1 cm anywhere in the colon or any HP > 5mm in the proximal colon

Table 2.

The absolute risk, odds ratio (OR) and adjusted OR* for metachronous advanced adenomas in individuals with index adenomas as classified by current guideline categories, stratified by adenoma size

Index findings	N	Absolute risk (%) (95% CI)	Unadjusted OR (95% CI)	*Adjusted OR (95% CI)	P value
1–2 diminutive adenomas	2568	4.0 (3.2–4.8) (n=103)	Reference (1.0)	1.0 Reference	…
1–2 adenomas < 1cm ** (one or more small)	1294	5.9 (4.7–7.3) (n=76)	1.49 (1.10–2.02)	1.54 (1.12–2.11)	0.008
3–10 diminutive adenomas	293	8.2(5.4–11.9) (n=24)	2.14(1.35–3.39)	1.75(1.03–2.95)	0.03
3–10 adenomas < 1cm (one or more small)	425	9.4(6.4–11.9) (n=40)	2.49(1.70–3.64)	2.14(1.39–3.29)	0.001
Advanced adenoma ***	1503	10.0(9.2–12.2) (n=150)	2.65 (2.05–3.44)	2.77 (2.05–3.74)	0.0001

*Adjusted for age, sex, BMI, family history of CRC, smoking, presence or serrated polyps and years since index exam.

**Subset of Group 2 of adults with 2 small adenomas (versus 1 or more small) absolute risk: 7.3% (95% CI; 5.0–10.4%)

***Advanced adenomas: adenomas ≥1cm or those with villous elements, high-grade dysplasia, or CRC.

Table 3

Co-variate factors' unadjusted and adjusted risks for advanced adenoma on surveillance exam

Factor	Unadjusted OR (95% Cl)	Adjusted OR (95% Cl)
Age (per year)	1.03(1.02–1.04)	1.02(1.02–1.04)
Sex (male reference)	0.76 (0.62–0.94)	0.87(0.68–1.11)
BMI	1.02(1.00–1.04)	1.02(1.00–1.04)
Family history of CRC (FDR) (none reference)	1.18(0.93–1.49)	1.18(0.91–1.53)
Current smokers (never reference)	1.28(0.91–1.78)	1.13(0.77–1.65)
Past (never reference)	1.17(0.93–1.46)	1.02(0.80–1.30)
Previous adenomas (none reference)	1.50(1.22–1.86)	1.28(1.00–1.63)
Aspirin use (regular use) (none reference)	1.25(1.02–1.53)	1.08(0.85–1.36)
Alcohol use (at least 5 drinks per week) (< 5 reference)	0.93(0.74–1.16)	1.00(0.78–1.28)
Education (HS or more versus lower level)	0.81 (0.57–1.16)	0.90(0.57–1.43)
Regular exercise (at least 1/week) (none reference)	0.74(0.60–0.91)	0.88(0.70–1.11)
Clinically significant serrated polyps at index (none reference)	1.55(1.13–2.12)	1.44(1.02–2.04)
ADR of endoscopist who completed index colonoscopy	1.00(0.99–1.01)	0.99(0.98–1.01)
ADR of endoscopist who conducted surveillance colonoscopy	1.00(1.00–1.01)	1.01 (1.00–1.02)
Months to surveillance exam	1.00(0.99–1.00)	1.01 (1.00–1.01)

Table 4.

The absolute and adjusted risk* for metachronous advanced adenomas in individuals with index adenomas as classified by current guideline categories, stratified by adenoma size, in patients with at least 36 months between index and surveillance colonoscopy

Index findings	Follow up time (mean months ± S.D.)	*Adjusted Risk (95% CI)	P value
1 −2 adenomas < 5 mm (both diminutive)	62.0 ± 16.0	1.0 Reference	…
1–2 adenomas < 1cm** (one or more small)	61.1 ±18.2	1.51 (1.08–2.09)	0.01
3–10 adenomas < 5 mm (all diminutive)	47.1 ±13.0	1.72(1.01–2.95)	0.05
3–10 adenomas < 1 cm (one or more small)	47.4 ± 13.5	2.00(1.25–3.18)	0.004
Advanced adenoma	53.9 ± 20.5	2.53(1.82–3.53)	0.0001

*Adjusted for age, sex, BMI, family history of CRC, smoking, presence or serrated polyps and years since index exam.