Lifestyle Risk Factors for Serrated Colorectal Polyps: a Systematic Review and Meta-Analysis

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Abbreviations: BMI: Body mass index; CI: Confidence intervals; CRC: Colorectal cancer; HP: Hyperplastic polyps; HRT: Hormone replacement therapy; NSAID: Non-steroidal anti-inflammatory drug; OR: Odds ratio; RR: Relative risk; SSA/P: Sessile serrated adenomas/polyps; SP: Serrated polyps; TSA: Traditional serrated adenomas.

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Author contributions: HC had the concept for the systematic review; LB, ML and HC designed and conducted the search strategy to identify included studies; LB and HC conducted data extraction; HC conducted statistical analysis; LB wrote the first draft of the manuscript; All authors edited and critically revised the final version of the manuscript.

Abstract:

Background & Aims: Certain subsets of colorectal serrated polyps (SP) have malignant potential. We performed a systematic review and meta-analysis to investigate the association between modifiable lifestyle factors and risk for SPs.

Methods: We conducted a systematic search of Medline, Embase, and Web of Science, for observational or interventional studies that contained the terms risk or risk factor, and serrated or hyperplastic, and polyps or adenomas, and colorectal (or synonymous terms), published by March 2016. Titles and abstracts of identified articles were independently reviewed by at least 2 reviewers. Adjusted relative risks (RR) and 95% CIs were combined using random effects meta-analyses to assess the risk of SP, when possible.

Results: We identified 43 studies of SP risk associated with 7 different lifestyle factors: smoking, alcohol, body fatness, diet, physical activity, medication and/or hormone replacement therapy. When we compared the highest and lowest categories of exposure, factors we found to significantly increase risk for SP included tobacco smoking (RR, 2.47; 95% CI, 2.12–2.87), alcohol intake (RR, 1.33; 95% CI, 1.17–1.52), body mass index (RR, 1.40; 95% CI, 1.22–1.61), and high intake of fat or meat. Direct associations for smoking and alcohol, but not body fat, tended to be stronger for sessile serrated adenomas/polyps than hyperplastic polyps. In contrast, factors we found to significantly decrease risks for SP included use of non-steroidal anti-inflammatory drugs (RR, 0.77; 95% CI, 0.65–0.92) or aspirin (RR, 0.81; 95% CI, 0.67–0.99), as well as high intake of folate, calcium, or fiber. No significant associations were detected between SP risk and physical activity or hormone replacement therapy.

Conclusions: Several lifestyle factors, most notably smoking and alcohol, are associated with SP risk. These findings enhance our understanding of mechanisms of SP development and indicate that risk of serrated pathway colorectal neoplasms could be reduced with lifestyle changes.

KEY WORDS: nutrition, NSAIDs, epidemiology, colon cancer

Introduction

Colorectal cancer (CRC) is a heterogeneous disease thought to result from the accumulation of various aberrant mutations in the epithelial cells lining the colorectal mucosa [1]. It is the third most common cancer in males and second most common cancer in females worldwide [2,3]. Estimates suggest that up to two thirds of CRC are attributable to major lifestyle and modifiable risk factors [4,5].

CRC arises from pre-malignant polyps, most commonly adenomatous polyps. Serrated polyps (SP) of the colorectum are a diverse group of lesions, largely distinct from adenomatous polyps, characterised morphologically by infolding of crypt epithelium. This infolding is thought to be due to a decrease in apoptosis [6] producing a characteristic "saw toothed" appearance [7] histologically. Before 2003, the vast majority of SP were classified as hyperplastic polyps (HP) [8], and were regarded by most pathologists as possessing little or no malignant potential [9]. Recent published evidence, however, has indicated that there are three distinct sub-categories of SP, most commonly classified as hyperplastic polyps (HP), sessile serrated adenomas/polyps (SSA/P) and traditional serrated adenomas (TSA) [10]. SSA/P and TSA are now understood to harbour malignant potential [11].

Historically, distinction of SSA/P from HP based on histopathological features has been fraught with uncertainty and confusion due to pathologists' unawareness of this new entity, inconsistent terminology and ambiguity over minimum diagnostic criteria for SSA/P [12]. Serrated adenocarcinomas have been noted to share morphological features of SP [13], and at least a subset of serrated adenocarcinomas have been demonstrated to arise from progression of dysplastic SSA/P.[14]. Thus we now understand that the serrated pathway is a route through which 10-30% of CRC develop [14,15]. This was supported by a recent systematic review and meta-analysis, by Gao *et al*, revealing a strong positive relationship between proximal SP and synchronous advanced neoplasia [16].

The role of various modifiable and lifestyle risk factors have been described for colorectal pathologies, most notably for colorectal adenomas [17-21]. To date, only alcohol has been evaluated

systematically with regards to SP risk and it was found that moderate and heavy alcohol intake significantly increased SP risk, by 19% and 60%, respectively [22]. That review included ten studies, however only one had analysed SSA/P separately from HP. To our knowledge, no other lifestyle factors have been analysed systematically to determine the effect on risk of serrated colorectal polyps. The relatively low prevalence of SSA/P or TSA compared with conventional adenomas also make this a suitable topic for meta-analysis, as single center studies may lack the sample size required for sufficient precision of statistical associations between lifestyle factors and risk.

The aim of this novel systematic review and meta-analysis therefore, is to evaluate modifiable and lifestyle factors and the risk of SP of the colorectum overall, and by SSA/P, TSA and HP subtypes, where possible.

Methods

Search strategy

A search of all relevant literature using the electronic databases Ovid MEDLINE (US National Library of Medicine, Bethesda, Maryland, USA), Embase (Reed Elselvier PLC, Amsterdam, Netherlands) and Web of Science (Thompson Reuters, Times Square, New York, USA) was conducted. The search encompassed all studies published from database inception to March week 1, 2016. The search strategy identified studies which contained at least one key word or Medical Subject Heading (MeSH) term from the following: risk OR risk factor(s) AND (serrated OR hyperplastic) AND (polyp(s) OR adenoma(s)) AND (colorectal OR colorectum OR colon* OR rectal OR rectum). The search terms did not include "metaplastic polyps" as a key word, due to this being outdated terminology.

Study selection

Titles and abstracts of identified articles were independently reviewed by at least two reviewers (LB and ML or HC). The following inclusion characteristics based on 'PICO(S)' criteria were agreed for screening papers:

(i) *Population*: adults aged 18 years and over, undergoing endoscopic investigation of the colorectum.

(ii) *Intervention*: Assessment of a modifiable risk factor, for example alcohol, smoking, diet, body fatness, physical activity, medications or infections.

(iii) *Comparator*: Exposure compared with non-exposure (or lower exposure) to a modifiable risk factor.

(iv) *Outcome*: Risk of serrated colorectal polyps, encompassing hyperplastic polyps (HP), sessile serrated adenomas/polyps (SSA/P) and/or traditional serrated adenomas (TSA), presented as relative risks (RR) with 95% confidence intervals (CI), or equivalent.

(v) Study design: Randomised Controlled Trials (RCTs), cohort, case-control or cross-sectional studies.

All titles and abstracts were reviewed to remove any which were apparently irrelevant to our review. Abstracts were eligible for inclusion if the above 'PICOS' criteria were fulfilled. The following exclusion criteria were also applied when reviewing studies: exclusive study populations of other co-morbidities, for example Crohn's Disease, ulcerative colitis, Barrett's oesophagus, acromegaly; studies of serrated or any other polyposis syndromes; studies of recurrent SP risk, future cancer risk and surveillance in polyp patients; studies with <30 individuals diagnosed with SP in total; studies of non-modifiable risk factors for SP, studies of diagnostic and endoscopic techniques for polyp detection; reviews. Full text articles and abstracts were reviewed to identify all relevant studies for inclusion. Bibliographies of included studies were also reviewed. Where multiple publications presented the same risk factor from a study sample, the most recent article was retained. Any discrepancies throughout were discussed and resolved by agreement.

Data extraction

Data extraction of included articles was carried out using piloted data extraction sheets. Detail information was recorded from all included studies individually regarding study design and location, population characteristics, exclusion criteria, exposure measurement, confounding factors and results. This information was reviewed by two reviewers independently (LB and HC), and is summarised in Supplementary Tables 1(a-f). A quality score was derived from applying the Newcastle Ottawa Scale [23] to case-control and cohort studies, as shown in Supplementary Table 2.

Statistical Analysis

Meta-analyses were carried out for SP risk and smoking, alcohol, body fatness, medications, physical activity, and dietary factors (including vitamin D, calcium, folate, fiber, fat and meat intakes). SP risk and medication use was conducted according to non-steroidal anti-inflammatory drugs (NSAIDs), aspirin and hormone replacement therapy (HRT) use individually. Risk estimates for each risk factor

were calculated and weighted to produce an overall pooled estimate with 95% Confidence Intervals (CI). These were produced using a random effects model to allow for the expected heterogeneity between studies. Two studies presented results by subgroups of HP type[24] or SP location[25] in the original papers – these were pooled prior to inclusion in the overall meta-analysis to avoid duplication of their respective controls. This step was not necessary where sex-specific results were presented. Direct results from RCT interventions were not combined with observational study results in meta-analyses, however results from nested case-control studies within RCTs were included. All statistical analyses were performed using Intercooled STATA version 11.2 (StataCorp 2005, College Station, Texas, USA). Heterogeneity within meta-analyses was quantified using I^2 tests. An I^2 value below 25% suggests there is low heterogeneity between the studies analysed, 50% signifies moderate heterogeneity and high heterogeneity is signified by an I^2 of 75% or over [26]. *Egger's* regression asymmetry test was applied to quantify the *P*-value for publication bias [27].

Sub-group and sensitivity analysis

Stratified analyses were carried out for studies which specified SSA/P or HP as the case group (no studies evaluated TSA only). Sensitivity analyses were carried out by systematically removing each study in turn in order to decipher its effect on the overall pooled result estimates (Supplementary Table 3 (a-f)). Additional post-hoc sensitivity/subgroup analyses were conducted by case-control or cross-sectional study design, excluding studies with adenoma patients in their comparator group, and combining studies comparing current versus never smoking only (Supplementary Table 3 (a-f).

Results

An overview of the study selection process is shown in Figure 1. A search of three databases yielded a potential n = 2,446 studies for inclusion, from which n = 43 papers remained for systematic review. Some papers reported on multiple risk factors, which included; smoking (n = 29), alcohol consumption (n = 14), body fatness (n = 20), physical activity (n = 8), patient medications (n = 12), and dietary factors (n = 15), with regards to risk of SP. Details of the included studies and their adjustments for relevant confounders are outlined in Supplementary Tables 1(a-f).

Smoking

The association between smoking and SP risk was assessed by 29 articles which reported information from 29 studies, of which 26 articles investigated HP/SP risk[24,25,28-50] and six investigated SSA/P risk [29-31,51-53]. Most studies originated from the USA, five from Europe, and five in Asian populations (Supplementary Table 1(a)).

In meta-analysis comparing the highest versus lowest exposure of smoking, a 2.5-fold increased SP risk was observed, (RR, 2.47; 95% CI, 2.12-2.87), as shown in Figure 2. The increased risk was evident for SP overall, but was stronger for SSA/P risk (RR, 3.40; 95% CI, 1.90-6.07), compared with HP risk (RR, 2.34; 95% CI, 2.00-2.73). High heterogeneity was present in all analyses, but there was no evidence of publication bias (P = 0.82). Sensitivity analysis excluding individual studies or subgroup analysis did not markedly alter associations (Supplementary Table 3(a)).

Alcohol

Alcohol intake and risk of SP was assessed by 14 articles reporting on 15 studies, of which three studies assessed SSA/P risk[29,30,53] and 13 articles reporting on 14 studies investigated HP/SP risk.[25,29,30,32,38-40,42-44,46,49,54] The majority of studies were conducted in USA populations, two from Asia and one from Germany (Supplementary Table 1(b)).

Figure 3 summarises the pooled results for studies comparing high versus low alcohol consumption and risk of SP, revealing a significant increased risk, RR, 1.33 (95% CI, 1.17-1.52) with moderate heterogeneity (I^2 = 38%). There was significant evidence of publication bias (*P* = <0.001). Risk of SSA/P when comparing high versus low alcohol intake yielded a RR of 1.85 (95% CI, 1.03-3.32), which was slightly attenuated when HP/SP risk was analysed (RR, 1.30; 95% CI, 1.15-1.48). Sensitivity analysis shows the higher result for SSA/P is not driven by the Burnett-Hartman et al study[29] (Supplementary Table 3(b)).

In addition, Omata *et al*. further investigated risk within classifications of alcoholic beverages. They reported non-significant adjusted odds ratios (OR) of 1.53, 1.19 and 0.85 for whisky, beer and sake drinkers, respectively [46].

Body fatness

Body fatness as represented by body mass index (BMI) and risk of SP was assessed by 20 studies, of which four investigated SSA/P risk [29,51,53,55] and 16 studies investigated HP/SP risk [25,29,32,35,39,42,44-48,50,54-57]. Additionally, some studies analysed SP risk according to waist size [58], waist-hip ratio/abdominal obesity [39,44,55], peri-colonic or visceral fat volume fraction [59]. The majority of studies were conducted in the USA, one in Poland, one in China and three in Taiwan (Supplementary Table 1(c)).

Meta-analyses were possible for studies investigating BMI and SP risk (Figure 4). A significant increased SP risk was observed in individuals with the highest versus lowest BMI category, RR, 1.42 (95% CI, 1.24-1.63). There was moderate heterogeneity, I^2 = 55%, and presence of publication bias (*P* = 0.002) in analysis of BMI and SP risk. The magnitude of association was similar for HP and SSA/P subtypes, although statistical significance was lost for the latter (Figure 4). Sensitivity analysis

showed similar results to main analysis, with reduced heterogeneity in case-control study meta-analyses (Supplementary Table 3(c)). One further study reported SP risk per 1 unit increase in BMI, and therefore wasn't included in high versus low BMI meta-analysis, but also reported a 2% increased SP risk per 1 unit increment [50].

When investigating SP risk and aspects of visceral adiposity, two studies found non-significant increased risks when assessing waist size [58] or waist-hip ratio [39,44], while others identified almost two-fold increased risks of HP in individuals with the highest waist-hip ratio [55], peri-colonic or visceral adipose volumes [59].

Physical activity

Eight studies investigated the risk of SP with regards to level of physical activity [29,40,42,44,49,54,55,60], of which two also investigated SSA/P risk [29,55]. All studies were conducted within the USA (Supplementary Table 1(d)). Figure 5 illustrates a non-significant decreased risk of SP with increased levels of physical activity, RR, 0.90 (95% CI, 0.78-1.03). This was consistent for SSA/P and HP subtypes (Figure 5) and in all except one sensitivity analysis (Supplementary Table 3(d)). No heterogeneity was observed between studies, nor was there evidence of publication bias (P = 0.62).

Medications

Twelve articles summarising results from one RCT[25] and 11 observational studies[29,30,40,42,44,45,47,50,54,61,62] investigated the risk of SP for individuals taking NSAIDs and/or aspirin, two of which also reported SSA/P risk [29,30], as outlined in Supplementary Table 1(e). The RCT (which was not included in meta-analyses due to the different study design) demonstrated a significant protective association for right-sided, but not left-sided, SP when taking 81mg or 325mg of aspirin compared with placebo [25]. As shown in Figure 6, significant protective effects were observed for SP development in observational studies, when combining overall use of NSAIDs (RR, 0.77; 95%CI, 0.65-

0.92) and aspirin, RR, 0.81 (95% CI, 0.67-0.99). The decreased risk was even stronger for NSAID use and SSA/P risk (Figure 6). Results were consistent across sensitivity analyses (Supplementary Table 3(e)). There was low heterogeneity and little evidence of publication bias for NSAID (*P* = 0.43) or aspirin analyses (*P* = 0.47). One study also reported a null association between SP risk and statin use [50].

Four studies reported on HRT use and SP risk [29,30,44,45], with two reporting on SSA/P risk separately from HP risk [29,30]. No significant associations were detected between HRT use and SP risk (RR, 0.99; 95% CI, 0.78-1.26; I^2=0%) or SSA/P risk (Figure 6). No publication bias was evident (*P* = 0.73).

Dietary factors

Fifteen articles published on a range of dietary factors and SP risk [25,28,32,38,40,42,44,54,55,63-68], only one of which reported SSA/P risk separately [55], as shown in Supplementary Table 1(f). One publication summarising RCTs of various supplements identified non-significant reductions in SP risk for those assigned to antioxidants or calcium, but not folate [25]. Reports from a US cohort also reported no significant associations between SP risk and antioxidant vitamin intake from foods [38].

In meta-analyses of observational studies, significant increased risks were observed for individuals consuming the highest compared with the lowest intakes of fat (RR, 1.25; 95% CI, 1.10-1.41), and red meat (RR, 1.23; 95% CI, 1.07-1.41), with associated low heterogeneity (Figure 7). The latter finding is in line with reports that processed meat also increases SP risk [32]. Reduced SP risks were detected for individuals consuming the highest compared with the lowest intakes of calcium, fiber and folate, although only the latter was significant (RR, 0.65; 95% CI, 0.49-0.85) and all estimates had moderate heterogeneity. Vitamin D intake was not associated with SP risk (Figure 7), which is in agreement with another study measuring circulating 25-hydroxyvitamin D status [63].

Other studies investigated SP risk and intake of total energy [25,38,55], carbohydrate [25,38], protein [38], magnesium [64], or fish [68] and largely reported non-significant associations, while one study demonstrated an increased risk of SP for men consuming high intakes of the polyunsaturated fatty acid, alpha-linolenic acid [66].

Discussion

This large systematic review and meta-analyses is the first, to our knowledge, to collectively investigate modifiable lifestyle factors and their influence on risk of serrated colorectal polyps. Meta-analyses revealed statistically significant increased risk of SP associated with smoking, alcohol consumption, body fatness, dietary fat and meat, with a statistically significant inverse relationship with NSAIDs and aspirin and dietary folate. The majority of studies related to HP risk; where reported, associations for SSA/P tended to be stronger than HP with the exception of body fatness. No studies reported on TSA risk. No associations were detected for physical activity or HRT use, and SP risk, while evidence was too sparse for other dietary factors to make any judgements.

There was a 2.5-fold increased risk of SP in smokers, and when risk of SSA/P was analysed, this increased to 3.4-fold increased risk. Potential mechanisms for this elevated risk may be explained on a molecular level. SP are significantly more likely to contain a *BRAF* mutation in comparison to non-SP [69]. Limsui *et al*, carried out a population-based cohort study to investigate smoking and CRC risk overall, and by mutation status. They revealed strong correlations between cigarette smoking and MSI-high, CIMP-positive and BRAF mutations [70]. These MSI-positive, CIMP-positive and/or BRAF-mutant tumours are thought to arise from SP, specifically SSA/P [44]. Smoking may increase the risk of DNA mutations within cells of the colorectal mucosa, such that malignant transformation may occur via the serrated pathway. Since tobacco smoking is also a potent risk factor for respiratory and upper gastrointestinal malignancies [71,72], it would be advisable that smokers abstain where possible, in order to reduce their risk of developing neoplasia including CRC.

Pooled analyses for alcohol intake revealed a statistically significant 33% increased risk of SP for highest versus lowest intakes. This increased to 85% for SSA/P risk specifically. Alcohol is a known risk factor for a number of cancers [73,74]. When alcohol is consumed it undergoes metabolism to acetaldehyde via alcohol dehydrogenase and cytochrome P450 2E1 (*CYP2E1*) [75,76]. These enzymes

are associated with a variety of cancers, however in normal physiology they play a role in the general detoxification of alcohol [75]. Reduced alcohol intake is recommended to reduce SP and CRC risk.

A 42% increased risk was observed when high versus low BMI and risk of SP was assessed, with other measures of body fatness also linked to increased risk. A wide range of inflammatory cytokines are produced from adipose tissue, some of which are thought to be pro-carcinogenic [77]. Individuals with high BMIs also have high levels of C-reactive protein [78], and a 2008 systematic review found a direct association between C-reactive protein and CRC risk [79]. This plausibly suggests that increasing BMI puts individuals at increased risk of developing CRC, via increased inflammation. As serrated adenocarcinoma accounts for 10-30% of all CRC it is difficult to distinguish if this increased risk is mediated through one or more colorectal pathways. Within the current systematic review, some studies used alternative measurement methods for body fatness and so further research is required using these alternative methods, particularly given suggestions that central adiposity may be of greatest importance for colorectal carcinogenesis [43,80].

Analyses for physical activity yielded a non-significant inverse risk of developing SP for highest versus lowest levels of activity. Difficulties in measuring an individual's level of physical activity may be a possible explanation. Studies using MET-hours per week showed greater strength of association [42,44], in comparison to those evaluating categorical variables such as *ever v. never* physical activity [49,81]. The lack of a significant association is surprising, given that several potential mechanisms regarding the protective role of physical activity for CRC risk have been postulated. These include enhanced immune function, lower bile acid secretions and a reduced stool transit time with increasing physical activity [82]. Perhaps the protective effect may act largely via the traditional adenoma-carcinoma pathway of CRC development, or influence the latter stages of tumorigenesis [83,84].

Use of NSAIDs and/or aspirin was associated with a significant 19-23% decreased risk of SP, corroborating results from an RCT of aspirin [25]. One included study, Noreen *et al*. found that women with SP carried a 48% increased rate of O^6-methylguanine DNA methyltransferase promoter methylation compared with women without polyps [45]. They reported a 50% suppression in DNA methylation with long-term aspirin use and concluded that regular use affects genes controlling critical pathways in cancer by stabilising DNA methylation at the promoters of these genes [45], resulting in a decreased CRC risk. Furthermore, as outlined earlier, CRC may be associated with an increase in inflammatory cytokines [79]. This provides a biological basis for the reduced risk of neoplasia with NSAID use evident in our meta-analyses. Contrary to noted protective effects of HRT for colon cancer risk [85], no associations with SP risk were observed in our meta-analysis.

Five dietary factors were determined to be significantly, or close to significantly, associated with SP risk. Dietary fat and meat intakes were linked with increased risks of SP, which correlates with evidence for adenomas and CRC [21,86]. Observed protective associations were also detected for dietary folate, and to a lesser extent, calcium and fiber, which again corroborates evidence for adenomas and CRC [21,86]. Only one dietary study reported SSA/P risk separately from HP risk, and few conclusions can be drawn from the other dietary factors investigated, but the overall findings do suggest that SP risk can be modified through dietary changes.

Although not an aim of the current review, further research needs to be conducted into the molecular epidemiology of SP, to determine the interaction between these lifestyle factors and known driver mutations involved in the serrated pathway. Several studies have investigated SP risk in relation to genetic variants linked to the metabolism of the risk factors outlined such as alcohol [87], smoking [88],body fatness [81] and diet [28,54,64]. However, only one study has investigated known CRC mutations – *APC, KRAS* and *MSI* interactions with lifestyle factors (namely, smoking status) and SP risk, and found that such mutations were only present in HP patients who smoked, and were not

seen in non-smokers [41]. Expansion of knowledge of such interactions would further aid prevention strategies for SP and serrated pathway CRC.

Our systematic review has many strengths, including its large size, and comprehensive inclusion of different modifiable lifestyle risk factors have been investigated systematically. Novel meta-analyses were carried out, with several yielding statistically significant results. All papers were reviewed by at least two independent reviewers and the use of three large databases ensured a large international collection of papers undergoing review. No language restrictions were applied in order to reduce any potential selection bias.

This systematic review has some limitations, especially regarding classifications used for SP. As histological sub-typing of SP is relatively new in the area of diagnostics, many earlier papers are likely to have SSA/P classified as HP. Accurate classification is dependent on awareness by the reporting pathologist and on robust diagnostic criteria in practice at the time of reporting. It is therefore impossible within this review to accurately assess if publications using 'hyperplastic polyps' as a case/control group solely include HP. As summarised in Supplementary Table 4, year of publication or recruitment period, pathologist review, or quality of colonoscopy reported did not clearly distinguish between SP sub-types in the majority of publications in the HP/unspecified SP analyses. However, the proportion of SSA/P cases within these overall groupings is likely to be small, as HP have much higher overall prevalence, and we still observe evidence that magnitudes and directions of associations differ between SSA/P only meta-analyses, and the HP/unspecified SP meta-analyses, at least for smoking and alcohol. Furthermore, we are confident that our SSA/P only meta-analyses do not include HP cases. A second potential limitation is the assessment methods used by the research groups. Some used only sigmoidoscopy to investigate the colon. SSA/P are typically located in the proximal colon and so these proximal polyps may be missed if only sigmoidoscopy, rather than full colonoscopy, has been performed. Again this is a potential area where detection bias could have

been introduced within individual studies, and SSA/P risk may be underestimated. Some meta-analyses also showed indications of publication bias (for alcohol and BMI) and heterogeneity (for smoking and BMI), reflecting a need for further studies of lifestyle factors and SP risk.

In conclusion, this large comprehensive systematic review has revealed statistically significant increases in risk of SP with smoking, alcohol intake, high body fatness, red meat and fat intakes. Direct associations for smoking and alcohol, but not body fatness, tended to be stronger for SSA/P than HP. There were significant decreased risks of SP with use of aspirin and NSAIDs, and dietary folate. There is a need for further studies to be carried out investigating SP risk in the setting of high quality colonoscopy and applying internationally agreed nomenclature and definitions [89]. Future molecular epidemiology studies are also warranted to investigate the underlying pathways linking these lifestyle factors in serrated carcinogenesis. Our results strengthen public health messages promoting awareness and change in order to reduce the risk of these precancerous lesions and consequently CRC.

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Author names in bold designate shared co-first authorship.

Figure Legends.

Figure 2 Legend. HPFUS: Health Professionals Follow-Up study; NHS: Nurses Health study.

Figure 3 Legend. HPFUS: Health Professionals Follow-Up study; NHS: Nurses Health study.

Figure 4 Legend. BMI: Body mass index.

Figure 6 Legend. HRT: Hormone Replacement Therapy; NSAID: Non-steroidal anti-inflammatory drug. One further Randomised Controlled Trial (which was not included in meta-analyses due to the different study design) also demonstrated a significant 42% reduced risk for right-sided, but not left-sided, SP when taking 81mg or 325mg of aspirin compared with placebo (Wallace et al, 2009).

Figure 7 Legend. HPFUS: Health Professionals Follow-Up study; NHS: Nurses Health study.
All studies reported dietary intakes comparing highest v. lowest tertile, quartile or quintile of intake, with the exceptions of Lieberman et al, which is presented per 100-International Unit increment of vitamin D intake and per 1g increment of fat and fiber intakes, and Burnett-Hartman et al, which compared ≥3 v. 0 servings red meat/week.

Figure 1. Flow diagram of the study selection process.

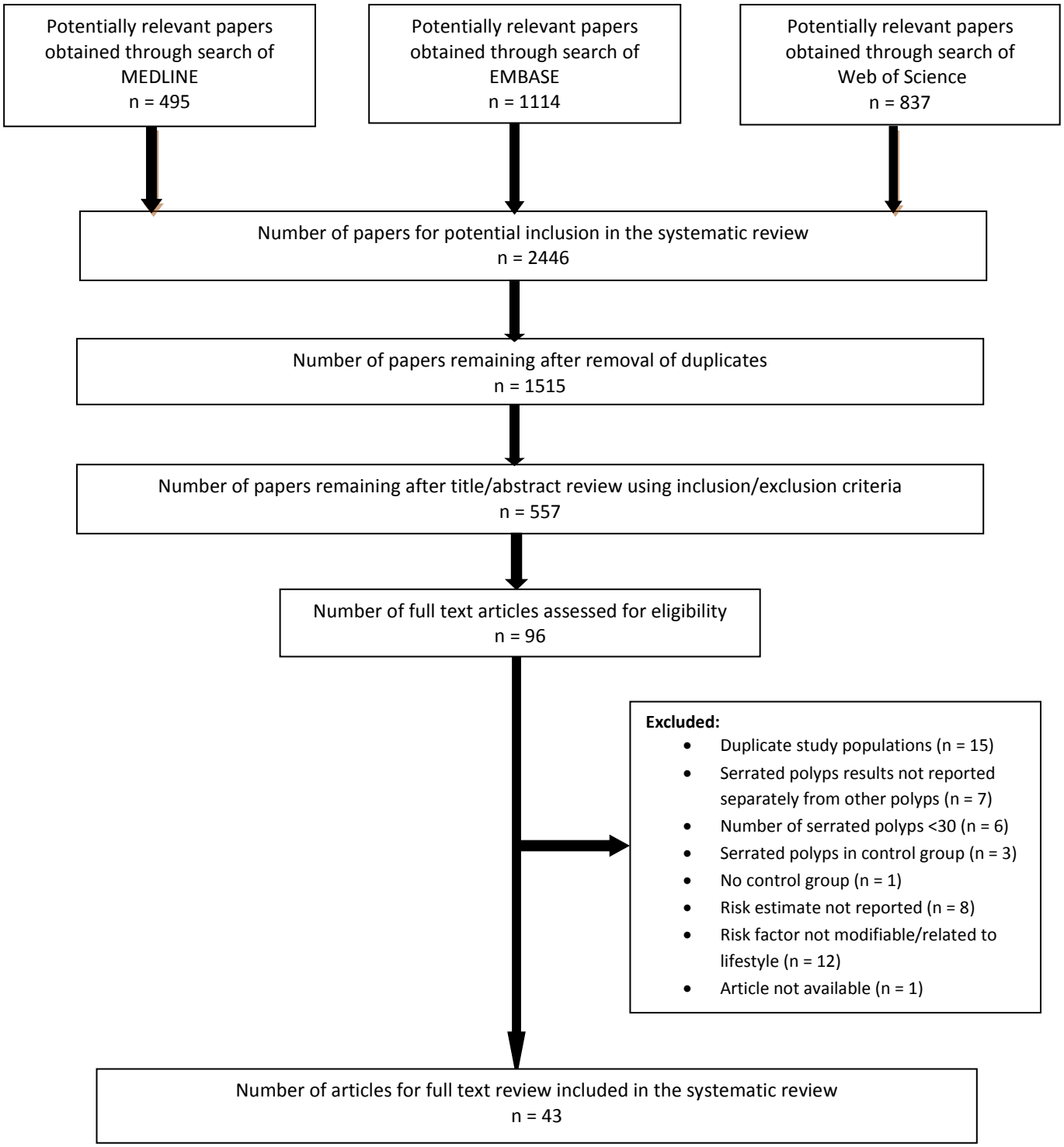
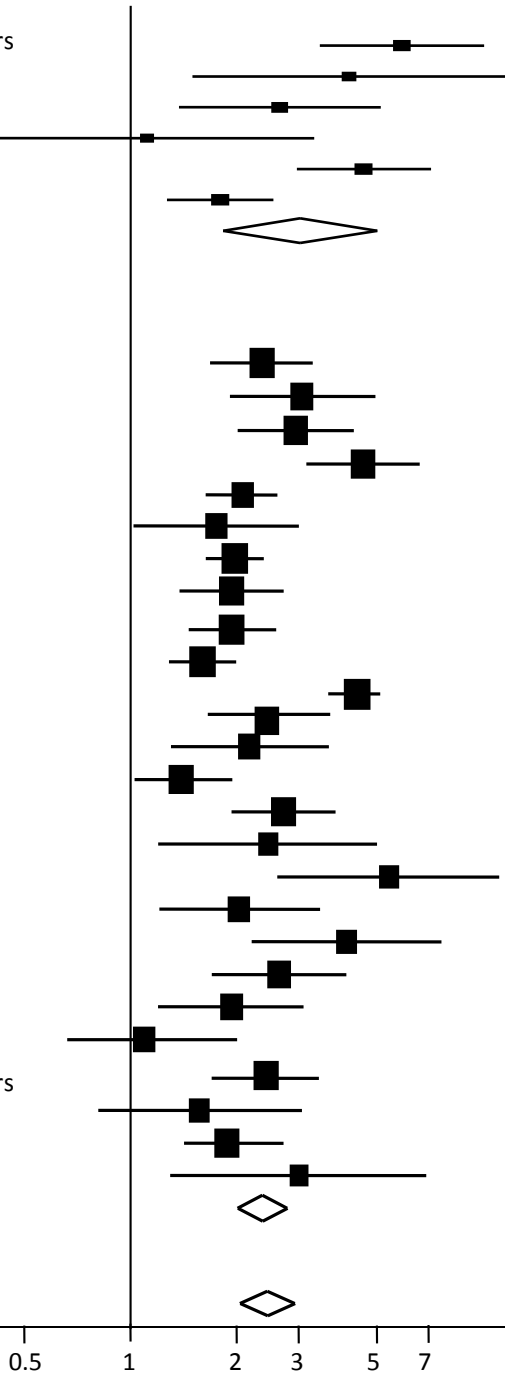


Figure 2. Forest plot of highest v. lowest category of smoking and serrated polyp risk.

Study-year	Smoking exposure comparison High/Low	Relative risk (95 percent CI)	Relative weight (percent)
Sessile serrated adenomas/polyps			
Anderson (2011)	Ever/Never ≥20 pack-yrs	7.31 (3.92-13.63)	18.7
Buda (2012)	Current/Never	4.90 (1.50-16.40)	11.8
Burnett-Hartman (2013)	Current/Never	2.91 (1.36-6.21)	16.9
Crockett (2014)	Current/Never	1.07 (0.30-3.78)	11.2
Davenport (2014)	Current/Never	5.50 (3.33-9.08)	20.1
Randles (2015)	Current/Never	1.86 (1.25-2.77)	21.3
Overall*		**3.40 (1.90-6.07)**	100
Hyperplastic/serrated polyps			
Burnett-Hartman (2011)	Current/Never	2.36 (1.69-3.30)	4.4
Burnett-Hartman (2013)	Current/Never	3.08 (1.91-4.96)	3.6
Crockett (2014)	Current/Never	2.95 (2.02-4.30)	4.1
Davenport (2014)	Current/Never	4.58 (3.16-6.64)	4.2
Drew (2016)	Current/Not current	2.02 (1.58-2.58)	4.8
Erhardt (2002)	Ever/Never	1.79 (1.04-3.06)	3.3
Figueiredo (2015)	Current/Never	2.01 (1.66-2.44)	5.1
Hassan (2010)	Ever/Never	1.98 (1.41-2.78)	4.3
Hirai (2013)	Ever/Never	1.98 (1.49-2.65)	4.6
Hoffmeister (2010)	Current/Never	1.63 (1.31-2.03)	4.9
Ji (2006)	Current/Never	4.40 (3.70-5.20)	5.1
Kearney, NHS (1995)	≥15cig-d/Never	2.44 (1.63-3.65)	4.0
Kearney, HPFUS (1995)	≥15cig-d/Never	2.14 (1.28-3.59)	3.4
Lai (2013)	Current/Not current	1.40 (1.02-1.93)	4.4
Lieberman (2003)	Current/Never	2.71 (1.93- 3.81)	4.3
Martinez (1997)	Current/Never	2.45 (1.20-4.98)	2.5
Martinez (2011)	Ever/Never	5.40 (2.60-11.10)	2.5
Michal (2012)	Current/Never	2.04 (1.21-3.44)	3.4
Morimoto (2002)	Current/Never	4.10 (2.20-7.60)	2.9
Noreen (2014)	≥20 pack-yrs/Never	2.67 (1.72-4.15)	3.8
Omata (2009)	Current/Never	1.95 (1.21-3.12)	3.6
Oza (2014)	Current/Not current	1.10 (0.66-2.00)	3.2
Qazi (2013)	Ever/Never ≥20 pack-yrs	2.42 (1.70-3.43)	4.3
Wallace (2009)	Current/Never	1.57 (0.81-3.06)	2.7
Wang (2014)	Current/Never	1.87 (1.42-2.71)	4.4
Yoshida (2006)	Current/Not current	3.00 (1.30-6.90)	2.1
Overall**		**2.34 (2.00-2.73)**	100
All serrated polyps			
Overall***		**2.47 (2.12-2.87)**	



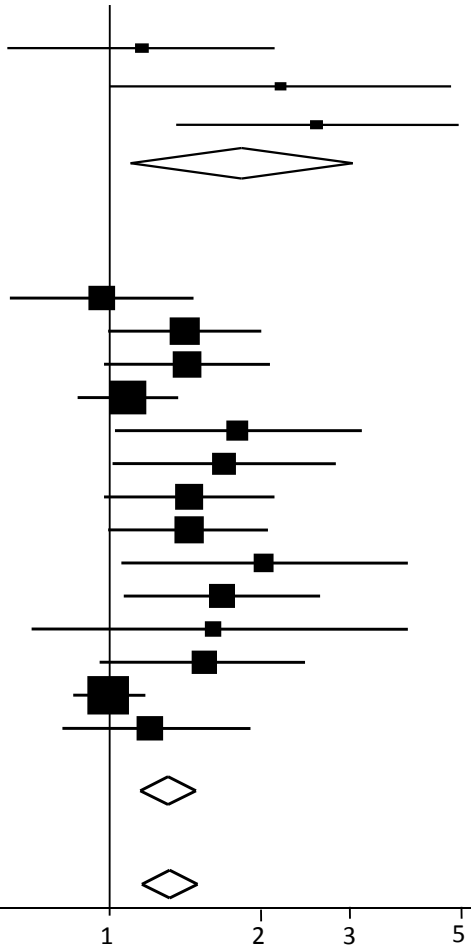
* Test for heterogeneity: I^2 = 77 percent, P = 0.001

** Test for heterogeneity: I^2 = 78 percent, P <0.001

*** Test for heterogeneity: I^2 = 79 percent, P <0.001, Crockett et al SSA/P results excluded due to overlap with HP/SP results.

Figure 3. Forest plot of highest v. lowest category of alcohol intake and serrated polyp risk.

Study-year	Alcohol exposure comparison High/Low	Relative risk (95 percent CI)	Relative weight (percent)
Sessile serrated adenomas/polyps			
Burnett-Hartman (2013)	≥14 v. <1 drink/week	1.09 (0.54-2.20)	37.2
Crockett (2014)	Quartile 4/Quartile 1	2.27 (0.92-5.58)	27.8
Randles (2015)	≥ v. <2 (men) or 1 (women) drink/day	2.75 (1.31-5.80)	35.0
Overall*		**1.85 (1.03-3.32)**	100
Hyperplastic/serrated polyps			
Burnett-Hartman (2013)	≥14 v. <1 drink/week	0.96 (0.63-1.46)	6.6
Crockett (2014)	Quartile 4/Quartile 1	1.40 (0.99-1.99)	8.4
Erhardt (2002)	>7 v. ≤ 7 g/d	1.42 (0.97-2.07)	7.6
Fu (2012)	Current/Never regular	1.08 (0.86-1.36)	13.3
Kearney, NHS (1995)	>30 v. 0 g/d	1.79 (1.02-3.15)	4.2
Kearney, HPFUS (1995)	>30 v. 0 g/d	1.69 (1.01-2.80)	4.9
Lai (2011)	Habitual/Non-drinker	1.43 (0.97-2.11)	7.3
Lieberman (2003)	>7 drinks/week v Never	1.43 (0.99-2.06)	8.0
Martinez (1997)	>9.4 v. 0 g/d	2.02 (1.05-3.91)	3.2
Michal (2012)	Regular/Unspecified	1.66 (1.06-2.61)	5.9
Morimoto (2002)	≥8 v. 0 g/d	1.60 (0.70-3.90)	2.0
Omata (2009)	Drinker/Non-drinker	1.53 (0.95-2.44)	5.6
Wallace (2009)	Drinker/Non-drinker	0.99 (0.84-1.17)	16.8
Yoshida (2006)	≥5 v. <5 drinking occasions/week	1.20 (0.80-1.90)	6.4
Overall**		**1.30 (1.15-1.48)**	100
All serrated polyps			
Overall***		**1.33 (1.17-1.52)**	



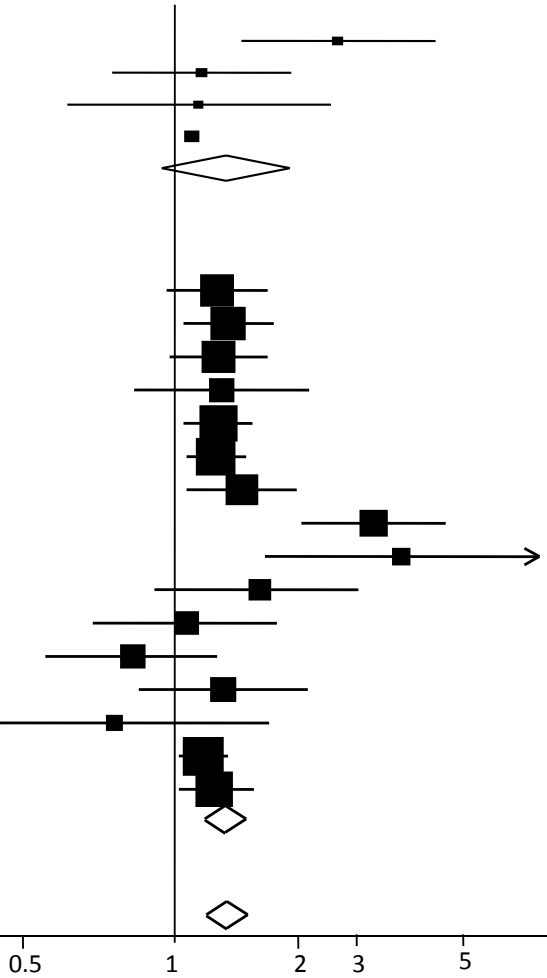
* Test for heterogeneity: I^2 = 41 percent, P = 0.18

** Test for heterogeneity: I^2 = 34 percent, P = 0.10

*** Test for heterogeneity: I^2 = 38 percent, P = 0.06, Crockett et al SSA/P results excluded due to overlap with HP/SP results.

Figure 4. Forest plot of highest v. lowest category of body mass index and serrated polyp risk.

Study-year	BMI exposure comparison High/Low	Relative risk (95 percent CI)	Relative weight (percent)
Sessile serrated adenomas/polyps			
Anderson (2011)	≥30 v. Unspecified	2.57 (1.44-4.62)	21.2
Burnett-Hartman (2013)	≥30 v. <25	1.13 (0.66-1.94)	22.8
Crockett (2015)	≥30 v. <25	1.11 (0.50-2.45)	15.0
Randles (2015)	Unspecified	1.06 (1.02-1.11)	41.0
Overall*		**1.31 (0.89-1.92)**	100
Hyperplastic/serrated polyps			
Burnett-Hartman (2013)	≥30 v. <25	1.35 (0.97-1.88)	7.6
Butterly (2014)	≥35 v. <25	1.45 (1.08-1.95)	8.3
Crockett (2015)	≥30 v. <25	1.36 (0.99-1.88)	7.8
Erhardt (2002)	>24 v. ≤24	1.39 (0.79-2.46)	4.0
Fu (2012)	≥30 v. 18-<25	1.36 (1.08-1.70)	10.0
Hirai (2013)	≥25 v. <25	1.34 (1.10-1.64)	10.7
Lai (2011)	≥27 v. <27	1.59 (1.10-2.28)	7.0
Leitzmann (2009)	≥30 v. <25	3.76 (2.35-6.01)	5.2
Martinez (1997)	>29.8 v. <23.4	4.50 (1.84-10.97)	2.0
Morimoto, males (2002)	>29.7 v. <24.2	1.79 (0.90-3.40)	3.2
Morimoto, females (2002)	>29.9 v. <22.7	1.10 (0.60-2.00)	3.7
Noreen (2014)	>30 v. 18.5-25	0.78 (0.44-1.35)	4.1
Omata (2009)	>25 v. <22	1.41 (0.81-2.44)	4.2
Oza et al (2014)	≥30 v. <25	0.69 (0.25-1.90)	1.6
Wallace et al (2009)	≥30 v. <25	1.23 (1.05-1.45)	11.5
Wang et al (2014)	≥25 v. <25	1.32 (1.05- 1.71)	9.5
Overall**		**1.42 (1.24-1.63)**	100
All serrated polyps			
Overall***		**1.40 (1.22-1.61)**	



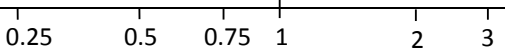
* Test for heterogeneity: I^2 = 66 percent, P = 0.03

** Test for heterogeneity: I^2 = 55 percent, P = 0.04

*** Test for heterogeneity: I^2 = 75 percent, P <0.001, Crockett et al SSA/P results excluded due to overlap with HP/SP results.

Figure 5. Forest plot of highest v. lowest category of physical activity and serrated polyp risk.

Study-year	Physical activity exposure comparison High/Low	Relative risk (95 percent CI)	Relative weight (percent)
Sessile serrated adenomas/polyps			
Burnett-Hartman (2013)	≥6 v. 0 hrs/wk	0.86 (0.39-1.87)	61.9
Crockett (2015)	Quartile 4/Quartile 1	0.71 (0.26-1.91)	38.1
Overall*		**0.80 (0.43-1.48)**	100
Hyperplastic/serrated polyps			
Burnett-Hartman (2013)	≥6 v 0 hrs/wk	0.82 (0.51-1.31)	8.4
Crockett (2015)	Quartile 4/Quartile 1	0.98 (0.67-1.43)	12.8
Fu (2012)	>20 v. <1MET-hr/wk	0.89 (0.68-1.17)	24.5
Lieberman (2003)	>36 v. 24-28 index	0.82 (0.60-1.10)	19.9
Martinez (1997)	≥2205 v. <600 kcal/wk	0.55 (0.25-1.19)	3.0
Morimoto, males (2002)	>47 v. <12.3 MET-hr/wk	0.70 (0.30-1.20)	3.9
Morimoto, females (2002)	>41.2 v. <11 MET-hr/wk	1.70 (0.90-3.20)	4.6
Wallace (2005)	>335 v. <263 MET-hr/wk	1.04 (0.73-1.49)	14.7
Yoshida (2006)	≥3 v. <3 activity occasions/week	0.80 (0.50-1.30)	8.2
Overall**		**0.90 (0.78-1.03)**	100
All serrated polyps			
Overall***		**0.90 (0.78-1.03)**	



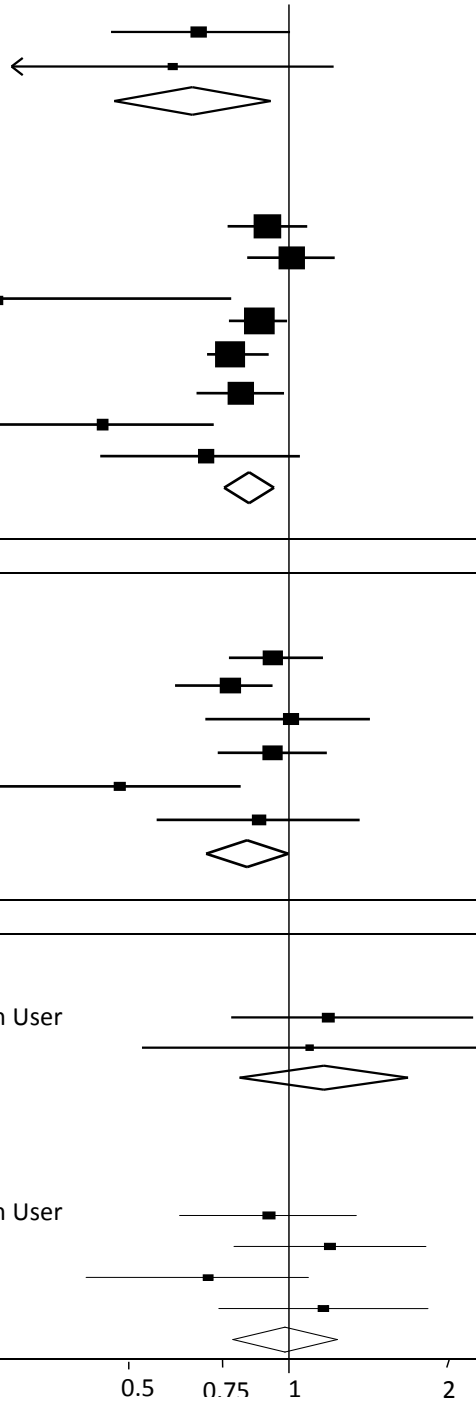
* Test for heterogeneity: I^2 = 0 percent, P = 0.77

** Test for heterogeneity: I^2 = 0 percent , P = 0.48

*** Test for heterogeneity: I^2 = 0 percent , P = 0.58, Crockett et al SSA/P results excluded due to overlap with HP/SP results.

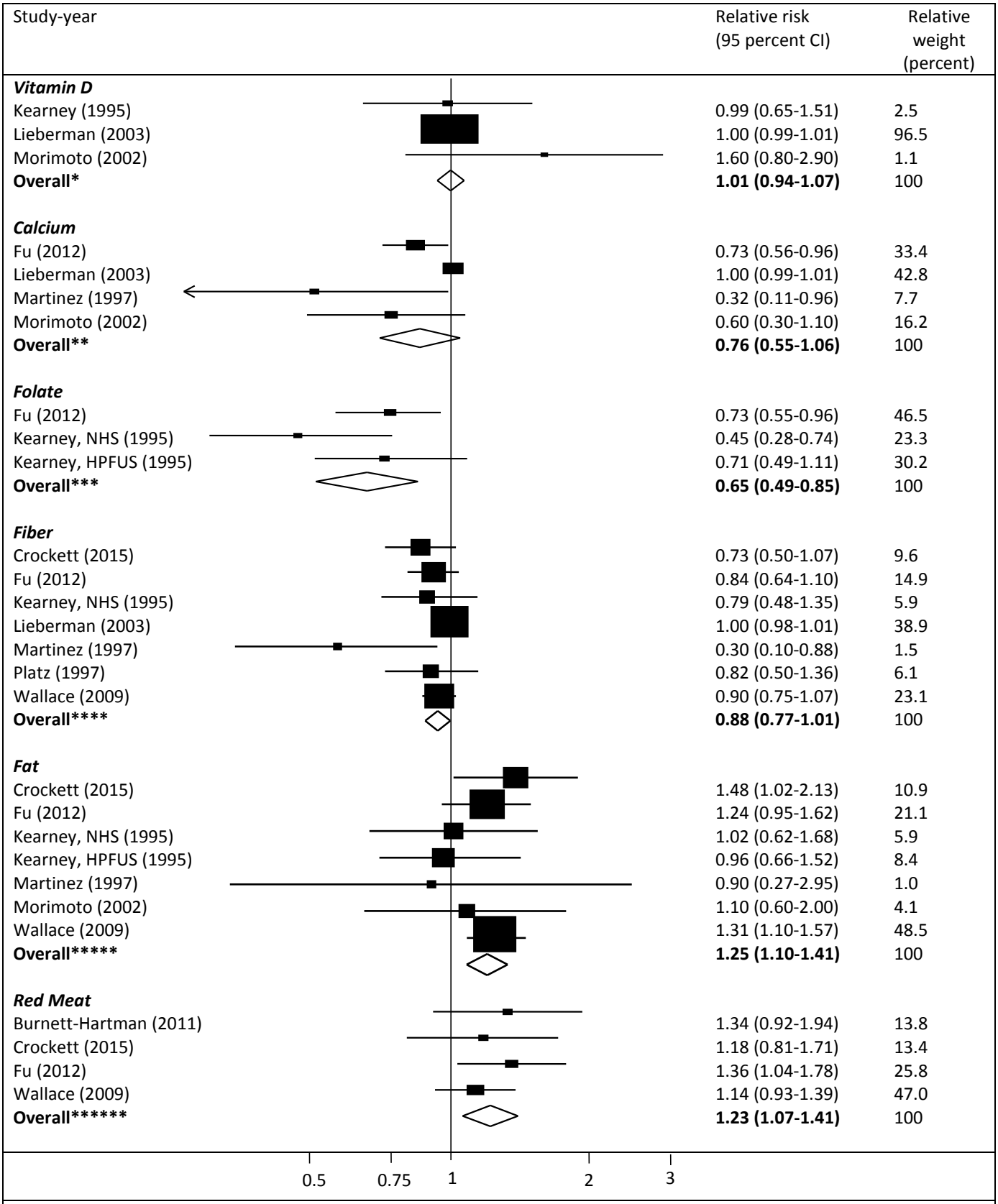
Figure 6. Forest plot of highest v. lowest category of medication use and serrated polyp risk.

Study-year	Medication exposure comparison High/Low	Relative risk (95 percent CI)	Relative weight (percent)
NSAIDs			
Sessile serrated adenomas/polyps			
Burnett-Hartman (2013)	Current/Never	0.64 (0.41-1.01)	76.4
Crockett (2014)	Regular user/Unspecified	0.56 (0.25-1.26)	23.6
Overall*		**0.62 (0.42-0.92)**	100
Hyperplastic/serrated polyps			
Burnett-Hartman (2013)	Current/Never	0.90 (0.69-1.16)	17.1
Crockett (2015)	Regular user/Unspecified	1.04 (0.78-1.38)	16.0
Drew (2016)	User/Non-user	0.10 (0.01-0.77)	0.7
Fu (2012)	Current/Never	0.84 (0.69-1.01)	20.6
Johnson (2010)	>60 v. <4 tablets/month	0.70 (0.60-0.90)	20.1
Lieberman (2003)	≥Daily v. Never user	0.75 (0.56-0.99)	16.0
Martinez (1997)	Use ≥7 v. <7 times/wk	0.29 (0.12-0.67)	3.7
Morimoto (2002)	Regular/Non-user	0.60 (0.30-1.10)	5.9
Overall**		**0.77 (0.65-0.92)**	100
Aspirin			
Hyperplastic/serrated polyps			
Drew (2016)	User/Non-user	0.92 (0.72-1.17)	28.6
Johnson (2010)	>60 v. <4 tablets/month	0.70 (0.50-0.90)	24.1
Morimoto (2002)	Regular/Non-user	1.00 (0.60-1.60)	12.0
Murff (2011)	Regular/Non-user	0.90 (0.65-1.25)	21.2
Noreen (2014)	≥2 years Use/Non-user	0.36 (0.16-0.74)	5.7
Oza (2014)	User/Non-user	0.83 (0.45-1.50)	8.5
Overall***		**0.81 (0.67-0.99)**	100
HRT			
Sessile serrated adenomas/polyps			
Burnett-Hartman (2013)	Postmenopausal Ever/Non User	1.45 (0.78-2.69)	75.2
Crockett (2014)	User/Non-user	1.29 (0.44-3.80)	24.8
Overall****		**1.41 (0.82-2.41)**	100
Hyperplastic/serrated polyps			
Burnett-Hartman (2013)	Postmenopausal Ever/Non User	0.92 (0.61-1.38)	30.6
Crockett (2015)	User/Non-user	1.22 (0.79-1.89)	26.5
Morimoto (2002)	Ever/Never User	0.70 (0.40-1.10)	20.3
Noreen (2014)	Ever age >50/Non User	1.19 (0.73-1.92)	22.6
Overall*****		**0.99 (0.78-1.26)**	100



* Test for heterogeneity: I^2 = 0 percent, *P* = 0.78
** Test for heterogeneity: I^2 = 56 percent, *P* = 0.03
*** Test for heterogeneity: I^2 = 33 percent, *P* = 0.19
**** Test for heterogeneity: I^2 = 0 percent, *P* = 0.85
***** Test for heterogeneity: I^2 = 0 percent, *P* = 0.34

Figure 7. Forest plot of highest v. lowest category of dietary intakes and serrated polyp risk.



* Test for heterogeneity: I^2 = 4 percent, P = 0.36
** Test for heterogeneity: I^2 = 74 percent, P = 0.009
*** Test for heterogeneity: I^2 = 35 percent, P = 0.21
**** Test for heterogeneity: I^2 = 48 percent, P = 0.07
***** Test for heterogeneity: I^2 = 0 percent, P = 0.72
****** Test for heterogeneity: I^2 = 0 percent, P = 0.72

Table 1 (a). Characteristics of studies investigating smoking and the development of serrated colorectal adenomas/polyps.

Study-year-location	Study design	Cases	Controls /cohort size	Study population	Comparison of population	Smoking Assessment method	Adjusted confounders												
							Age	Sex	Race	Alcohol	BMI	Phys activity	Diet	Diabetes	Study site	Education	Family Hx	NSAID use	HRT use
SESSILE SERRATED ADENOMA/POLYPS																			
Anderson et al (2011) USA	Cross-sectional study	90	200	Screening participants undergoing colonoscopy	SSA v. No polyps	Medical record review	✓				✓								
Buda et al (2012) Italy	Hospital-based case control	23*	258	Symptomatic and screening patient undergoing colonoscopy	SSA v. No polyps	Not reported	✓	✓											
Burnett-Hartman et al (2013) USA	Hospital-based case-control	149	1037	Patients undergoing index colonoscopy for any indication	SSA v. No polyps	Interviewed Questionnaire	✓	✓	✓	✓	✓	✓				✓	✓	✓	✓
Crockett et al (2014) USA	Pooled data from cross-sectional studies	39	1316	Patients undergoing colonoscopy	SSA v No polyps	Standardised interview	✓	✓											
Davenport et al (2014) USA	Hospital-based case control	139	4402	Patients undergoing colonoscopy	SSA v. No polyps	Telephone survey	✓	✓						✓	✓	✓			
Randles et al (2015) USA	Hospital-based case-control	157	Not reported	Symptomatic and screening patients undergoing colonoscopy	SSA v. No polyps	Not reported	✓		✓	✓	✓								
HYPERPLASTIC POLYPS/SERRATED POLYPS UNSPECIFIED																			
Burnett-Hartman et al (2011) USA	Hospital-based case-control	691	772	Patients undergoing colonoscopy for any indication	HP v. No polyps	Telephone interview	✓	✓	✓	✓	✓		✓			✓		✓	✓
Burnett-Hartman et al (2013) USA	Hospital-based case-control	431	1037	Patients undergoing index colonoscopy for any indication	SP v. No polyps	Interviewed Questionnaire	✓	✓	✓	✓	✓	✓				✓	✓	✓	✓
Crockett et al (2014) USA	Pooled data from cross-sectional studies	311	1316	Patients undergoing colonoscopy	SP v No polyps	Standardised interview	✓	✓											
Davenport et al (2014) USA	Hospital-based case control	265	4402	Patients undergoing colonoscopy	HP v. No polyps	Telephone survey	✓	✓						✓	✓	✓			

Table 1 (a) continued. Characteristics of studies investigating smoking and the development of serrated colorectal adenomas/polyps.

Study-year-location	Study design	Cases	Controls /cohort size	Study population	Comparison of population	Smoking Assessment method	Adjusted confounders												
							Age	Sex	Race	Alcohol	BMI	Phys activity	Diet	Diabetes	Study site	Education	Family Hx	NSAID use	HRT use
HYPERPLASTIC POLYPS/SERRATED POLYPS UNSPECIFIED																			
Drew et al (2016) USA	Cross-sectional study	1076	1646	Patients undergoing colonoscopy	SP v. No polyps	Routine interview	✓	✓			✓						✓	✓	
Erhardt et al (2002) Germany	Hospital-based case-control	71	224	Patients undergoing colonoscopy	HP v. No polyps	Interview	✓		✓				✓						
Figueiredo et al (2015) USA	Nested case-control study in RCT	633	2667	Patients with history of conventional adenomas undergoing colonoscopy	SP v. No SP	Questionnaire	✓	✓							✓				
Hassan et al (2010) USA	Cross-sectional study in RCT	157	786	Screening participants undergoing CTC and colonoscopy	HP v. No polyps	Questionnaire	#	#		#	#								
Hirai et al (2013) China	Cross-sectional study	532	3647	Patients who had complete colonoscopy	HP/SP v. No polyps	Not reported	✓												
Hoffmeister et al (2010) Germany	Population-based case-control	654	1846	Screening participants undergoing colonoscopy	HP v. No polyps	Self-reported questionnaire	✓	✓			✓	✓	✓			✓	✓		✓
Ji et al (2006) USA	Nested case-control study in RCT	1545	33667	Screening arm of PLCO Trial, participants undergoing sigmoidoscopy	HP v. No polyps	Self-reported questionnaire	✓	✓		✓	#	#	✓		✓	✓	#		
Kearney et al (1995) USA	Cohort studies: NHS HPFUS	 175 219	 15984 12922	Participants who had undergone sigmoidoscopy/colonoscopy within follow-up period	HP v. No polyps	Mailed questionnaire	✓	#					✓				✓		
Lai et al (2013) Taiwan	Cross-sectional study	243	3759	Self-referred patients undergoing flexible sigmoidoscopy	HP v. No polyps	Questionnaire	✓	✓		✓				✓					
Lieberman et al (2003) USA	Cross-sectional study	391	1441	Asymptomatic patients from 13 Veteran Affairs medical centres undergoing colonoscopy	HP v. No polyps	Clinical survey	✓			✓	✓	✓	✓				✓	✓	
Martinez et al (1997) USA	Cross-sectional study	81	480	Patients undergoing endoscopy	HP v. No polyps	Personal interview	✓	✓	✓	✓	✓							✓	

Table 1 (a) continued. Characteristics of studies investigating smoking and the development of serrated colorectal adenomas/polyps.

Study-year-location	Study design	Cases	Controls /cohort size	Study population	Comparison of population	Smoking Assessment method	Adjusted confounders												
							Age	Sex	Race	Alcohol	BMI	Phys activity	Diet	Diabetes	Study site	Education	Family Hx	NSAID use	HRT use
HYPERPLASTIC POLYPS/SERRATED POLYPS UNSPECIFIED																			
Martinez et al (2011) Spain	Cross-sectional study	90	436	Screening participants (males) undergoing colonoscopy.	HP v. No polyps	Questionnaire	✓	#					✓						
Michal et al (2012) USA	Hospital-based case-control	215	963	Participants undergoing screening colonoscopy	HP v. No polyps	Computer-assisted interview	Not reported – did state multivariate analysis.												
Morimoto et al (2002) USA	Hospital-based case-control	219	708	Symptomatic and screening patient undergoing colonoscopy	HP v. No polyps	Self-administered questionnaire	✓	✓	✓	✓	✓	✓	✓					✓	✓
Noreen et al (2014) Poland	Population-based case-control	106	440	Screening participants (females) undergoing colonoscopy	HP/SSA v. No polyps	Self-administered questionnaire	✓	#			✓							✓	✓
Omata et al (2009) Japan	Hospital-based case-control	132	586	Patients undergoing full colonoscopy	HP v. No polyps	Questionnaire	✓												
Oza et al (2014) Not reported	Hospital-based case-control	53**	1041	Screening patients undergoing colonoscopy	PSP v. No PSP	Medical record review		✓											
Qazi et al (2013) USA	Hospital-based case-control	397	1983	Screening participants undergoing colonoscopy	HP v. No polyps	38-item survey	Not reported – did state multivariate analysis.												
Wallace et al (2009) USA	Nested case-control study within RCTs***	812	2018	Patients with history of colorectal adenoma and undergoing surveillance colonoscopy	HP/SSA v. No polyps	Questionnaire	✓	✓	#	#	#	#	#	#	✓	#	#	#	#
Wang et al (2014) Taiwan	Cross-sectional study	210	1379	Asymptomatic participants undergoing colonoscopy	HP v. No HP	Interview	✓			✓	✓	#	#			#	#	#	
Yoshida et al (2006) Japan	Hospital-based case-control	35	183	Symptomatic patients undergoing colonoscopy	HP v. No polyps	Questionnaire	✓	✓		✓									

Adjusted confounders: Age; Sex; Race; Alcohol; BMI: Body mass index; Phys activity: Physical activity; Diet: any aspect of dietary intake; Diabetes; Study site; Education; Family Hx: Family history; NSAID use: Non-steroidal anti-inflammatory drug use; HRT use: Hormone replacement therapy use.

Abbreviations: FFQ: Food frequency questionnaire; HP: Hyperplastic polyps; HPFUS: Health Professionals Follow Up Study; NHS: Nurses Health Study; PSP: Proximal serrated polyp; RCT: Randomised Controlled Trial; SSA : Sessile Serrated Adenomas.

* Buda et al did include >30 serrated polyps including hyperplastic polyps and therefore met inclusion criteria, but only reported results for sessile serrated adenomas.

** Oza et al case numbers estimated from polyp detection rates.

***Wallace et al included pooled data from three separate placebo-controlled randomised controlled trials of antioxidants, calcium, or aspirin/folate supplements.

#: Confounder tested for but not included in model or confounder not applicable due to homogenous study population or randomisation.

Table 1 (b). Characteristics of studies investigating alcohol and the development of serrated colorectal adenomas/polyps.

Study-year-location	Study design	Cases	Controls /cohort size	Study population	Comparison of population	Alcohol Assessment method	Adjusted confounders												
							Age	Race	Sex	Smoking	BMI	Phys activity	Diet	Diabetes	Study site	Education	Family Hx	NSAID use	HRT use
SESSILE SERRATED ADENOMA/POLYPS																			
Burnett-Hartman et al (2013) USA	Hospital-based case-control	149	1037	Patients undergoing index colonoscopy for any indication	SSA v. No polyps	Interviewed Questionnaire	✓	✓	✓	✓	✓	✓				✓	✓	✓	✓
Crockett et al (2014) USA	Pooled data from cross-sectional studies	39	1316	Patients undergoing colonoscopy	SSA v No polyps	Standardised interview	✓		✓										
Randles et al (2015) USA	Hospital-based case-control	157	Not reported	Symptomatic and screening patient undergoing colonoscopy	SSA v. No polyps	Not reported	✓		✓	✓	✓								
HYPERPLASTIC POLYPS/SERRATED POLYPS UNSPECIFIED																			
Burnett-Hartman et al (2013) USA	Hospital-based case-control	431	1037	Patients undergoing index colonoscopy for any indication	SP v. No polyps	Questionnaire	✓	✓	✓	✓	✓	✓				✓	✓	✓	✓
Crockett et al (2014) USA (2)	Pooled data from cross-sectional studies	311	1316	Patients undergoing colonoscopy	SP v No polyps	Standardised interview	✓		✓										
Erhardt et al (2002) Germany	Hospital-based case-control	71	224	Patients undergoing colonoscopy	HP v. No polyps	Interview	✓	✓					✓						
Fu et al (2012) USA	Hospital based case-control	662	3,764	Symptomatic and screening patients undergoing colonoscopy	HP v. No polyps	Telephone survey	✓	✓	✓	✓					✓	✓		✓	
Kearney et al (1995) USA	Cohort studies: NHS HPFUS	 175 219	 15984 12922	Participants who had undergone sigmoidoscopy/colonoscopy within follow-up period	HP v. No polyps	Mailed questionnaires and FFQs	✓		#	✓			✓				✓		
Lai et al (2010) Taiwan	Cross-sectional study	243	3759	Self-referred patients undergoing flexible sigmoidoscopy.	HP v. No polyps	Questionnaire	✓		✓	#				✓					
Lieberman et al (2003) USA	Hospital-based case-control	391	1441	Asymptomatic participants undergoing colonoscopy	HP v. No polyps	Questionnaire	✓												

Table 1 (b) continued. Characteristics of studies investigating alcohol and the development of serrated colorectal adenomas/polyps.

Study-year-location	Study design	Cases	Controls /cohort size	Study population	Comparison of population	Alcohol Assessment method	Adjusted confounders												
							Age	Race	Sex	Smoking	BMI	Phys activity	Diet	Diabetes	Study site	Education	Family Hx	NSAID use	HRT use
HYPERPLASTIC POLYPS/SERRATED POLYPS UNSPECIFIED																			
Martinez et al (1997) USA	Cross-sectional study	81	480	Symptomatic and screening patients (males) undergoing sigmoidoscopy or colonoscopy	HP v. No polyps	Interviewed 138-item FFQ	✓	✓	#	✓	✓							✓	
Michal et al (2012) USA	Hospital-based case-control	215	963	Screening patients undergoing colonoscopy	HP v. No polyps	Interview	Not reported												
Morimoto et al (2002) USA	Hospital-based case-control	219	708	Symptomatic and screening patients undergoing colonoscopy	HP v. No polyps	Self-administered FFQ	✓		✓	✓	✓							✓	✓
Omata et al (2009) Japan	Hospital-based case-control	132	586	Symptomatic patients undergoing colonoscopy	HP v. No polyps	Questionnaire	✓												
Wallace et al (2009) USA	Nested case-control study within RCTs*	812	2018	Patients with history of colorectal adenoma and undergoing surveillance colonoscopy	HP/SSA v. No polyps	Questionnaire	✓	#	✓	✓	#	#	#	#	✓	#	#	#	#
Yoshida et al (2006) USA	Hospital-based case-control	35	183	Symptomatic patients undergoing colonoscopy	HP v. No polyps	Questionnaire	✓		✓	✓		✓							

Adjusted confounders: Age; Race; Sex; Smoking; BMI: Body mass index; Phys activity: Physical activity; Diet: any aspect of dietary intake; Diabetes; Study site; Education; Family Hx: Family history; NSAID use: Non-steroidal anti-inflammatory drug use; HRT use: Hormone replacement therapy use.
Abbreviations**:** CTC: Computed Tomography Colonography; FFQ: Food frequency questionnaire; HP: Hyperplastic polyps; SSA: Sessile Serrated Adenomas.
#: Confounder tested for but not included in model or confounder not applicable due to homogenous study population.
*Wallace et al included pooled data from three separate placebo-controlled randomised controlled trials of antioxidants, calcium, or aspirin/folate supplements; Met inclusion criteria since individuals had a history of adenoma, but not serrated polyps.

Table 1 (c). Characteristics of studies investigating body fatness and the development of serrated colorectal adenomas/polyps.

Study-year-location	Study design	Cases	Controls /cohort size	Study population	Comparison of population	Body fatness Assessment method (measure)	Adjusted confounders												
							Age	Race	Sex	Smoking	Phys activity	Diet	Diabetes	Study site	Education	Family Hx	NSAID use	HRT use	Alcohol
SESSILE SERRATED ADENOMA/POLYPS																			
Anderson et al (2011)	Cross-sectional study	90	200	Symptomatic and screening patients undergoing colonoscopy	SSA v. No polyps	Medical note review (BMI)	✓						✓						
Burnett-Hartman et al (2013) USA	Hospital-based case-control	149	1037	Patients undergoing index colonoscopy for any indication	SSA v. No polyps	Interviewed Questionnaire (BMI)	✓	✓	✓	✓	✓				✓	✓	✓	✓	✓
Crockett et al (2015) USA	Pooled data from cross-sectional studies	39	1316	Patients undergoing colonoscopy	SSA v No polyps	Standardised interview (BMI; WH ratio)	✓		✓										
Randles et al (2015) USA	Hospital-based case-control	157	Not reported	Symptomatic and screening patient undergoing colonoscopy	SSA v. No polyps	Not reported (BMI)	✓		✓	✓	✓								
HYPERPLASTIC POLYPS/SERRATED POLYPS UNSPECIFIED																			
Burnett-Hartman et al (2013) USA	Hospital-based case-control	431	1037	Patients undergoing index colonoscopy for any indication	SP v. No polyps	Questionnaire (BMI)	✓	✓	✓	✓	✓				✓	✓	✓	✓	✓
Butterly et al (2014) USA	Population-based case-control	666	4198	Screening participants undergoing colonoscopy	SP v. No polyps	Questionnaire (BMI)	✓	✓	✓										
Crockett et al (2015) USA	Pooled data from cross-sectional studies	311	1316	Patients undergoing colonoscopy	SP v No polyps	Standardised interview (BMI; WH ratio)	✓		✓										
Drew et al (2016) USA	Cross-sectional study	1076	1646	Patients undergoing colonoscopy	SP v. No polyps	Routine interview (BMI)	✓		✓	✓						✓	✓		
Erhardt et al (2002) Germany	Hospital-based case-control	71	224	Patients undergoing colonoscopy	HP v. No polyps	Interview	✓	✓				✓							
Fu et al (2012) USA	Hospital-based case-control	662	3764	Symptomatic and screening patients undergoing colonoscopy	HP v. No polyps	Interview (BMI)	✓		✓					✓	✓				

Table 1 (c) continued. Characteristics of studies investigating body fatness and the development of serrated colorectal adenomas/polyps.

Study-year-location	Study design	Cases	Controls /cohort size	Study population	Comparison of population	Body fatness Assessment method (measure)	Adjusted confounders												
							Age	Race	Sex	Smoking	Phys activity	Diet	Diabetes	Study site	Education	Family Hx	NSAID use	HRT use	Alcohol
HYPERPLASTIC POLYPS/SERRATED POLYPS UNSPECIFIED																			
Hirai et al (2013) China	Cross-sectional study	532	3647	Patients undergoing complete colonoscopy	SP v. No polyps	Not reported (BMI)	✓												
Lai et al (2013) Taiwan	Cross-sectional study	243	3759	Self-referred patients undergoing flexible sigmoidoscopy.	HP v. No polyps	Anthropometric measurement (BMI)	✓		✓	✓			✓						✓
Leitzmann et al (2009) USA	Cross-sectional study	175	953	Asymptomatic screening participants (females) undergoing colonoscopy.	HP v. No polyps	Self-administered Questionnaire (BMI)	✓	✓	#	✓	✓	✓		✓		✓	✓	✓	✓
Liu et al (2010) Taiwan	Cross-sectional study	341	3062	Screening patients undergoing colonoscopy	HP v. No polyps	Anthropometric measurement (Waist size)	✓		✓	✓									✓
Liu et al (2015) USA	Cross-sectional study in RCT	240	929	Asymptomatic patients undergoing colonoscopy	HP v. No HP	CTC (PFVF, VFVF)	✓		✓										
Martinez et al (1997) USA	Cross-sectional study	81	480	Symptomatic and screening patients (males) undergoing sigmoidoscopy or colonoscopy	HP v. No polyps	Interviewed questionnaire (BMI)	✓	✓	#	✓							✓		
Morimoto et al (2002) USA	Hospital-based case-control	219	708	Symptomatic and screening patients undergoing colonoscopy	HP v. No polyps	Self-administered questionnaire (BMI, WH ratio)	✓	✓	✓	✓	✓						✓	✓	✓
Noreen et al (2014) Poland	Population-based case-control	106	440	Screening participants (females) undergoing colonoscopy	HP/SSA v. No polyps	Self-administered questionnaire (BMI)	✓		#	✓							✓	✓	
Omata et al (2009) Japan	Hospital-based case-control	132	586	Symptomatic patients undergoing colonoscopy	HP v. No polyps	Questionnaire (BMI)	✓												
Oza et al (2014) Not reported	Hospital-based case-control	53*	1041	Screening patients undergoing colonoscopy	PSP v. No PSP	Medical record review (BMI)			✓										

Table 1 (c) continued. Characteristics of studies investigating body fatness and the development of serrated colorectal adenomas/polyps.

Study-year-location	Study design	Cases	Controls /cohort size	Study population	Comparison of population	Body fatness Assessment method (measure)	Adjusted confounders												
							Age	Race	Sex	Smoking	Phys activity	Diet	Diabetes	Study site	Education	Family Hx	NSAID use	HRT use	Alcohol
HYPERPLASTIC POLYPS/SERRATED POLYPS UNSPECIFIED																			
Wallace et al (2009) USA	Nested case-control study within RCTs*	812	2018	Patients with history of colorectal adenoma and undergoing surveillance colonoscopy	HP/SSA v. No polyps	Questionnaire (BMI)	✓	#	✓	✓	#	#	#	#	✓	#	#	#	#
Wang et al (2014) Taiwan	Hospital-based case-control	210	1379	Asymptomatic participants undergoing colonoscopy	HP v. No HP	Interview (BMI)	✓				#	#			#	#	#		✓

Adjusted confounders: Age; Race; Sex; Smoking; Phys activity: Physical activity; Diet: any aspect of dietary intake; Diabetes; Study site; Education; Family Hx: Family history; NSAID use: Non-steroidal anti-inflammatory drug use; HRT use: Hormone replacement therapy use; Alcohol.
Abbreviations: BMI: Body mass index; CTC: Computed tomographic colonography; FFQ: Food frequency questionnaire; GCHP: goblet cell hyperplastic polyp; HP: Hyperplastic polyps; MVHP: microvesicular hyperplastic polyp; PFVF: Pericolonic fat volume fraction; PSP: Proximal Serrated Polyps; RCT: Randomised Controlled Trial; SSA: Sessile Serrated Adenomas; SP: Serrated polyps; VFVF: Visceral fat volume fraction; WH ratio: Waist-hip ratio.
* Oza et al case numbers estimated from polyp detection rates.
** Randomised controlled trial of calcium supplements – this is adjusted for in analysis; Met inclusion criteria since individuals had a history of adenoma, but not serrated polyps.
#: Confounder tested for but not included in model or confounder not applicable due to homogenous study population or randomisation.

Table 1 (d). Characteristics of studies investigating physical activity and the development of serrated colorectal adenomas/polyps.

Study-year-location	Study design	Cases	Controls /cohort size	Study population	Comparison of population	Physical activity Assessment method	Adjusted confounders												
							Age	Race	Sex	Smoking	BMI	Diet	Diabetes	Study site	Education	Family Hx	NSAID use	HRT use	Alcohol
SESSILE SERRATED ADENOMA/POLYPS																			
Burnett-Hartman et al (2013) USA	Hospital-based case-control	149	1037	Patients undergoing index colonoscopy for any indication	SSA v. No polyps	Interviewed Questionnaire	✓	✓	✓	✓	✓	✓				✓	✓	✓	✓
Crockett et al (2015) USA	Pooled data from cross-sectional studies	39	1316	Patients undergoing colonoscopy	SSA v No polyps	Standardised interview	✓		✓										
HYPERPLASTIC POLYPS/SERRATED POLYPS UNSPECIFIED																			
Burnett-Hartman et al (2013) USA	Hospital-based case-control	431	1037	Patients undergoing index colonoscopy for any indication	SP v. No polyps	Questionnaire	✓	✓	✓	✓	✓	✓				✓	✓	✓	✓
Crockett et al (2015) USA	Pooled data from cross-sectional studies	311	1316	Patients undergoing colonoscopy	SP v No polyps	Standardised interview	✓		✓										
Fu et al (2012) USA	Hospital-based case-control	662	3764	Symptomatic and screening patients undergoing colonoscopy	HP v. No polyps	Interview	✓	✓	✓	✓				✓	✓		✓		
Lieberman et al (2003) USA	Hospital-based case-control	391	1441	Asymptomatic participants undergoing colonoscopy	HP v. No polyps	Questionnaire	✓												
Martinez et al (1997) USA	Cross-sectional study	81	480	Symptomatic and screening patients (males) undergoing sigmoidoscopy or colonoscopy	HP v. No polyps	Interview													
Morimoto et al (2002) USA	Hospital-based case-control	219	708	Symptomatic and screening patients undergoing colonoscopy	HP v. No polyps	Self-administered questionnaire	✓	✓	✓	✓	✓	✓					✓		✓
Wallace et al (2005) USA*	Nested case-control study within RCT	156	787	Patients with history of colorectal adenoma and undergoing surveillance colonoscopy.	HP v. No HP	Interviewed Questionnaire	✓		✓		✓			✓					
Yoshida et al (2006) USA	Hospital-based case-control	35	183	Symptomatic patients undergoing colonoscopy	HP v. No polyps	Questionnaire	✓		✓	✓									✓

Adjusted confounders: Age; Race; Sex; Smoking; BMI: Body mass index; Diet: any aspect of dietary intake; Diabetes; Study site; Education; Family Hx: Family history; NSAID use: Non-steroidal anti-inflammatory drug use; HRT use: Hormone replacement therapy use; Alcohol. Abbreviations: HP: Hyperplastic polyps; SSA: Sessile Serrated Adenomas; SP: Serrated polyps; RCT: Randomised Controlled Trial. * Randomised controlled trial of calcium supplements – this is adjusted for in analysis; Met inclusion criteria since individuals had a history of adenoma, but not serrated polyps. #: Confounder tested for but not included in model or confounder not applicable due to homogenous study population.

Table 1 (e). Characteristics of studies investigating medication use and the development of serrated colorectal adenomas/polyps.

Study-year-location	Study design	Cases	Controls /cohort size	Study population	Comparison of population	Medication use Assessment method (Medications)	Adjusted confounders												
							Age	Race	Sex	Smoking	BMI	Phys activity	Diet	Diabetes	Study site	Education	Family Hx	HRT use	Alcohol
SESSILE SERRATED ADENOMA/POLYPS																			
Burnett-Hartman et al (2013) USA	Hospital-based case-control	149	1037	Patients undergoing index colonoscopy for any indication	SSA v. No polyps	Interviewed Questionnaire (NSAID, HRT)	✓	✓	✓	✓	✓	✓			✓	✓	✓	✓	✓
Crockett et al (2014) USA	Pooled data from cross-sectional studies	39	1316	Patients undergoing colonoscopy	SSA v No polyps	Standardised interview (NSAID, HRT)	✓		✓										
HYPERPLASTIC POLYPS/SERRATED POLYPS UNSPECIFIED																			
Burnett-Hartman et al (2012) USA	Hospital-based case-control	431	1037	Patients undergoing index colonoscopy for any indication	SP v. No polyps	Questionnaire (NSAID, HRT)	✓	✓	✓	✓	✓	✓			✓	✓	✓	✓	✓
Crockett et al (2014) USA	Pooled data from cross-sectional studies	311	1316	Patients undergoing colonoscopy	SP v No polyps	Standardised interview (NSAID, HRT)	✓		✓										
Drew et al (2016) USA	Cross-sectional study	1076	1646	Patients undergoing colonoscopy	SP v. No polyps	Routine interview (NSAID, Aspirin, Statin)	✓		✓	✓	✓						✓		
Fu et al (2012)* USA	Hospital-based case-control	662	3764	Symptomatic and screening patients undergoing colonoscopy	HP v. No polyps	Interview (NSAID)	✓	✓	✓	✓					✓	✓			
Johnson et al (2010) USA	Nested case-control study within PLCO Trial	1646	38,396	Screening participants undergoing sigmoidoscopy	Left-sided HP v. No polyps	Self-administered questionnaire (Aspirin, Ibuprofen)	✓	✓	✓	✓	✓	✓	#					✓	
Lieberman et al (2003) USA	Hospital-based case-control	391	1441	Asymptomatic participants undergoing colonoscopy.	HP v. No polyps	Questionnaire (NSAID)	✓												
Martinez et al (1997) USA	Cross-sectional study	81	480	Symptomatic and screening patients (males) undergoing sigmoidoscopy or colonoscopy	HP v. No polyps	Questionnaire (NSAID)	✓	✓	✓	✓	✓	✓	✓						✓

Table 1 (e) continued. Characteristics of studies investigating medication use and the development of serrated colorectal adenomas/polyps.

Study-year-location	Study design	Cases	Controls /cohort size	Study population	Comparison of population	Medication use Assessment method (Medications)	Adjusted confounders												
							Age	Race	Sex	Smoking	BMI	Phys activity	Diet	Diabetes	Study site	Education	Family Hx	HRT use	Alcohol
HYPERPLASTIC POLYPS/SERRATED POLYPS UNSPECIFIED																			
Morimoto et al (2002) [40] USA	Hospital-based case-control	219	708	Symptomatic and screening patients undergoing colonoscopy	HP v. No polyps	Self-administered questionnaire (NSAID, Aspirin, HRT)	✓		✓	✓	✓							✓	✓
Murff et al (2011)* USA	Hospital-based case-control	499	3431	Symptomatic and screening patients undergoing colonoscopy.	HP v. No polyps	Telephone interview (Aspirin)	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓
Noreen et al (2014) Poland	Population-based case-control	106	440	Screening participants (females) undergoing colonoscopy	HP/SSA v. No polyps	Self-administered questionnaire (Aspirin, HRT)	✓		#	✓								✓	
Oza et al (2014) Not reported	Hospital-based case-control	53**	1041	Screening patients undergoing colonoscopy	PSP v. No PSP	Medical record review (Aspirin)			✓										
Wallace et al (2009) USA***	RCT	812	2018	Patients with history of colorectal adenoma and undergoing surveillance colonoscopy	HP/SSA v. No polyps	RCT of aspirin 81mg or 325 mg v. placebo	✓	#	✓	✓	#	#	#	#	✓	#	#	#	#

Adjusted confounders: Age; Race; Sex; Smoking; BMI: Body mass index; Phys activity: Physical activity; Diet: any aspect of dietary intake; Diabetes; Study site; Education; Family Hx: Family history; HRT use: Hormone replacement therapy use (for NSAID/Aspirin analyses only); Alcohol.
Abbreviations: BMI: Body mass index;; HP: Hyperplastic polyps; NSAID: Non-steroidal anti-inflammatory drug; PLCO: Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; PSP: Proximal Serrated Polyps; RCT: Randomised Controlled Trial; SSA: Sessile Serrated Adenomas; SP: Serrated polyps.
* Fu et al 2012 and Murff et al 2011 reported results from the same population (Tennessee Colorectal Polyp Study) – Fu et al results were maintained for overall 'NSAID' results in corresponding meta-analysis, and Murff et al results were used for aspirin-specific analysis.
** Oza et al case numbers estimated from polyp detection rates.
***Wallace et al met inclusion criteria since individuals had a history of adenoma, but not serrated polyps.
#: Confounder tested for but not included in model or confounder not applicable due to homogenous study population or randomisation.

Table 1 (f). Characteristics of studies investigating dietary factors and the development of serrated colorectal adenomas/polyps.

Study-year-location	Study design	Cases	Controls /cohort size	Study population	Comparison of population	Dietary Assessment method (Diet factors)	Adjusted confounders												
							Age	Race	Sex	Smoking	BMI	Phys activity	Alcohol	Diabetes	Study site	Education	Family Hx	NSAID use	HRT use
SESSILE SERRATED ADENOMA/POLYPS																			
Crockett et al (2015) USA (2)	Pooled data from cross-sectional studies	39	1316	Patients undergoing colonoscopy	SSA v No polyps	FFQ (Fat; Red meat; Fibre)	✓		✓										
HYPERPLASTIC POLYPS/SERRATED POLYPS UNSPECIFIED																			
Adams et al (2011) USA	Cross-sectional study	85	225	Participants of a clinic-based study undergoing colonoscopy.	HP v. No polyps	LC MS (25-hydroxy-vitamin D)	✓	#	✓	✓	✓	✓							
Burnett-Hartman et al (2011) USA	Hospital-based case-control	691	772	Patients undergoing colonoscopy for any indication	HP v. No polyps	Telephone interview (Red meat)	✓	✓	✓	✓	✓					✓		✓	✓
Crockett et al (2015) USA (2)	Pooled data from cross-sectional studies	311	1316	Patients undergoing colonoscopy	SP v No polyps	FFQ (Fat; Red meat; Fibre)	✓		✓										
Dai et al (2007) USA*	Hospital-based case-control	210	1306	Symptomatic and screening patients undergoing colonoscopy	HP v. No polyps	Telephone survey, FFQ (Magnesium; calcium; ratio)	✓	✓	✓	✓	✓	✓	✓		✓	✓		#	
Erhardt et al (2002) Germany	Hospital-based case-control	71	224	Symptomatic patients undergoing colonoscopy	HP v. No polyps	Interviewed diet history (Ham, sausage)	✓		✓	✓									
Fu et al (2012) USA*	Hospital-based case-control	662	3764	Symptomatic and screening patients undergoing colonoscopy	HP v. No polyps	Telephone survey, FFQ (Red meat; Fiber, Calcium; Folate)	✓	✓	✓	✓					✓	✓		✓	
Fu et al (2011) USA*	Hospital-based case-control	662	3764	Symptomatic and screening patients undergoing colonoscopy	HP v. No polyps	Telephone survey, FFQ (Processed meat, white meat)	✓	✓	✓	✓	✓	✓	✓		✓	✓		✓	✓

Table 1 (f) continued. Characteristics of studies investigating dietary factors and the development of serrated colorectal adenomas/polyps.

Study-year-location	Study design	Cases	Controls /cohort size	Study population	Comparison of population	Dietary Assessment method (Diet factors)	Adjusted confounders												
							Age	Race	Sex	Smoking	BMI	Phys activity	Alcohol	Diabetes	Study site	Education	Family Hx	NSAID use	HRT use
HYPERPLASTIC POLYPS/SERRATED POLYPS UNSPECIFIED																			
Kearney et al (1995) USA	Prospective cohort (Nurses Health Study)	175	15984	Participants who self-reported that they had undergone sigmoidoscopy or colonoscopy during study follow-up period	Distal HP v. No HP	Two 61-item and 121-item FFQs (Folate; Fat; Protein; Fiber; Carbohydrates; Vit A,C,D,E)	✓		#	✓							✓		
Kearney et al (1995) USA	Prospective cohort (Health Professionals Follow-Up Study)	219	12922	Participants who self-reported that they had undergone sigmoidoscopy or colonoscopy during study follow-up period	Distal HP v. No HP	131-item FFQ (Folate; Vitamins Fat; Protein; Carbohydrates)	✓		#	✓							✓		
Lieberman et al (2003) USA	Hospital-based case-control	391	1441	Asymptomatic participants undergoing colonoscopy	HP v. No polyps	FFQ (Fat; Fiber; Calcium; Vit D; multivitamins)	✓			✓	✓	✓	✓				✓	✓	
Martinez et al (1997) Spain	Cross-sectional study	81	480	Symptomatic and screening patients undergoing sigmoidoscopy or colonoscopy	HP v. No polyps	Interviewed 138-item FFQ (Fiber; Calcium; Total fat)	✓	✓	✓	✓	✓							✓	
Morimoto et al (2002) USA	Hospital-based case-control	219	708	Symptomatic and screening patients undergoing colonoscopy	HP v. No polyps	FFQ (Fat; Vit D; Calcium; multivitamins)	✓		✓	✓	✓		✓					✓	✓
Murff et al (2012) USA*	Hospital-based case-control	544	3166	Patients undergoing colonoscopy.	HP v. No polyps	Telephone survey, FFQ (PUFAs)	✓	✓	#	✓	✓	✓	✓		✓	✓	✓	✓	✓
Platz et al (1997) USA	Prospective cohort (Health Professionals Follow-up study)	327	16448	Participants who underwent endoscopy during study follow-up period.	HP v. No HP	131-item FFQ (Fiber)	✓		#	✓	✓	✓	✓				✓		
Poole et al (2007) USA	Hospital-based case-control	194	626	Symptomatic and screening patients scheduled for colonoscopy.	HP v. No polyps	FFQ (Fish)	✓	✓	✓	✓	✓	✓	✓					✓	✓

Table 1 (f) continued. Characteristics of studies investigating dietary factors and the development of serrated colorectal adenomas/polyps.

Study-year-location	Study design	Cases	Controls /cohort size	Study population	Comparison of population	Dietary Assessment method (Diet factors)	Adjusted confounders												
							Age	Race	Sex	Smoking	BMI	Phys activity	Alcohol	Diabetes	Study site	Education	Family Hx	NSAID use	HRT use
HYPERPLASTIC POLYPS/SERRATED POLYPS UNSPECIFIED																			
Wallace et al (2009) USA***	Pooled data from RCTs and nested case-control studies within these	812	2018	Patients with history of colorectal adenoma and undergoing surveillance colonoscopy	HP/SSA v. No polyps	RCT of calcium, antioxidants, folate v. placebo FFQ (Fiber; Fat; Red meat; Energy; Carbohydrates)	✓	#	✓	✓	#	#	#	#	✓	#	#	#	#

Adjusted confounders: Age; Race; Sex; Smoking; BMI: Body mass index; Phys activity: Physical activity; Alcohol consumption; Diabetes; Study site; Education; Family Hx: Family history; NSAID use: Non-steroidal anti-inflammatory drug use; HRT use: Hormone replacement therapy use.
Abbreviations: CTC: Computed tomographic colonography; FFQ: Food frequency questionnaire; HP: Hyperplastic polyps; PUFAs: Poly-unsaturated Fatty Acid; SSA: Sessile Serrated Adenomas; SP: Serrated polyps; Vit: Vitamins.
* Studies all reported results from the same population (Tennessee Colorectal Polyp Study) – where dietary factors overlapped, the most recent publication was used for meta-analysis.
** Studies all reported results from the same population (Health Professionals Follow Up Study) – where dietary factors overlapped, the most recent publication was used for meta-analysis.
***Wallace et al met inclusion criteria since individuals had a history of adenoma, but not serrated polyps.
#: Confounder tested for but not included in model or confounder not applicable due to homogenous study population.

Supplementary Table 2. Summary of Newcastle Ottawa Scale* scores for studies investigating lifestyle risk factors for serrated polyps.

Author-date	Selection (maximum 4 marks)	Comparability (maximum 2 marks)	Outcome/ Exposure (maximum 3 marks)	Total (maximum 9 marks)**
Adams et al (2011)	* 0 0 *	* *	* * *	7
Anderson et al (2011)	* * 0 *	* 0	* * *	7
Buda et al (2012)	* * 0 *	* *	0 * *	7
Burnett-Hartman et al (2011)	* * 0 *	* *	0 * *	7
Burnett-Hartman et al (2013)	* * 0 *	* *	0 * *	7
Butterly et al (2014)	* * * *	* *	* * *	9
Crockett et al (2014) Abstract	* 0 * *	* *	* * *	8
Crockett et al (2015) Abstract	* 0 * *	* *	* * *	8
Dai et al (2007)	* 0 0 *	* *	0 * *	6
Davenport et al (2014) Abstract	* 0 0 *	* *	0 * *	6
Drew et al (2016)	* * 0 *	* *	* * *	8
Erhardt et al (2002)	* 0 0 *	* *	* * *	7
Figueiredo et al (2015)	0 * * *	* *	* * 0	7
Fu et al (2011)	* 0 0 *	* *	0 * *	6
Fu et al (2012)	* 0 0 *	* *	0 * *	6
Hassan et al (2010)	* 0 0 *	* *	* * *	7
Hirai et al (2013) Abstract	* 0 0 *	* 0	0 * *	5
Hoffmeister et al (2010)	* * * *	* *	* * *	9
Ji et al (2006)	* 0 * *	* *	* * *	8
Johnson et al (2010)	* 0 * *	* *	* * *	8
Kearney et al (1995)	0 * * *	* *	0 * *	7
Lai et al (2011)	* * 0 *	* *	* * *	8
Lieberman et al (2003)	* 0 0 *	* *	* * *	7
Lietzmann et al (2009)	* 0 0 *	* *	* * *	7
Liu et al (2010)	* * 0 *	* *	* * *	8
Liu et al (2015)	* * 0 *	* *	* * *	8
Martinez et al (1997)	* * 0 *	* *	0 * *	7
Martinez et al (2011)	* 0 * *	* *	* * *	8
Michal et al (2012)	* 0 0 *	* 0	* * *	6
Morimoto et al (2002)	* * 0 *	* *	* * *	8
Murff et al (2011)	* 0 0 *	* *	0 * *	6
Murff et al (2012)	* 0 0 *	* *	0 * *	6
Noreen et al (2014)	* 0 * *	* *	0 * *	7
Omata et al (2009)	* * 0 *	* 0	* * *	7
Oza et al (2014) Abstract	0 * 0 *	0 0	* * *	5
Platz et al (1997)	0 * * *	* *	0 * *	7
Poole et al (2007)	* * 0 *	* *	* * *	8
Qazi et al (2013) Abstract	* 0 * *	* 0	* * *	7
Randles et al (2015) Abstract	* 0 0 *	* *	0 * *	6
Wallace et al (2005)	* 0 * *	* *	* * *	8
Wallace et al (2009)	* 0 * *	* *	* * *	8
Wang et al (2014)	* * 0 *	0 *	* * *	7
Yoshida et al (2006)	* * 0 *	* *	* * *	8

*Categories for Case-control studies include: Selection (adequate SP case definition, SP case representativeness, control selection, non-SP control definition), Comparability (adjustment/study design accounts for important factors – we selected age and sex), and Exposure (ascertainment of risk factor, similar method of risk factor ascertainment for cases and controls, and response rates). Categories for Cohort studies include: Selection (risk factor-exposed cohort representativeness, cohort selection, ascertainment of risk factors, evidence of no SP at the start of the study), Comparability (adjustment/study design accounts for important factors – we selected age and sex), and Outcome (SP assessment, adequate follow-up length for SP detection, and adequacy of cohort follow-up).

**It should be noted that scoring is somewhat subjective due to potential non-reporting of each of these factors, particularly for abstracts, rather than being reflective of the study design itself.

Supplementary Table 3 (a). Sensitivity and subgroup meta-analyses of smoking and serrated polyp risk.

Study omitted	Pooled relative risk (95 percent CI)	Heterogeneity estimate, I-squared percent, P-value
Smoking – Sessile serrated adenoma/polyp only – Excluding individual studies		
Anderson	2.86 (1.58-5.16)	71%, *P* = 0.008
Buda	3.22 (1.69-6.14)	81%, *P* <0.001
Burnett-Hartman	3.48 (1.73-7.00)	81%, *P* <0.001
Crockett	3.92 (2.15-7.15)	78%, *P* <0.001
Davenport	3.01 (1.53-5.92)	76%, *P* = 0.003
Randles	4.17 (2.45-7.09)	56%, *P* = 0.06
OVERALL	3.40 (1.90-6.07)	77%, *P* = 0.001
Smoking – Hyperplastic/serrated polyps – Excluding individual studies		
Burnett-Hartman 2011	2.34 (1.99-2.75)	79%, *P* <0.001
Burnett-Hartman 2013	2.32 (1.98-2.71)	79%, *P* <0.001
Crockett	2.32 (1.98-2.72)	79%, *P* <0.001
Davenport	2.27 (1.95-2.65)	77%, *P* <0.001
Drew	2.36 (2.00-2.77)	79%, *P* <0.001
Erhardt	2.36 (2.02-2.77)	79%, *P* <0.001
Figueiredo	2.36 (2.00-2.78)	79%, *P* <0.001
Hassan	2.36 (2.01-2.77)	79%, *P* <0.001
Hirai	2.36 (2.01-2.77)	79%, *P* <0.001
Hoffmeister	2.38 (2.04-2.79)	77%, *P* <0.001
Ji	2.24 (1.98-2.52)	58%, *P* <0.001
Kearney (Nurses Health Study)	2.34 (1.99-2.74)	79%, *P* <0.001
Kearney (Health Professionals FUS)	2.35 (2.00-2.75)	79%, *P* <0.001
Lai	2.40 (2.05-2.79)	77%, *P* <0.001
Lieberman	2.32 (1.98-2.73)	79%, *P* <0.001
Martinez 1997	2.34 (2.00-2.74)	79%, *P* <0.001
Martinez 2011	2.29 (1.96-2.67)	78%, *P* <0.001
Michal	2.35 (2.01-2.76)	79%, *P* <0.001
Morimoto	2.30 (1.97-2.69)	79%, *P* <0.001
Noreen	2.33 (1.98-2.73)	79%, *P* <0.001
Omata	2.36 (2.01-2.76)	79%, *P* <0.001
Oza	2.40 (2.06-2.80)	78%, *P* <0.001
Qazi	2.34 (1.99-2.75)	79%, *P* <0.001
Wallace	2.37 (2.02-2.77)	79%, *P* <0.001
Wang	2.36 (2.01-2.77)	79%, *P* <0.001
Yoshida	2.33 (1.99-2.72)	79%, *P* <0.001
OVERALL	2.34 (2.00-2.72)	78%, *P* <0.001
Smoking – Hyperplastic/serrated polyps – Excluding Figueiredo and Oza studies (which may have had adenoma patients in comparator group)		
	2.42 (2.06-2.85)	78%, *P* <0.001
Smoking – Sessile serrated adenoma/polyp only – Studies of current v. never comparisons only		
	2.86 (1.58-5.16)	71%, *P* <0.001
Smoking – Hyperplastic/serrated polyps – Studies of current v. never comparisons only		
	2.55 (2.03-3.20)	84%, *P* <0.001
Smoking – Sessile serrated adenoma/polyp only – Sub-group analysis by study design		
Including Case-control studies only	3.30 (1.77-6.15)	74%, *P* = 0.009
Including Cross-sectional studies only	3.04 (0.47-19.83)	86%, *P* = 0.008
Smoking – Hyperplastic/serrated polyps – Sub-group analysis by study design*		
Including Case-control studies only	2.43 (1.95-3.03)	83%, *P* <0.001
Including Cross-sectional studies only	2.11 (1.73-2.57)	57%, *P* = 0.02

*Cohort studies were not analysed since only two cohort studies were published.

Supplementary Table 3 (b). Sensitivity and subgroup meta-analyses of alcohol and serrated polyp risk.

Study omitted	Pooled relative risk (95 percent CI)	Heterogeneity estimate, I-squared percent, P-value
Alcohol – Sessile serrated adenoma/polyp only – Excluding individual studies		
Burnett-Hartman	2.54 (1.43-4.51)	0%, *P* = 0.75
Crockett	1.72 (0.70-4.23)	68%, *P* = 0.08
Randles	1.49 (0.74-3.02)	36%, *P* = 0.21
OVERALL	1.85 (1.03-3.32)	41%, *P* = 0.18
Alcohol – Hyperplastic/serrated polyps – Excluding individual studies		
Burnett-Hartman	1.33 (1.17-1.52)	35%, *P* = 0.10
Crockett	1.30 (1.13-1.49)	37%, *P* = 0.09
Erhardt	1.30 (1.13-1.49)	37%, *P* = 0.09
Fu	1.35 (1.17-1.55)	35%, *P* = 0.10
Kearney (Nurses Health Study)	1.28 (1.13-1.45)	33%, *P* = 0.12
Kearney (Health Professionals FUS)	1.28 (1.13-1.46)	34%, *P* = 0.11
Lai	1.30 (1.13-1.48)	37%, *P* = 0.09
Lieberman	1.30 (1.13-1.48)	37%, *P* = 0.09
Martinez	1.28 (1.13-1.44)	31%, *P* = 0.14
Michal	1.28 (1.12-1.45)	33%, *P* = 0.12
Morimoto	1.30 (1.14-1.48)	38%, *P* = 0.08
Omata	1.29 (1.13-1.47)	36%, *P* = 0.10
Wallace	1.34 (1.20-1.50)	0%, *P* = 0.53
Yoshida	1.32 (1.15-1.51)	39%, *P* = 0.07
OVERALL	1.30 (1.15-1.48)	34%, *P* = 0.10
Alcohol – Sessile serrated adenoma/polyp only – Sub-group analysis by study design		
Including Case-control studies only	1.72 (0.70-4.23)	68%, *P* = 0.08
Including Cross-sectional study only	2.27 (0.92-5.58)	Not applicable – one study
Alcohol – Hyperplastic/serrated polyps – Sub-group analysis by study design*		
Including Case-control studies only	1.20 (1.04-1.37)	30%, *P* = 0.18
Including Cross-sectional studies only	1.49 (1.17-1.89)	0%, *P* = 0.62

*Cohort studies were not analysed since only two cohort studies were published.

Supplementary Table 3 (c). Sensitivity and subgroup meta-analyses of body mass index and serrated polyp risk.

Study omitted	Pooled relative risk (95 percent CI)	Heterogeneity estimate, I-squared percent, P-value
Body mass index – Sessile serrated adenoma/polyp only – Excluding individual studies		
Anderson	1.06 (1.02-1.11)	0%, *P* = 0.97
Burnett-Hartman	1.41 (0.79-2.51)	77%, *P* = 0.01
Crockett	1.37 (0.84-2.23)	77%, *P* = 0.01
Randles	1.50 (0.85-2.64)	59%, *P* = 0.09
OVERALL	1.30 (0.89-1.92)	66%, *P* = 0.03
Body mass index – Hyperplastic/serrated polyps – Excluding individual studies		
Burnett-Hartman	1.43 (1.24-1.66)	58%, *P* = 0.002
Butterly	1.42 (1.23-1.65)	58%, *P* = 0.002
Crockett	1.43 (1.24-1.66)	58%, *P* = 0.002
Erhardt	1.43 (1.24-1.64)	58%, *P* = 0.002
Fu	1.43 (1.23-1.67)	58%, *P* = 0.002
Hirai	1.44 (1.23-1.68)	58%, *P* = 0.002
Lai	1.41 (1.23-1.63)	58%, *P* = 0.003
Leitzmann	1.34 (1.22-1.46)	10%, *P* = 0.34
Martinez	1.39 (1.23-1.57)	48%, *P* = 0.002
Morimoto (males)	1.41 (1.23-1.62)	58%, *P* = 0.003
Morimoto (females)	1.44 (1.25-1.65)	58%, *P* = 0.003
Noreen	1.46 (1.28-1.66)	53%, *P* = 0.008
Omata	1.43 (1.24-1.64)	58%, *P* = 0.002
Oza	1.44 (1.26-1.65)	56%, *P* = 0.004
Wallace	1.45 (1.25-1.69)	56%, *P* = 0.005
Wang	1.44 (1.24-1.67)	58%, *P* = 0.002
OVERALL	1.42 (1.24-1.63)	55%, *P* = 0.004
Body mass index – Hyperplastic/serrated polyps – Excluding Oza and Wang studies (which may have had adenoma patients in comparator group)		
	1.46 (1.26-1.69)	59%, *P* = 0.003
Body mass index – Sessile serrated adenoma/polyp only – Sub-group analysis by study design		
Including Case-control studies only	1.06 (1.02-1.11)	0%, *P* = 0.83
Including Cross-sectional studies only	1.76 (0.78-3.99)	64%, *P* = 0.10
Body mass index – Hyperplastic/serrated polyps – Sub-group analysis by study design		
Including Case-control studies only	1.29 (1.16-1.43)	0%, *P* = 0.63
Including Cross-sectional studies only	1.76 (1.31-2.36)	78%, *P* <0.001

Supplementary Table 3 (d). Sensitivity and subgroup meta-analyses of physical activity and serrated polyp risk.

Study omitted	Pooled relative risk (95 percent CI)	Heterogeneity estimate, I-squared percent, P-value
Physical activity – Hyperplastic/serrated polyps – Excluding individual studies*		
Burnett-Hartman	0.91 (0.78-1.05)	5%, *P* = 0.39
Crockett	0.89 (0.76-1.03)	4%, *P* = 0.40
Fu	1.50 (0.85-2.64)	7%, *P* = 0.38
Lieberman	0.92 (0.79-1.07)	1%, *P* = 0.42
Martinez	0.91 (0.79-1.05)	0%, *P* = 0.55
Morimoto (males)	0.91 (0.79-1.04)	0%, *P* = 0.43
Morimoto (females)	0.87 (0.76-1.00)	0%, *P* = 0.84
Wallace	0.87 (0.75-1.01)	0%, *P* = 0.46
Yoshida	0.91 (0.78-1.05)	4%, *P* = 0.40
OVERALL	0.90 (0.78-1.03)	0%, *P* = 0.48
Physical activity – Hyperplastic/serrated polyps – Sub-group analysis by study design		
Including Case-control studies only	0.90 (0.77-1.05)	0%, *P* = 0.45
Including Cross-sectional studies only	0.81 (0.48-1.38)	42%, *P* = 0.19

*Not conducted for sessile serrated adenoma studies since only two studies published.
**May have included individuals with adenomas in the comparator group.

Supplementary Table 3 (e). Sensitivity and subgroup meta-analyses of medication use and serrated polyp risk.

Study omitted	Pooled relative risk (95 percent CI)	Heterogeneity estimate, I-squared percent, P-value
Medications, NSAIDs – Hyperplastic/serrated polyps – Excluding individual studies*		
Burnett-Hartman	0.74 (0.60-0.92)	60%, *P* = 0.02
Crockett	0.74 (0.61-0.88)	50%, *P* = 0.06
Drew	0.79 (0.67-0.93)	52%, *P* = 0.05
Fu	0.74 (0.59-0.93)	61%, *P* = 0.02
Johnson	0.79 (0.64-0.97)	56%, *P* = 0.03
Lieberman	0.77 (0.62-0.95)	62%, *P* = 0.02
Martinez	0.81 (0.70-0.94)	43%, *P* = 0.10
Morimoto	0.78 (0.65-0.95)	61%, *P* = 0.02
OVERALL	0.74 (0.60-0.92)	60%, *P* = 0.02
Medications, NSAIDs – Hyperplastic/serrated polyps – Sub-group analysis by study design		
Including Case-control studies only	0.78 (0.70-0.87)	0%, *P* = 0.46
Including Cross-sectional studies only	0.42 (0.12-1.44)	83%, *P* = 0.003
Medications, Aspirin – Hyperplastic/serrated polyps – Excluding individual studies		
Drew**	0.77 (0.60-0.98)	35%, *P* = 0.19
Johnson	0.85 (0.68-1.07)	30%, *P* = 0.22
Morimoto	0.79 (0.63-0.98)	41%, *P* = 0.15
Murff	0.78 (0.61-1.00)	44%, *P* = 0.13
Noreen	0.85 (0.73-0.99)	0%, *P* = 0.60
Oza***	0.81 (0.65-1.01)	46%, *P* = 0.12
OVERALL	0.81 (0.67-0.99)	33%, *P* = 0.19
Medications, Hormone Replacement Therapy – Hyperplastic/serrated polyps* – Excluding individual studies*		
Burnett-Hartman	1.02 (0.72-1.44)	36%, *P* = 0.21
Crockett	0.92 (0.70-1.23)	9%, *P* = 0.33
Morimoto	1.09 (0.84-1.40)	0%, *P* = 0.60
Noreen	0.94 (0.70-1.27)	25%, *P* = 0.26
OVERALL	0.99 (0.78-1.26)	0%, *P* = 0.34
Medications, Aspirin – Hyperplastic/serrated polyps– Sub-group analysis by study design		
Including Case-control studies only	0.92 (0.70-1.22)	9%, *P* = 0.33
Including Cross-sectional study only	1.22 (0.79-1.89)	Not applicable – one study

*Not conducted for sessile serrated adenoma studies since only two studies published.
** Denotes cross-sectional study design. All other studies were case-control studies.
**May have included individuals with adenomas in the comparator group.

Supplementary Table 3 (f). Sensitivity analyses excluding individual studies from meta-analyses of dietary factors and serrated polyp risk.

Study omitted	Pooled relative risk (95 percent CI)	Heterogeneity estimate, I-squared percent, P-value
Vitamin D – Hyperplastic/serrated polyps		
Kearney**	1.13 (0.75-1.69)	52%, *P* = 0.15
Lieberman	1.18 (0.75-1.86)	34%, *P* = 0.22
Morimoto	1.00 (0.99-1.01)	0%, *P* = 0.96
OVERALL	1.00 (0.94-1.07)	4%, *P* = 0.36
Calcium – Hyperplastic/serrated polyps		
Fu	0.69 (0.38-1.25)	70%, *P* = 0.04
Lieberman	0.66 (0.49-0.90)	13%, *P* = 0.32
Martinez*	0.83 (0.62-1.12)	73%, *P* =0.03
Morimoto	0.80 (0.56-1.14)	79%, *P* = 0.01
OVERALL	0.76 (0.55-1.06)	74%, *P* = 0.009
Total folate – Hyperplastic/serrated polyps		
Fu	1.02 (0.72-1.44)	51%, *P* = 0.15
Kearney (Nurses' Health Study)**	0.92 (0.70-1.23)	0%, *P* = 0.91
Kearney (Health Professionals FUS)**	1.09 (0.84-1.40)	66%, *P* = 0.09
OVERALL	0.99 (0.78-1.26)	0%, *P* = 0.34
Dietary fiber – Hyperplastic/serrated polyps		
Crockett*	0.91 (0.79-1.04)	44%, *P* = 0.11
Fu	0.88 (0.76-1.03)	50%, *P* = 0.07
Kearney (Nurses' Health Study)**	0.89 (0.77-1.02)	53%, *P* = 0.06
Lieberman	0.84 (0.74-0.95)	0%, *P* = 0.48
Martinez*	0.93 (0.85-1.03)	27%, *P* = 0.23
Platz**	0.88 (0.76-1.02)	54%, *P* = 0.05
Wallace	0.85 (0.70-1.03)	51%, *P* = 0.07
OVERALL	0.88 (0.77-1.01)	48%, *P* = 0.07
Total fat – Hyperplastic/serrated polyps		
Crockett*	1.22 (1.07-1.39)	0%, *P* = 0.74
Fu	1.25 (1.09-1.43)	0%, *P* = 0.60
Kearney (Nurses' Health Study)**	1.26 (1.11-1.43)	0%, *P* = 0.70
Kearney (Health Professionals FUS)**	1.28 (1.12-1.45)	0%, *P* = 0.84
Martinez*	1.25 (1.11-1.41)	0%, *P* = 0.65
Morimoto	1.25 (1.11-1.42)	0%, *P* = 0.62
Wallace	1.19 (1.00-1.41)	0%, *P* = 0.69
OVERALL	1.25 (1.10-1.41)	0%, *P* = 0.72
Red meat – Hyperplastic/serrated polyps		
Burnett-Hartman	1.21 (1.04-1.40)	0%, *P* = 0.57
Crockett*	1.23 (1.06-1.43)	0%, *P* = 0.52
Fu	1.18 (1.01-1.39)	0%, *P* = 0.76
Wallace	1.31 (1.08-1.58)	0%, *P* = 0.76
OVERALL	1.23 (1.07-1.41)	0%, *P* = 0.72

*Denotes cross-sectional study design. All other studies were case-control studies or cohort studies (Kearney/Platz).
**May have included individuals with adenomas in the comparator group.

Supplementary Table 4. Details of pathology review, serrated polyp definition and colonoscopy quality in included studies.

Study-year of publication-location	Years of study recruitment	Serrated polyp definition	Pathology review details	Quality of colonoscopy (bowel prep/withdrawal time etc)	Case-control or cross-sectional assessment of lifestyle factors
SESSILE SERRATED ADENOMA/POLYPS					
Anderson et al (2011) USA	Jan 2007-Sept 2010	SSA/P excluding TSA and HP (all, and subgroup analysis by size - ≥1cm and ≥6mm)	All pathologists at University of Connecticut Health Center	Not reported.	Cross-sectional study
Buda et al (2012) Italy	June 2007 - Dec 2008	SSA/P including SSA/P with dysplasia. TSA and HP excluded.	Two experienced gastrointestinal pathologists conducted independent review including consensus agreement where appropriate.	All colonoscopies conducted by one of four gastroenterologists. Poor bowel preparation colonoscopies were excluded.	Hospital-based case control
Burnett-Hartman et al (2013) USA	1998-2007	SSA/P. TSA and HP excluded.	Two study pathologists re-reviewed polyps to identify SSA/P (displaying exaggerated crypt serration, crypt dilatation, crypt, branching, horizontal crypt extensions at base or other distortions).	Poor bowel preparation colonoscopies were excluded.	Hospital-based case-control
Crockett et al (2014)/ Crockett et al (2015) USA	1998-2010	Proximal and large SSA/P	Proximal and large SPs diagnosed at the University of North Carolina were re-reviewed by an expert pathologist.	Not reported (abstract).	Pooled data from cross-sectional studies
Davenport et al (2014) USA	2003-2010	SSA/P	All polyps within the Tennessee Colorectal Polyp Study were re-reviewed by a study pathologist.	Colonoscopy that reached the caecum.	Hospital-based case control
Randles et al (2015) USA	July 2009 – Oct 2008	SSA/P (all, subgroup analysis by size and location)	All SSA/Ps re-reviewed by one of two expert gastrointestinal pathologists according to 2012 guidelines.	Colonoscopies conducted at University of Vermont Medical Cancer. Quality not reported (abstract).	Hospital-based case-control
HYPERPLASTIC POLYPS/SERRATED POLYPS UNSPECIFIED OR COMBINED					
Adams et al (2011) USA	1999-2003	HP	Unspecified, routine pathology review.	All subjects underwent colonoscopy at the Group Health Central Gastroenterology Clinic.	Cross-sectional study
Burnett-Hartman et al (2011) USA	Dec 2004 – Sept 2007	HP	Unspecified, routine pathology review.	Colonoscopies not reaching the caecum or those with inadequate bowel preparation were excluded.	Hospital-based case-control
Burnett-Hartman et al (2013) USA	1998-2007	HP SSA/P and TSA excluded. A combined HP and SSA/P subgroup analysis was conducted by proximal/distal site.	Two study pathologists re-reviewed polyps to identify HP	Poor bowel preparation colonoscopies were excluded.	Hospital-based case-control

Supplementary Table 4 continued. Details of pathology review, serrated polyp definition and colonoscopy quality in included studies.

Study-year of publication-location	Years of study recruitment	Serrated polyp definition	Pathology review details	Quality of colonoscopy (bowel prep/withdrawal time etc)	Case-control or cross-sectional assessment of lifestyle factors
HYPERPLASTIC POLYPS/SERRATED POLYPS UNSPECIFIED OR COMBINED					
Butterly et al (2014) USA	6 April 2009 - 22 March 2011	SSA/P and HP combined	All pathology reports in the New Hampshire Colonoscopy Registry.	Poor, fair or unknown bowel preparation colonoscopies were excluded. Colonoscopies excluded where endoscopist unknown or by two endoscopists who didn't provide withdrawal time. Normal withdrawal times ranged from 3->10 minutes.	Population-based case-control
Crockett et al (2014) USA	1998-2010	Proximal and large SP (including SSA/P)	Proximal and large SPs diagnosed at the University of North Carolina were re-reviewed by an expert pathologist.	Not reported (abstract).	Pooled data from cross-sectional studies
Dai et al (2007)/ Fu et al (2011 & 2012)/ Murff et al (2011 & 2012) USA	1 Feb 2003 - 31 May 2008	HP	Unspecified, routine pathology review.	Screening or diagnostic colonoscopies that reached the caecum at Vanderbilt Gastroenterology Clinic or Veteran's Affairs Tennessee Valley Health System.	Hospital-based case-control
Davenport et al (2014) USA	1 Feb 2003 - 31 May 2008	HP only (excluding SSA).	All polyps within the Tennessee Colorectal Polyp Study were re-reviewed by a study pathologist.	Colonoscopy that reached the caecum.	Hospital-based case-control
Drew et al (2016) USA	Jan 2011 - June 2014	SSA/HP/TSA combined	Unspecified, routine pathology review.	Colonoscopy. Split-dose bowel prep used.	Cross-sectional study
Erhardt et al (2002) Germany	March 1995 – Oct 1997	HP	Histological assessment was performed by one of two staff pathologists at the Robert-Bosch Hospital.	Colonoscopy was performed jointly by a staff gastroenterologist and an experienced endoscopy nurse. Incomplete colonoscopies (not reaching caecum) or unsatisfactory colon preparation were excluded.	Hospital-based case-control
Figueiredo et al (2015) USA	Three trials conducted in 1990s	SSA/HP/TSA combined Subgroup analysis of large SP (≥1cm)	All slides reviewed by a single study pathologist.	Colonoscopy or surgery specimens collected within the trial protocols.	Nested case-control study in RCT
Hassan et al (2010) / Liu et al (2015) USA	May 2002-June 2003	HP	Histological review within trial. Pathologist detail not reported.	All individuals underwent standard bowel preparation and optical colonoscopy by one of 17 colonoscopists in a low-dose CT colonography screening trial (that also included optical colonoscopy).	Cross-sectional study in RCT
Hirai et al (2013) China	2007-2013	SSA/HP combined	Not reported (abstract).	Not reported (abstract).	Cross-sectional study

Supplementary Table 4 continued. Details of pathology review, serrated polyp definition and colonoscopy quality in included studies.

Study-year of publication-location	Years of study recruitment	Serrated polyp definition	Pathology review details	Quality of colonoscopy (bowel prep/withdrawal time etc)	Case-control or cross-sectional assessment of lifestyle factors
HYPERPLASTIC POLYPS/SERRATED POLYPS UNSPECIFIED OR COMBINED					
Hoffmeister et al (2010) Germany	May 2005 - Dec 2007	HP	All pathology reports from population-based KolosSal study in Saarland, South-West Germany, were reviewed by two independent investigators.	Screening colonoscopies from 33 gastroenterology practices in Saarland. Colonoscopies unable to reach caecum or inadequate bowel preparation excluded.	Population-based case-control
Ji et al (2006) / Johnson et al (2010) USA	Sept 1993-Sept 2000	Distal HP	Histological review within trial. Pathologist detail not reported.	Screening flexible sigmoidoscopies within the PLCO Cancer Screening trial, and multi-centre study in the USA.	Nested case-control study in RCT
Kearney et al (1995) / Platz et al (1997) USA	NHS: 1976-1990 HPFUS: 1986-1994	Distal HP	Review of histopathology reports following self-report of a colorectal polyp diagnosis.	All subjects underwent colonoscopy or sigmoidoscopy during cohort study follow-up period. Quality not reported.	Cohort studies: NHS HPFUS
Lai et al (2013) Taiwan	2001-2004	Distal HP (assumed distal due to flexible sigmoidoscopy)	All medical records from one medical center at Taichung city were reviewed. Pathologist detail not reported.	All subjects underwent 60cm flexible sigmoidoscopy. Quality not reported.	Cross-sectional study
Lieberman et al (2003) USA	Feb 1994 – Jan 1997	HP	All retrieved polyps were sent to local pathology laboratories for histologic evaluation. Slides were sent to a designated pathology expert at the Veterans Affairs Medical Center in Hines, Illinois, for an independent, blinded review. The results of the third review were used to classify any disagreements.	All subjects underwent complete colonoscopy at one of 13 Veterans Affairs medical centers in the USA. If the colonoscopic examination was incomplete because of problems with bowel preparation or failure to reach the cecum, the patient was asked to return for a second attempt	Hospital-based case-control
Lietzmann et al (2009)	1 July 1999 - 31 Dec 2002	HP (all, subgroup analysis conducted for small, large, multiple, proximal, distal, rectal HP)	All histological specimens were reviewed by one expert gastrointestinal pathologist.	>99% colonoscopies performed by gastroenterologists or colorectal surgeons. Quality not reported.	Cross-sectional study
Liu et al (2010)	Jan 2006 - May 2008	HP	All specimens reviewed by pathologists at China Medical University Hospital.	Screening colonoscopy performed by a gastroenterologist.	Cross-sectional study
Martinez et al (1997) USA	Sept 1991-June1993	HP	Medical record review from medical centres of participating gastroenterologists.	Endoscopies performed by one of eight gastroenterologists. Quality not reported.	Cross-sectional study
Martinez et al (2011) USA	Jan 1998 – Feb 2001	HP	Not reported.	All subjects underwent 60cm flexible sigmoidoscopy performed by the same endoscopist. Quality not reported.	Cross-sectional study

Supplementary Table 4 continued. Details of pathology review, serrated polyp definition and colonoscopy quality in included studies.

Study-year of publication-location	Years of study recruitment	Serrated polyp definition	Pathology review details	Quality of colonoscopy (bowel prep/withdrawal time etc)	Case-control or cross-sectional assessment of lifestyle factors
HYPERPLASTIC POLYPS/SERRATED POLYPS UNSPECIFIED OR COMBINED					
Michal et al (2012) USA	Not reported (abstract)	HP	Not reported (abstract).	Patients undergoing screening colonoscopy at one institution. Quality not reported (abstract).	Hospital-based case-control
Morimoto et al (2002) / Poole et al (2007) USA	April 1991-April 1994	HP	Review by study pathologist.	Colonoscopy that reached the caecum, performed at a large multicenter private gastroenterology practice. Quality of bowel preparation not reported.	Hospital-based case-control
Noreen et al (2014) Poland	2000-2004	SSA and HP combined	Local pathology review at participating centres.	Colonoscopies within 40 centres participating in a national screening programme. Quality not reported.	Population-based case-control
Omata et al (2009) Japan	Not reported	HP	Not reported.	Patients undergoing colonoscopy at Tokai University Oiso Hospital. Quality not reported.	Hospital-based case-control
Oza et al (2014) Not reported	Three month period in 2012	Proximal SP (HP/SSA/TSA combined)	Not reported (abstract).	Adequate bowel preparation (good, very good or excellent) for outpatients undergoing screening colonoscopy at a single academic tertiary care referral center.	Hospital-based case-control
Qazi et al (2013) USA	Not reported (abstract)	HP (microvesicular or goblet cell)	All specimens reviewed by a study pathologist.	Not reported (abstract).	Hospital-based case-control
Wallace et al (2005) USA	Nov 1988-April 1992, follow-up to Dec 1996	HP	All specimens reviewed by a study pathologist.	All subjects underwent two follow-up colonoscopies as part of their routine clinical care, usually by the same physician who had conducted the initial examination.	Nested case-control study within RCT.
Wallace et al (2009) USA	Three trials conducted in 1990s/early 2000s	HP/SSA/TSA and mixed serrated polyps combined	All specimens reviewed by study pathologists, with noted change from HP to serrated adenoma towards latter study years.	Colonoscopy that reached the caecum, with endoscopist attesting to removal of all polyps/suspicious areas for neoplasia being removed.	Nested case-control study within RCTs***
Wang et al (2014) Taiwan	Jan 2009 – Dec 2011	HP only (excluding SSA and TSA).	Pathologist categorised polyps into HP, SSA/P, TSA or adenomatous polyps.	Colonoscopies performed by one of three experienced endoscopists. Quality of bowel preparation not reported.	Cross-sectional study
Yoshida et al (2006) Japan	Sept 2002-May 2004	HP	Not reported.	Colonoscopies reaching the caecum, performed by one of three experienced endoscopists following careful bowel preparation of patients.	Hospital-based case-control

HPFUS: Health Professionals Follow Up Study; HP: Hyperplastic polyp; NHS: Nurses' Health Study RCT: Randomised controlled trial; SSA/P: Sessile serrated adenoma/polyp; SP: Serrated Polyp; TSA: Traditional serrated adenoma.