Cancer Causes Control (2016) 27:749–757
DOI 10.1007/s10552-016-0752-3

ORIGINAL PAPER

# A prospective study of oral contraceptive use and colorectal adenomas

**Brittany M. Charlton[1,2,3] · Edward Giovannucci[1,4,5] · Charles S. Fuchs[6] · Andrew T. Chan[5,7] · Jung Eun Lee[8] · Yin Cao[4] · Stacey A. Missmer[1,5,9] · Bernard A. Rosner[5] · Susan E. Hankinson[1,5,10] · Walter Willett[1,4,5] · Kana Wu[4] · Karin B. Michels[1,5,11]**

Received: 25 September 2015 / Accepted: 16 April 2016 / Published online: 28 April 2016


**Abstract**
*Purpose* The influence of reproductive factors on colorectal cancer, including oral contraceptive (OC) use, has been examined, but less research is available on OC use and adenomas.
*Methods* Participants of the Nurses' Health Study who had a lower bowel endoscopy between 1986 (when endoscopies were first assessed) and 2008 were included in this study. Multivariable logistic regression models for clustered data were used to estimate odds ratios and 95 % confidence intervals [OR (95 % CIs)].
*Results* Among 73,058 participants, 51 % ($n = 37{,}382$) reported ever using OCs. Ever OC use was associated with a slight increase in non-advanced adenomas [OR 1.11, 95 % CI (1.02, 1.21)] but not with any other endpoints. Duration of OC use was not associated with adenomas, but longer times since last OC use were associated with increased odds of adenomas [e.g., compared to never use, 15+ years since last use: OR 1.17 (1.07, 1.27)]. Shorter times since last OC use were inversely associated [e.g., ≤4 years since last use: OR 0.74 (0.65, 0.84)].
*Conclusions* We observed a modest borderline increase in risk of colorectal adenomas with any prior OC use. Additionally, more recent OC use may decrease risk, while exposure in the distant past may modestly increase risk of adenomas.

Kana Wu and Karin B. Michels have contributed equally to this work.

**Electronic supplementary material** The online version of this article (doi:10.1007/s10552-016-0752-3) contains supplementary material, which is available to authorized users.

✉ Brittany M. Charlton
bcharlton@mail.harvard.edu

[1] Department of Epidemiology, Harvard T.H. Chan School of Public Health, 677 Huntington Avenue, Boston, MA 02115, USA

[2] Division of Adolescent and Young Adult Medicine, Boston Children's Hospital, 300 Longwood Avenue, Boston, MA 02115, USA

[3] Department of Pediatrics, Harvard Medical School, 25 Shattuck Street, Boston, MA 02115, USA

[4] Department of Nutrition, Harvard T.H. Chan School of Public Health, 677 Huntington Avenue, Boston, MA 02115, USA

[5] Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, 181 Longwood Avenue, Boston, MA 02115, USA

[6] Department of Medical Oncology, Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA 02115, USA

[7] Division of Gastroenterology, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114, USA

[8] Department of Food and Nutrition, Sookmyung Women's University, Cheongpa-ro 47-gil 100, Yongsan-gu, Seoul 04310, South Korea

[9] Division of Reproductive Medicine, Brigham and Women's Hospital and Harvard Medical School, 45 St. Francis Street, Boston, MA 02115, USA

[10] Division of Biostatistics and Epidemiology, School of Public Health and Health Sciences, University of Massachusetts, 715 North Pleasant Street, Amherst, MA 01003, USA

[11] Obstetrics and Gynecology Epidemiology Center, Brigham and Women's Hospital and Harvard Medical School, 221 Longwood Avenue, Boston, MA 02115, USA

**Keywords** Adenoma · Colorectal neoplasms · Contraceptives · Oral · Intestinal polyps · Reproductive history

## Introduction

Most colorectal cancers, the third most common cancer in the USA [1], arise from abnormal tissue growths called "colorectal adenomas." The influence of reproductive factors on colorectal cancer [2], including the use of exogenous hormones such as oral contraceptives (OC), has been studied for decades, but less research is available on the role of OC use on adenomas. Some studies have identified an inverse association between OC use and colorectal cancer [3–22], but only a few studies have examined its association with adenomas, and no evidence of an association has been found [23–25]. If OC use is not associated with adenomas but is inversely associated with colorectal cancer, this may indicate that any protective role that exists from OC use takes place during the later carcinogenic phases, rather than initiation.

Yet, there is evidence that sex hormones such as estrogens may be involved in the development of adenomas. For example, other exogenous hormones including hormone therapy (HT) are inversely associated with adenomas [23, 24, 26–32]. Estrogens may reduce the risk of adenomas by altering bile acid composition [33], modulating colonic transit [34], and decreasing production of mitogenic insulin-like growth factor 1 [35]. However, studies on OC use and adenomas have been limited in statistical power and unable to explore various details of OC exposure such as duration and recency of use, formulation (different chemical substances), and generation (different chemical substances grouped by progestin type), as well as particulars of the adenoma outcome such as subsite, stage, and multiplicity (e.g., number) of adenomas. Other cancer outcomes have varied by OC formulations [36]; thus, it is important to explore this effect. Studies from the HT literature also suggest that there is heterogeneity of risk by adenoma subtypes, with HT use being protective for adenomas with advanced histology compared to individuals without any adenomas [37], which could provide information about etiology. A better understanding of the association between OC use and adenomas may provide insight into the mechanism through which hormones impact colorectal carcinogenesis, which may influence clinical care.

We examined the association between OC use and colorectal adenomas using detailed data from a large prospective cohort study. Previous work in this cohort focused on OC use and colorectal adenomas ($n = 982$) between 1980 and 1994, and no evidence of an association was observed [relative risk (RR) = 1.0, 95 % CI 0.8, 1.1] [25]. We have now been able to leverage 14 more years of follow-up, which is especially useful due to colorectal cancer's lengthy latency, six times as many cases ($n = 6{,}090$), which enables us to examine associations by subtypes (i.e., subsite, stage, number), and more detailed information about the exposure.

## Materials and methods

### Study population

The Nurses' Health Study (NHS) is a cohort established in 1976 composed of 121,701 female registered nurses aged 30–55 from 11 states in the USA. Participants have been mailed questionnaires every 2 years to collect medical, lifestyle, and other health-related information. Dietary information was first collected in 1980 and updated in 1984, 1986, and every 4 years thereafter using a semi-quantitative validated food frequency questionnaire (FFQ). The current follow-up rate is over 90 %. Further details of the study have been described elsewhere [38].

Because adenomas are generally asymptomatic, a lower gastrointestinal endoscopic procedure (colonoscopy or sigmoidoscopy) is needed to identify adenomas. Starting with the 1988 questionnaire and every 2 years thereafter, participants were asked whether they had undergone sigmoidoscopy or colonoscopy in the past 2 years and what the indications for these procedures were (i.e., screening, symptoms). We started follow-up for this analysis in 1986, after the first endoscopy report, and excluded women who had not reported having had at least one endoscopy during the study period ($n = 40{,}149$). We also excluded participants who had a history of adenomas, familial adenomatous polyposis, or cancer [except for non-melanoma skin cancer ($n = 8{,}370$)] before follow-up started for this analysis in 1986. After applying the exclusion criteria, 73,058 women remained in our study population. The study was approved by the Institutional Review Board of Brigham and Women's Hospital in Boston; return of the questionnaires was considered informed consent.

### Assessment of exposure

A detailed lifetime history of OC use was obtained on the baseline questionnaire in 1976. Follow-up data were collected in 1978, 1980, and 1982, at which point less than 1 % of participants reported OC use. Information was collected on starting/stopping dates, so we could calculate age at first use (13–19, 20–24, 25–29, 30–34, 35+), time since last use ($\leq 4$, $> 4$ to $< 10$, $\geq 10$ to $< 15$,

15+ years), and duration of use ($\leq 1$, $> 1$ to $< 2$, $\geq 2$ to $< 5$, $\geq 5$ to $< 10$, 10+), as has been done in the previous literature. We also calculated a cross-product of duration-by-time since last use (e.g., $\leq$1-year duration and $\leq$4 years since last use, see Table S2) as well as a cross-product of duration-by-age at first use (e.g., 1-year duration and 13–19 years of age at first use, see Table S3). We estimated duration of use by summing OC use across questionnaire cycles. The follow-up person-time was reassigned at the beginning of each of the two-year intervals according to the respondents' status from 1976 to 1982. No information was collected on formulation or brand of the OCs, though, given the time frame, these would have been exclusively first-generation (estrane progestins) and second-generation (gonane progestins) OCs. We roughly estimated the generation of OC used by the date of use, i.e., we assumed that if all OC use occurred before 1970, exposure was to first-generation pills only; if OC use occurred before and after 1970, then exposure included first- and second-generation pills; and if all use occurred after 1970, then this exposure was to second-generation pills only.

## Case ascertainment

Biennial follow-up questionnaires were used to identify newly diagnosed cases of colorectal adenomas. We sought permission to obtain medical records and pathology reports for those who reported a diagnosis. Study physicians who were blinded to exposure information extracted information on histopathology, anatomic location, and size of the reported adenoma.

Adenomas were classified according to subsite location (i.e., proximal, distal, or rectal). We defined adenomas of the cecum, ascending colon, hepatic flexure, transverse colon, and splenic flexure as proximal, those in the descending and sigmoid colon as distal, and those in the rectosigmoid junction or rectum as rectal.

Furthermore, we classified adenoma by stage (non-advanced defined as small and tubular histology, advanced defined as large or any mention of villous histology) and multiplicity (1 or 2+). If more than one adenoma was diagnosed, the subject was classified according to the adenoma of the most advanced histological characteristics. We considered hyperplastic polyps, which are not precursors of colorectal cancer, non-cases.

Cases and non-cases were defined in each two-year period: all diagnosed adenomas were considered as cases, and all the participants who reported endoscopy but without diagnosis of adenoma were defined as non-cases. We included prevalent colorectal adenoma cases from 1986 to 2008.

## Assessment of covariate information

All regression models adjusted for age (five-year intervals), height (continuous inches), BMI [<18.5, 18.5–22.9, 23–24.9, 25–29.9, and 30+ kilogram/meter$^2$ (kg/m$^2$)], physical activity (continuous MET-hours/week), smoking (continuous pack-years), processed and red meat (quintiles), folate (quintiles), calcium (quintiles), total energy (quintiles), alcohol [<5, 5–9.9, 10–14.9, and 15+ grams (g)/day], aspirin use (0–3, 4–6, 7–10, and 11+ times/week), age at first birth (<24, 24–25, 26–29, and 30+ years), parity (0, 1, 2, and 3+), HT use (premenopausal, never, past, or current), HT duration (premenopausal, never, <5, 5–<10, and 10+ years), history of colorectal cancer in a first-degree relative (yes, no), reason for endoscopy (screening, symptoms), time period of endoscopy (two-year intervals), number of endoscopies (continuous), and time in years since the most recent endoscopy (continuous).

Participant's height (inches) was reported once at baseline in 1976. Current weight (pounds) was collected on every questionnaire and has high validity in this cohort [39]. From height and weight, we calculated body mass index (BMI) for each questionnaire year. Detailed questions about physical activity were asked every 4 years beginning in 1986. Based on the duration and type of activities, we derived a value of total metabolic (MET)-hours/week. Information about smoking was collected on all questionnaires, from which we calculated total pack-years.

Intake of folate [microgram (mcg)/day], calcium (mcg/day), processed and red meat (servings/day), and total energy [kilocalories (kcal)/day] was accessed using FFQs. We calculated the medians of the quintiles of intake for each dietary variable and used it as a continuous variable. Alcohol intake was also assessed on the FFQs. Information on aspirin use was reported starting in 1980, and frequency of use was reported starting in 1984.

Information on age at menarche, age at first birth, and parity was collected at baseline in 1976. Age at first birth and parity were ascertained biennially until 1984. The use of HT, including duration, was asked on every questionnaire. Family history of colon or rectal cancer in immediate family members was asked in 1982, updated in 1988, 1992 and 1996, and 2000. Information on colon cancer screening was provided in 1988, 1990, 1992, and every 2 years thereafter.

## Statistical analyses

To take into account that one person may have undergone multiple endoscopies between 1988 and 2008 and to minimize potential bias due to time-varying exposures,

Andersen-Gill data structure [40] with a new record for each two-year follow-up period during which a participant underwent an endoscopy was used (the risk set). Each 2-year period was considered separately. For example, if a participant underwent several endoscopies between 1986 and 2008, that participant was included in multiple risk sets and, therefore, would have had more than one record in the entire dataset. Once a participant was diagnosed with adenoma for a first time, she was censored for all later follow-up cycles. Age and multivariate-adjusted logistic regressions (PROC GENMOD) for clustered data (each participant defined as a cluster) were used to calculate odds ratios (ORs) and 95 % confidence intervals (CI). For proximal adenomas, we performed sensitivity analysis excluding participants without a colonoscopy.

All covariates were updated up to the 2-year follow-up period preceding the most recent endoscopy including dietary intake which was assessed using cumulative average intake. All regression models adjusted for age, height, BMI, physical activity, smoking, processed and red meat, folate, calcium, total energy, alcohol, aspirin use, age at first birth, parity, HT use, HT duration, history of colorectal cancer in a first-degree relative, reason for endoscopy, time period of endoscopy, number of endoscopies, and time in years since the most recent endoscopy.

We performed interaction analyses to assess whether associations varied across categories of BMI (<25, 25+ kg/m$^2$), smoking status (never, ever), and alcohol consumption (<5, 5+ g/d). We performed all analyses with SAS software version 9.2. All statistical analyses were two-sided, using a 5 % significance level. Trend tests were performed by modeling the median values of exposure categories as a continuous variable and using the Wald statistic to test for statistical significance.

## Results

Among 73,058 participants who had a lower bowel endoscopy, 49 % ($n$ = 35,676) reported never using OCs and 51 % ($n$ = 37,382) reported 2+ months of use. Ever-users reported a 4.2-year mean duration of use. Compared to never-users, ever-users were younger, had more children, and were more likely to have used HT (Table 1).

After 22 years of follow-up, we recorded 6,090 participants with adenomas: 2,981 never-users compared to 3,109 ever-users. Ever OC use was marginally associated with colorectal adenomas [OR 1.05 (0.99, 1.11)], including proximal adenomas [OR 1.08 (1.00, 1.18)], and was associated with a slight increase in non-advanced adenomas [OR 1.11 (1.02–1.21)]. Ever OC use was not associated with any other adenoma endpoints including distal [OR 1.03 (0.96, 1.12)], rectal [OR 0.98 (0.86, 1.12)], advanced [OR 1.02 (0.93, 1.12)], one adenoma [OR 1.04 (0.97, 1.11)], or 2+ adenomas [OR 1.05 (0.94, 1.18)] (Table 2).

Duration of OC use was not associated with adenomas (Table 3), but there were a number of modest but significant associations between time since last OC use and all of the adenoma outcomes (test for trend $p$ = <0.0001, Table 4). For example, compared to never use, 15+ years

**Table 1** Age-standardized characteristics of ever and never OC users among 73,058 NHS participants at the midpoint of follow-up (1998) between 1986 and 2008 [means (SD) or %]

| | Never-users ($n$ = 35,676) | Ever-users ($n$ = 37,382) |
|---|---|---|
| Age, years | 71.0 (6.4) | 65.5 (6.3) |
| Height, inches | 64.5 (2.4) | 64.6 (2.4) |
| Physical activity, MET-hours/week | 16.8 (19.8) | 17.7 (20.7) |
| Smoking, pack-years | 11.8 (18.7) | 11.8 (17.9) |
| Processed or red meat, servings/day | 0.4 (0.2) | 0.4 (0.2) |
| Folate intake, μg/day | 653 (253) | 657 (255) |
| Calcium, mg/day | 1,277 (508) | 1,290 (507) |
| BMI, kg/m$^2$[a] | | |
| <25 | 41 | 43 |
| 25–29.9 | 33 | 33 |
| 30+ | 21 | 21 |
| Aspirin use, times/week | | |
| 0–3 | 68 | 69 |
| 4–6 | 18 | 17 |
| 7–10 | 8 | 8 |
| 11+ | 7 | 6 |
| Alcohol intake, gm/day[a] | | |
| <5 | 64 | 61 |
| 5–9.9 | 9 | 11 |
| 10–14.9 | 7 | 8 |
| 15+ | 7 | 9 |
| Age at first birth, years[a,b] | | |
| <24 | 34 | 38 |
| 24–25 | 29 | 28 |
| 26–29 | 26 | 24 |
| 30+ | 10 | 9 |
| Parity[a] | | |
| 0 | 7 | 4 |
| 1 | 7 | 6 |
| 2 | 25 | 30 |
| 3+ | 59 | 59 |
| HT duration, years | | |
| Never/premenopausal | 30 | 22 |
| <5 | 26 | 28 |
| 5–<10 | 17 | 22 |
| 10+ | 27 | 29 |

[a] May not add to 100 % due to missing data

[b] Distribution among parous women

**Table 2** Colorectal adenomas in ever and never OC users among 73,058 NHS participants

| | Cases | | OR (95 % CI) | | |
|---|---|---|---|---|---|
| | Never-users | Ever-users | Never-users | Age-adjusted Ever-users | Multivariable[a] Ever-users |
| Colorectal adenoma | 2,981 | 3,109 | Ref. | 0.98 (0.93, 1.04) | 1.05 (0.99, 1.11) |
| Subsites | | | | | |
| Proximal colon | 1,309 | 1,423 | Ref. | 1.12 (1.04, 1.21) | 1.08 (1.00, 1.18) |
| Distal colon | 1,536 | 1,531 | Ref. | 0.90 (0.84, 0.97) | 1.03 (0.96, 1.12) |
| Rectum | 556 | 528 | Ref. | 0.85 (0.75, 0.96) | 0.98 (0.86, 1.12) |
| Stage | | | | | |
| Non-advanced | 1,210 | 1,445 | Ref. | 1.15 (1.06, 1.24) | 1.11 (1.02, 1.21) |
| Advanced | 1,228 | 1,118 | Ref. | 0.85 (0.78, 0.93) | 1.02 (0.93, 1.12) |
| Multiplicity | | | | | |
| 1 | 1,945 | 2,145 | Ref. | 1.05 (0.98, 1.12) | 1.04 (0.97, 1.11) |
| 2+ | 788 | 770 | Ref. | 1.03 (0.93, 1.14) | 1.05 (0.94, 1.18) |

[a] Adjusted for age, BMI, height, physical activity, smoking, processed and red meat, folate intake, calcium, total energy intake, aspirin use, HT duration, family history, reason for endoscopy, time period of endoscopy, number of endoscopies, and years since most recent endoscopy

**Table 3** Colorectal adenomas by OC duration among 73,058 NHS participants

| Duration of OC use (years) | *n* cases OR (95 % CI)[a] | | | | | | Test for trend *p* |
|---|---|---|---|---|---|---|---|
| | Never | ≤1 | >1 to <2 | ≥2 to <5 | ≥5 to <10 | 10+ | |
| Colorectal adenoma | 3,124 | 818 | 327 | 787 | 721 | 313 | |
| | Ref. | 1.10 (0.98, 1.25) | 1.08 (0.96, 1.22) | 1.03 (0.95, 1.12) | 1.07 (0.98, 1.17) | 1.10 (0.98, 1.25) | 0.09 |
| Subsites | | | | | | | |
| Proximal colon | 1,363 | 398 | 161 | 332 | 340 | 138 | |
| | Ref. | 1.18 (1.05, 1.33) | 1.20 (1.01, 1.42) | 0.98 (1.86, 1.11) | 1.14 (1.01, 1.29) | 1.10 (0.92, 1.31) | 0.24 |
| Distal colon | 1,611 | 395 | 159 | 396 | 351 | 155 | |
| | Ref. | 1.02 (0.91, 1.15) | 1.06 (0.89, 1.25) | 1.04 (0.92, 1.17) | 1.04 (0.92, 1.17) | 1.09 (0.92, 1.29) | 0.31 |
| Rectum | 582 | 132 | 48 | 154 | 112 | 56 | |
| | Ref. | 0.94 (0.77, 1.15) | 0.87 (0.65, 1.18) | 1.11 (0.92, 1.34) | 0.91 (0.73, 1.12) | 1.09 (0.82, 1.44) | 0.83 |
| Stage | | | | | | | |
| Non-advanced | 1,277 | 389 | 158 | 360 | 333 | 138 | |
| | Ref. | 1.15 (1.02, 1.30) | 1.14 (0.96, 1.36) | 1.04 (0.92, 1.18) | 1.11 (0.98, 1.27) | 1.13 (0.94, 1.35) | 0.17 |
| Advanced | 1,277 | 295 | 113 | 303 | 237 | 121 | |
| | Ref. | 1.04 (0.91, 1.18) | 1.04 (0.85, 1.27) | 1.10 (0.96, 1.25) | 0.96 (0.83, 1.11) | 1.14 (0.94, 1.38) | 0.51 |
| Multiplicity | | | | | | | |
| 1 | 2,033 | 564 | 223 | 547 | 511 | 212 | |
| | Ref. | 1.07 (0.97, 1.18) | 1.04 (0.90, 1.20) | 1.02 (0.92, 1.12) | 1.09 (0.99, 1.21) | 1.10 (0.95, 1.27) | 0.10 |
| 2+ | 828 | 200 | 85 | 195 | 168 | 82 | |
| | Ref. | 1.05 (0. 90, 1.24) | 1.15 (0.91, 1.45) | 1.04 (0.89, 1.23) | 0.99 (0.83, 1.18) | 1.13 (0. 90, 1.42) | 0.59 |

[a] Adjusted for age, BMI, height, physical activity, smoking, processed and red meat, folate intake, calcium, total energy intake, aspirin use, HT duration, family history, reason for endoscopy, time period of endoscopy, number of endoscopies, and years since most recent endoscopy

since last use was positively associated with adenomas [OR 1.17 (1.07, 1.27)]. Conversely, shorter times since last OC use were inversely associated with adenomas. For example, ≤4 years since last use was inversely associated with adenomas [OR 0.74 (0.65, 0.84)]. We further analyzed these findings to investigate whether the earlier OC formulations might be driving the increased risk among women who had longer times since last OC use, but no

**Table 4** Colorectal adenomas by time since last OC among 73,058 NHS participants

| Time since last OC use (years) | *n* cases OR (95 % CI)[a] Never | ≤4 | >4 to <10 | ≥10 to <15 | 15+ | Test for trend *p* |
|---|---|---|---|---|---|---|
| Colorectal adenoma | 3,094 | 303 | 876 | 1,110 | 717 | |
| | Ref. | 0.74 (0.65, 0.84) | 1.09 (1.01, 1.18) | 1.10 (1.02, 1.18) | 1.17 (1.07, 1.27) | <0.0001 |
| Subsites | | | | | | |
| Proximal colon | 1,351 | 134 | 403 | 508 | 336 | |
| | Ref. | 0.72 (0.60, 0.87) | 1.13 (1.01, 1.27) | 1.15 (1.03, 1.28) | 1.25 (1.10, 1.41) | <0.0001 |
| Distal colon | 1,594 | 148 | 434 | 545 | 346 | |
| | Ref. | 0.73 (0.61, 0.87) | 1.08 (0.96, 1.21) | 1.09 (0.98, 1.21) | 1.11 (0.99, 1.26) | 0.006 |
| Rectum | 576 | 62 | 140 | 179 | 127 | |
| | Ref. | 0.83 (0.63, 1.10) | 0.95 (0.79, 1.16) | 0.99 (0.82, 1.18) | 1.13 (0.93, 1.38) | 0.38 |
| Stage | | | | | | |
| Non-advanced | 1,262 | 142 | 398 | 525 | 328 | |
| | Ref. | 0.76 (0.64, 0.91) | 1.11 (0.99, 1.26) | 1.18 (1.05, 1.31) | 1.23 (1.08, 1.39) | <0.0001 |
| Advanced | 1,269 | 105 | 315 | 401 | 256 | |
| | Ref. | 0.71 (0.58, 0.87) | 1.06 (0.93, 1.21) | 1.09 (0.97, 1.23) | 1.11 (0.97, 1.27) | 0.02 |
| Multiplicity | | | | | | |
| 1 | 2,012 | 205 | 617 | 770 | 486 | |
| | Ref. | 0.70 (0.61, 0.82) | 1.10 (1.00, 1.21) | 1.10 (1.01, 1.21) | 1.16 (1.05, 1.29) | <0.0001 |
| 2+ | 819 | 80 | 210 | 267 | 182 | |
| | Ref. | 0.78 (0.61, 0.98) | 1.05 (0.89, 1.23) | 1.09 (0.94, 1.26) | 1.20 (1.01, 1.41) | 0.01 |

[a] Adjusted for age, BMI, height, physical activity, smoking, processed and red meat, folate intake, calcium, total energy intake, aspirin use, HT duration, family history, reason for endoscopy, time period of endoscopy, number of endoscopies, and years since most recent endoscopy

such association was present (data not shown). Upon examining the age at first OC use (Table 5), we saw that starting OC use at an older age (e.g., 30+ years) was positively associated with adenomas ($p_{trend} = 0.04$) including the proximal ($p_{trend} = 0.04$) and non-advanced adenomas ($p_{trend} = 0.01$). Adjusting for age at first use, the longer times since last use remained positively associated, while the shorter times since last use were not associated with adenomas (see Table S1 in supplementary online material). When analyzing duration and time since last use simultaneously using a cross-product term, the association of OC use and longer times since last use remains statistically significant. A couple of the tests for trend in the simultaneous analyses of duration and age at first use were statistically significant ($p = 0.04$), but these were not consistently linear. None of these associations varied by BMI, smoking, or alcohol intake (data not shown, all $p$ for interaction >0.10).

## Discussion

In this large cohort of women, ever OC use was marginally associated with adenomas, including a small increase in non-advanced adenomas. Longer times since last use and older age at first use were modestly positively associated with the risk of adenomas, while shorter times were inversely associated. However, further consideration of age at first OC use and duration of OC use did not add to the plausibility of the findings associated with time since last OC use.

The association between OC use and adenomas in NHS was initially examined by Platz et al. [25] in 1997 after 14 years of follow-up including 982 participants with adenomas. While the original analysis did not identify any associations with adenomas for ever/never OC use or for duration of OC use, it did not specifically separate out adenomas in the proximal colon, multiplicity of adenomas, or age at first OC use. No evidence of an association was found in that original analysis with non-advanced adenomas nor time since last OC use, but statistical power was limited.

Two previous case–control studies, one by Peipins et al. [24] including 115 cases and another by Jacobson et al. [23] including 128 cases, have examined OC use and adenomas. Neither identified any association, though these studies also had substantially less statistical power than the current analysis and only examined adenomas as a single endpoint rather than separately by subsites, stage, and multiplicity. They also did not examine detailed OC use information beyond ever/never use and duration.

**Table 5** Colorectal adenomas by age at first OC among 73,058 NHS participants

| Age at first OC use (years) | *n* cases OR (95 % CI)[a] | | | | | | Test for trend *p* |
|---|---|---|---|---|---|---|---|
| | Never | 13–19 | 20–24 | 25–29 | 30–34 | 35+ | |
| Colorectal adenoma | 2,981 | 190 | 836 | 877 | 588 | 618 | |
| | Ref. | 0.99 (0.85, 1.15) | 1.02 (0.93, 1.12) | 1.06 (0.98, 1.16) | 1.05 (0.95, 1.15) | 1.08 (0.99, 1.18) | 0.04 |
| Subsites | | | | | | | |
| Proximal colon | 1,309 | 80 | 396 | 404 | 262 | 281 | |
| | Ref. | 0.95 (0.75, 1.19) | 1.07 (0.93, 1.23) | 1.09 (0.96, 1.23) | 1.05 (0.91, 1.20) | 1.15 (1.00, 1.31) | 0.04 |
| Distal colon | 1,536 | 94 | 384 | 441 | 297 | 315 | |
| | Ref. | 0.97 (0.78, 1.20) | 0.96 (0.84, 1.10) | 1.07 (0.96, 1.21) | 1.04 (0.92, 1.18) | 1.05 (0.93, 1.19) | 0.29 |
| Rectum | 556 | 35 | 133 | 145 | 108 | 107 | |
| | Ref. | 0.98 (0.69, 1.39) | 0.89 (0.70, 1.12) | 0.96 (0.78, 1.18) | 1.05 (0.85, 1.29) | 1.00 (0.81, 1.23) | 0.90 |
| Stage | | | | | | | |
| Non-advanced | 1,210 | 88 | 415 | 420 | 277 | 245 | |
| | Ref. | 1.07 (0.85, 1.33) | 1.06 (0.92, 1.22) | 1.13 (1.00, 1.27) | 1.16 (1.01, 1.32) | 1.10 (0.96, 1.27) | 0.01 |
| Advanced | 1,228 | 69 | 266 | 302 | 218 | 263 | |
| | Ref. | 0.93 (0.73, 1.19) | 0.93 (0.79, 1.10) | 1.01 (0.88, 1.16) | 1.01 (0.87, 1.17) | 1.10 (0.96, 1.26) | 0.41 |
| Multiplicity | | | | | | | |
| 1 | 1,945 | 123 | 623 | 620 | 399 | 380 | |
| | Ref. | 0.93 (0.77, 1.12) | 1.02 (0.91, 1.14) | 1.06 (0.96, 1.17) | 1.05 (0.94, 1.18) | 1.06 (0.94, 1.18) | 0.17 |
| 2+ | 788 | 52 | 189 | 216 | 150 | 163 | |
| | Ref. | 1.09 (0.82, 1.45) | 1.01 (0.83, 1.23) | 1.07 (0.91, 1.27) | 1.03 (0.86, 1.24) | 1.07 (0.90, 1.27) | 0.34 |

[a] Adjusted for age, BMI, height, physical activity, smoking, processed and red meat, folate intake, calcium, total energy intake, aspirin use, HT duration, family history, reason for endoscopy, time period of endoscopy, number of endoscopies, and years since most recent endoscopy

OC use was positively associated with non-advanced adenomas in this cohort, but not with advanced adenomas, which are more likely to progress to colorectal cancer. Previous analyses of current HT users in this cohort identified a decreased risk [0.74 (0.55, 0.99)] for large adenomas, but no evidence of an association with small adenomas [26]. Overall, the HT literature has been fairly consistent in identifying an inverse association with adenomas, suggesting that estrogens may be involved in the development of adenomas. This may be due to HT exposure occurring closer, or even simultaneously, to the time that adenomas develop.

The mechanisms that have been proposed [33, 41–48] for how OC use could impact colorectal cancer primarily focus on different ways in which the estrogen in OCs could alter bile acid [33] or even the insulin-like growth factor pathway [47]. OCs may also protect the estrogen receptor gene from methylation [42]. There is less literature on how OCs may mechanistically impact adenomas, but one recent paper suggested that exogenous estrogens may bind to estrogen receptor beta (ER-β) acting like a selective ER-β agonist [49] and therefore prevent adenoma development.

Further exploration of the age at first OC use and time since last OC use associations is warranted. One potential hypothesis to explain our findings is that OCs may have an immediate beneficial effect, but then a long-term adverse effect. All previous analyses had considerably less follow-up, and therefore younger populations, than the current analyses. Our results suggest that any protective effect of OC use may be more pronounced among younger women who have more recent OC use, whereas OC use may no longer be protective among older women who stopped taking OCs many years before their adenomas developed. Among older women, OC use may possibly promote adenoma growth.

Our analysis was limited in its exploration of different formulations and generations of OCs. Although we could roughly examine the different generations of OCs by estimating the year of use, this was prone to exposure misclassification. Our findings pertain to past use of first- and second-generation OCs, and these include pills with progestin types that are still prescribed, such as levonorgestrel. However, many of these early OCs had estrogen doses between 50 and 150 mcg compared to current OCs which contain lower estrogen doses (20–35 mcg) [50]. We were unable to examine associations with current OC use. The NHS cohort is predominantly white and has homogenous educations and profession, which may limit our generalizability. However, due to access to the healthcare system, our study participants are more likely to seek endoscopic

screening making differential screening by OC use unlikely. It is also possible that we observed a significant finding due to testing a number of different associations. Nonetheless, our work draws from the largest cohort on this question with the longest follow-up time and greatest number of cases. Due to the longitudinal nature of the NHS cohort, we can also control for potential confounders and other hormonal exposures such as HT use across the life span that may be associated with adenomas.

In conclusion, while the association between OC use and colorectal adenomas is borderline, more recent OC use may decrease, while more distant use may slightly increase risk of adenoma. We found OC use associated with certain stages of colorectal adenomas (e.g., non-advanced), and further exploration of the age at first OC use and time since last OC use associations is warranted. Bringing more research on adenomas into the colorectal cancer literature may help illuminate etiologically relevant information that could be useful in clinical and public health settings.

**Acknowledgments** The NHS was supported by research Grants UM1CA186107 and P01CA87969 of the National Institutes of Health. BMC was supported by the Training Programs in Cancer Epidemiology (T32CA09001) from the National Cancer Institute and in Reproductive, Perinatal, and Pediatric Epidemiology (T32HD060454) as well as Grant F32HD084000 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health. WW was supported by Entertainment Foundation National Colon Cancer Research Alliance. An abstract of this work was presented at the Association for Cancer Research Annual Meeting on 7 April 2014 and the Society for Epidemiologic Research Annual Conference on 26 June 2014. We would like to thank the participants and staff of the Nurses' Health Study for their valuable contributions as well as the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, WY. The authors assume full responsibility for analyses and interpretation of these data. Also, special thanks to Scott Smith for his programming assistance.

**Compliance with ethical standards**

**Conflict of interest** The authors declare that they have no conflict of interest.

**Informed consent** Return of the questionnaires was considered informed consent.

**Research involving human participants** The study was approved by the Institutional Review Board of Brigham and Women's Hospital in Boston.

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