Risk of developing gallbladder cancer in patients with gallbladder polyps detected on transabdominal ultrasound: a systematic review and meta-analysis

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Objective: To estimate the risk of malignancy in gallbladder polyps of incremental sizes detected during transabdominal ultrasound (TAUS).

Methods: We searched databases including MEDLINE, Embase, and Cochrane Library for eligible studies recording the polyp size from which gallbladder malignancy developed, confirmed following cholecystectomy, or by subsequent follow-up. Primary outcome was the risk of gallbladder cancer in patients with polyps. Secondary outcome was the effect of polyp size as a prognostic factor for cancer. Risk of bias was assessed using the Quality in Prognostic Factor Studies (QUIPS) tool. Bayesian meta-analysis estimated the median cancer risk according to polyp size. This study is registered with PROSPERO (CRD42020223629).

Results: 82 studies published since 1990 reported primary data for 67,837 patients. 67,774 gallbladder polyps and 889 cancers were reported. The cumulative median cancer risk of a polyp measuring 10 mm or less was 0.60% (99% credible range 0.30–1.16%). Substantial heterogeneity existed between studies (I² = 99.95%, 95% credible interval 99.86–99.98%). Risk of bias was generally high and overall confidence in evidence was low. 13 studies (15.6%) were graded with very low certainty, 56 studies (68.3%) with low certainty, and 13 studies (15.6%) with moderate certainty. In studies considered moderate quality, TAUS monitoring detected 4.6 cancers per 10,000 patients with polyps less than 10 mm.

Conclusion: Malignant risk in gallbladder polyps is low, particularly in polyps less than 10 mm, however the data are heterogeneous and generally low quality. International guidelines, which have not previously modelled size data, should be informed by these findings.

Advances in knowledge: This large systematic review and meta-analysis has shown that the mean cumulative risk of small gallbladder polyps is low, but heterogeneity and missing data in larger polyp sizes (>10 mm) means the risk is uncertain and may be higher than estimated. Studies considered to have better methodological quality suggest that previous estimates of risk are likely to be inflated.

INTRODUCTION

Gallbladder polyps are commonly detected in adults during transabdominal ultrasound examination (TAUS).1 Gallbladder polyps can be separated into two categories; true polyps, or adenomas, that have malignant potential, and pseudopolyps consisting predominately of cholesterol, which have no malignant potential at all. The latter group is estimated to constitute 70% of all reported gallbladder polyps.2

Gallbladder cancer has been shown to develop from polypoid adenomas.3,4 More than 200,000 patients are diagnosed with gallbladder cancer each year worldwide.5 Gallbladder cancer carries a poor prognosis (15–20% 5-year survival) because patients commonly present at an advanced stage of disease and are unsuitable for radical therapy.6 The risk of malignant transformation of polyps to cancer is thought to be small, however accurate estimates of risk are unknown. Predicting which of the many patients with gallbladder polyps will develop gallbladder cancer is extremely difficult, but clinically important.
The assessment and monitoring of gallbladder polyps represent an ongoing clinical challenge that requires considerable resources from radiology departments around the world. Several international societies have attempted to provide evidence-based clinical guidance, based on size thresholds for intervention. Generally, it is recommended that patients with gallbladder polyps measuring 10 mm or more should undergo cholecystectomy. Recently updated European guidelines recommend ultrasound monitoring for up to 2 years in patients with polyps measuring 6 mm or more, provided polyp size is stable, or for polyps 5 mm or less if risk factors are present. In contrast, the Canadian Association of Radiologists recently endorsed the American College of Radiology recommendations that surveillance of polyps measuring 7 mm or more should be performed for up to 2 years, with polyps less than 7 mm not requiring follow-up. The available evidence is largely considered to be low quality, and international guidance has never modelled polyp size for malignant risk to justify their recommendations for appropriate intervention. Additional limitations include strong selection, detection, and reporting bias which significantly hinders confidence in any current estimated malignant risk.

Therefore, to address this gap, a systematic review and meta-analysis was conducted to establish the overall risk of gallbladder cancer in patients with polyps detected by TAUS. We examined TAUS measured polyp size as a prognostic factor for gallbladder cancer and explored other potentially important clinical co-variates for their associated malignant risk.

**METHODS AND MATERIALS**

This study was prospectively registered with PROSPERO (CRD42020223629) and results were reported following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.12

**Search strategy**

A comprehensive search strategy using Medical Subject Headings (MeSH) and free-text terms was designed for this systematic review using MEDLINE. This strategy was adapted to run in the following electronic databases: MEDLINE, Embase, Cochrane Library, Cumulative Index of Nursing and Allied Health Literature (CINAHL), Scopus, Web of Science, and ClinicalTrials.gov. (Supplementary Material 1) The initial search was performed on October 28, 2020, and updated on December 4, 2020. The search was limited to English language.

**Study selection**

The systematic review included randomised control trials, observational cohort, cross-sectional and case–control studies published since 1990. We included studies that reported consecutive or random primary data in adult participants (18 years or older), diagnosed with a gallbladder polyp on TAUS, that recorded the size of polyp from which a gallbladder malignancy occurred, confirmed either following cholecystectomy, or by monitoring the polyp to determine its natural history. A monitoring period of at least 12 months was required. A polyp is often termed a mass once it measures 30 mm, however, to maximise the capture of continuous data, sizes of polypoid lesions more than 30 mm were also recorded. Studies were excluded that did not contain any primary data or did not provide polyp or cancer measurements. Attempt was made to discover translations of any non-English language article that was inadvertently retrieved. Reference lists of all eligible studies were checked and underwent citation tracking for additional eligible studies. Search of the grey literature was not performed.

**Outcomes**

The pre-specified primary outcome was the risk of gallbladder cancer in adult patients with polyps detected by TAUS. The secondary outcome was the effect of polyp size as a prognostic factor for gallbladder cancer. Additional secondary outcomes were the malignant risk of associated clinical co-variates: age at diagnosis, gender, presence of gallstones, presence of symptoms, and the presence of single or multiple polyps.

**Data extraction**

Two investigators (KGF/ZR) independently screened all titles and abstracts, assessed full texts for eligibility, and extracted data based on the CHARMS13 and CHARMS-PF14 checklists. Disagreements were resolved after review by a third investigator (SAR). Data extracted (Supplementary Material 1) included study identifiers, study design, setting and population characteristics, sample size, polyp and cancer size, and follow-up. Where an included study reported missing data, the corresponding author was contacted inviting them to share the complete data set.

**Quality assessment**

Risk of bias was assessed using the Quality in Prognostic Factor Studies (QUIPS) tool for each study.15 The strength of the overall weight of evidence for both primary and secondary outcomes was judged using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group methodology.16 (Supplementary Material 1)

**Data analysis**

A Bayesian meta-analysis model which incorporated the effects of polyp size and other covariates on the risk of cancer was developed. This was a random intercept and random gradient model to allow the effects of polyp size on the risk of cancer to vary across studies. The model was expanded to account for extensive missing data amongst the response and the predictor variables. The data were modelled by assuming separate multinomial distributions for the number of cancers and polyps at different sizes and imputing new data for each iteration of the Bayesian model. As a result, all eligible studies could be included in the analysis. The model was supplemented with individual patient data, where available. The Bayesian meta-analysis model was developed in JAGS19 interfacing with R20 via the rjags package. (Supplementary Material 1) Between-study heterogeneity was assessed by inspection of prediction plots, and the I² statistic.22,23 To assess the effects of the GRADE rating on the Bayesian model, sensitivity analyses were conducted where studies rated with very low certainty were first excluded, followed by the exclusion of low and very low certainty studies.
RESULTS
The initial search identified 3067 studies, of which 1615 were duplicates. Four additional studies were identified through other sources. The titles and abstracts of 1456 studies were screened and after screening, 1322 records were excluded for being irrelevant to this systematic review, leaving 134 full-text articles for review. Both reviewers identified 122 of the 134 full-text articles (91.0%) and the remaining 12 were included after agreement by the third reviewer. Of the 134 full-text articles, 52 were excluded (agreed by both reviewers) leaving 82 articles published since 1990 for inclusion (Figure 1). Important characteristics of the 82 included studies are detailed in Table 1.

Overall, 67,837 patients were included for evidence synthesis. In total, 67,774 gallbladder polyps and 889 gallbladder cancers were reported. The median age ranged between 40 and 62, and 57,670 were male (73.7%). All patients had gallbladder polyps detected by TAUS. In total, 20,543 were evaluated following cholecystectomy. More than half of all polyps (n = 41,041, 53.1%) were monitored with TAUS to determine their natural history. The two largest studies provided 46,782 patients, but only 38 cancers.

There were 82 studies which provided data on the number of gallbladder polyps and cancers. Sixty studies provided data on at least one polyp size and the associated number of gallbladder cancers that developed in polyp sizes up to 15 mm. Size measurements could be extracted in 59,225 polyps and 425 malignant polyps, respectively, from these studies. In one study, the authors provided individual patient data on 558 patients. 16 studies (19.5%) reported cohorts with zero cancer events within the first year of follow-up. 44 studies reported non-zero cancer events in one or more polyp
| Author            | Year | Country | Design   | Sites | Start date | End date | Patients | Median age (months) | Female | Polyps | Cancers | Malignancy rate | Cholecystectomy | Monitoring |
|-------------------|------|---------|----------|-------|------------|----------|----------|---------------------|--------|--------|---------|-----------------|----------------|------------|
| Abdullah et al.   | 2019 | UK      | Retrospective | 1    | 2011  | 2013     | 244      | NR                  | 160    | 100    | 43 (21.4%) | 0.1%            | 36             | 36         |
| Ahmadi et al.     | 2016 | USA     | Retrospective | 1    | 1988  | 1995     | 294      | 57                  | 125    | 125    | 24 (19.2%) | 0.8%            | 182            | 182        |
| Akyurek et al.    | 2013 | Turkey  | Retrospective | 1    | 2000  | 2004     | 112      | 50                  | 56     | 56     | 20 (35.7%) | 0.0%            | 96             | 96         |
| Akyurek et al.    | 2018 | Turkey  | Retrospective | 1    | 2014  | 2018     | 202      | 70                  | 272    | 272    | 70 (34.7%) | 0.0%            | 180            | 180        |
| Aldouri et al.    | 2010 | Jordan  | Retrospective | 1    | 2002  | 2016     | 457      | NR                  | 2429   | 2429  | 10 (0.4%)  | 0.0%            | 2429           | 2429       |
| Aliyazicioglu et al. | 2017 | Turkey  | Retrospective | 1    | 2004  | 2015     | 185      | 44                  | 94     | 94     | 2 (1.1%)   | 0.0%            | 185            | 185        |
| Ansari et al.     | 2009 | Bangladesh | Prospective | 1    | 2002  | 2004     | 57       | NR                  | 57     | 57     | 1 (1.8%)   | 0.0%            | 57             | 57         |
| Azuma et al.      | 2001 | Japan   | Retrospective | 1    | 1989  | 1998     | 118      | NR                  | 118    | 118    | 4 (3.4%)   | 0.0%            | 118            | 118        |
| Cairns et al.     | 2012 | UK      | Retrospective | 1    | 2000  | 2011     | 986      | 57                  | 986    | 986    | 134 (13.6%) | 0.0%            | 986            | 986        |
| Cha et al.        | 2011 | South Korea | Retrospective | 1    | 2003  | 2009     | 210      | 40                  | 210    | 210    | 40 (19.0%) | 0.0%            | 210            | 210        |
| Channa et al.     | 2009 | Pakistan | Retrospective | 1    | 1999  | 2008     | 30       | NR                  | 30     | 30     | 1 (3.3%)   | 0.0%            | 30             | 30         |
| Chattopadhyay et al. | 2005 | UK      | Retrospective | 1    | 1993  | 2002     | 23       | 56.8                | 16 (69.6%) | 23  | 23 (100.0%) | 0.0%            | 16             | 16         |
| Cheon et al.      | 2009 | South Korea | Retrospective | 1    | 1996  | 2006     | 94       | NR                  | 94     | 94     | 94 (100.0%) | 0.0%            | 94             | 94         |
| Chijiiwa et al.   | 1994 | Japan   | Retrospective | 1    | 1982  | 1990     | 44       | NR                  | 24     | 24     | 12 (50.0%) | 0.0%            | 24             | 24         |
| Choi et al.       | 2008 | South Korea | Retrospective | 1    | 2006  | 2007     | 59       | NR                  | 59     | 59     | 16 (27.1%) | 0.0%            | 59             | 59         |
| Chou et al.       | 2017 | Taiwan  | Retrospective | 1    | 2004  | 2013     | 1204     | 51.8                | 527    | 527    | 111 (9.3%) | 0.0%            | 1204           | 1204       |
| Colecchia et al.  | 2009 | Italy   | Prospective  | 1    | 1999  | 2001     | 56       | 48.3                | 22     | 22     | 0 (0.0%)  | 0.0%            | 0              | 0          |
| Collett et al.    | 1998 | New Zealand | Prospective | 1    | 1989  | 1994     | 38       | NR                  | 38     | 38     | 0 (0.0%)  | 0.0%            | 0              | 0          |
| Corwin et al.     | 2011 | USA     | Prospective  | 1    | 1999  | 2001     | 346      | NR                  | 346    | 346    | 10 (2.9%)  | 0.0%            | 346            | 346        |
| Csendes et al.    | 2001 | Chile   | Prospective  | 1    | 1987  | 1996     | 111      | NR                  | 111    | 111    | 27 (24.3%) | 0.0%            | 111            | 111        |
| Dacka et al.      | 2004 | Poland  | Retrospective | 1    | 1998  | 2002     | 25       | NR                  | 25     | 25     | 9 (36.0%)  | 0.0%            | 9              | 9          |
| Damore et al.     | 2001 | USA     | Retrospective | 1    | 1988  | 1995     | 41       | 47.4                | 18      | 18     | 4 (22.2%)  | 0.0%            | 18             | 18         |
| Donald et al.     | 2013 | USA     | Retrospective | 1    | 2002  | 2011     | 27       | NR                  | 27     | 27     | 5 (18.5%)  | 0.0%            | 5              | 5          |
| Drews et al.      | 2005 | Poland  | Retrospective | 1    | 1993  | 2003     | 39       | NR                  | 39     | 39     | 17 (43.6%) | 0.0%            | 17             | 17         |
| Escalona et al.   | 2006 | Chile   | Retrospective | 1    | 1991  | 2004     | 123      | NR                  | 123    | 123    | 95 (77.2%) | 0.0%            | 95             | 95         |
| French et al.     | 2013 | Canada  | Retrospective | 1    | 2000  | 2010     | 262      | 49                  | 157    | 157    | 10 (3.8%)  | 0.0%            | 10             | 10         |
| Fujiwara et al.   | 2020 | Japan   | Retrospective | 1    | 2003  | 2019     | 227      | NR                  | 99     | 99     | 23 (10.1%) | 0.0%            | 23             | 23         |
| Guo et al.        | 2015 | China   | Retrospective | 1    | 1999  | 2012     | 160      | NR                  | 90     | 90     | 60 (37.5%) | 0.0%            | 60             | 60         |
| Heitz et al.      | 2019 | Germany | Prospective Multi | 2002  | 2013  | 2019     | 262      | 59                  | 59     | 59     | 20 (7.6%)  | 0.0%            | 20             | 20         |
| Huang et al.      | 2001 | Taiwan  | Retrospective | 1    | 1990  | 1998     | 153      | NR                  | 76     | 76     | 62 (40.5%) | 0.0%            | 62             | 62         |
| (Continued)
### Table 1. (Continued)

| Author                  | Year  | Country   | Design        | Sites     | Start date | End date | Patients | Median age (months) | Female | Pseudops | Cancers | Malignancy rate | Cholecystectomy | Monitoring | Median follow-up (months) |
|-------------------------|-------|-----------|---------------|-----------|------------|----------|----------|---------------------|--------|-----------|---------|------------------|-----------------|------------|------------------------|
| Isozaki et al.          | 1995  | Japan     | Retrospective | 1         | 1978       | 1992     | 62       | NR                  | 31 (50.0%) | 144       | 29      | 14.5%            | 62 (43.1%)      | 0 (0.0%)  | NR                     |
| Ito et al.              | 2009  | USA       | Retrospective | 1         | 2007       | 2007     | 144      | NR                  | 576 (7.0%) | 126       | 8       | 20.1%            | 144 (100.0%)    | 0 (0.0%)  | 143 (43.4%)          |
| Jang et al.             | 2009  | South Korea | Prospective   | 1         | 2008       | 2012     | 26       | 19 (73.1%)          | 20     | 26        | 1       | 3.0%             | 26 (100.0%)     | 0 (0.0%)  | NR                     |
| Jeong et al.            | 2010  | South Korea | Retrospective | 1         | 2007       | 2011     | 53       | NR                  | 576 (7.0%) | 126       | 8       | 15.1%            | 144 (100.0%)    | 0 (0.0%)  | NR                     |
| Kamali Polat et al.     | 2010  | Turkey    | Retrospective | 1         | Missing    | Missing  | 34       | NR                  | 672 (1.4%) | 34        | 1       | 2.9%             | 3 (91.2%)       | 0 (0.0%)  | NR                     |
| Khan et al.             | 2012  | South Korea | Retrospective | 1         | 2008       | 2012     | 26       | 19 (73.1%)          | 20     | 26        | 1       | 3.0%             | 26 (100.0%)     | 0 (0.0%)  | NR                     |
| Kim et al.              | 2016  | South Korea | Retrospective | 1         | 2007       | 2011     | 53       | NR                  | 576 (7.0%) | 126       | 8       | 15.1%            | 144 (100.0%)    | 0 (0.0%)  | NR                     |
| Koundouris et al.       | 2012  | USA       | Retrospective | 1         | 2000       | 2010     | 213      | NR                  | 147 (69.0%) | 213       | 6       | 2.9%             | 213 (100.0%)    | 0 (0.0%)  | 15.5                   |
| Kowal et al.            | 1995  | Japan     | Retrospective | 1         | 1994       | 1994     | 72       | NR                  | 32 (44.4%) | 72        | 16      | 22.2%            | 72 (100.0%)     | 12 (16.7%) | 12                     |
| Kwon et al.             | 2016  | South Korea | Retrospective | 1         | 2002       | 2016     | 126      | NR                  | 66 (52.4%) | 516       | 24      | 6.3%             | 126 (24.4%)     | 0 (0.0%)  | NR                     |
| Kwon et al.             | 2019  | South Korea | Retrospective | 1         | 2005       | 2014     | 516      | NR                  | 219 (42.4%) | 109       | 1       | 4.7%             | 516 (100.0%)    | 109 (21.1%) | 60                     |
| Liu et al.              | 2015  | China     | Retrospective | 1         | 2013       | 2017     | 109      | NR                  | 60 (55.0%) | 109       | 23      | 21.1%            | 109 (100.0%)    | 0 (0.0%)  | NR                     |
| Maciejewski et al.      | 2014  | Poland    | Retrospective | 1         | 2010       | 2013     | 64       | NR                  | 529 (82.6%) | 64        | 1       | 1.6%             | 64 (100.0%)     | 0 (0.0%)  | NR                     |
| Mainprize et al.        | 2010  | UK        | Retrospective | 1         | 1993       | 1997     | 36       | NR                  | 19 (50.0%) | 18        | 2       | 11.1%            | 3 (16.7%)       | 0 (0.0%)  | NR                     |
| Matlok et al.           | 2013  | Poland    | Retrospective | 1         | 1997       | 2012     | 152      | NR                  | 94 (64.9%) | 152       | 1       | 0.7%             | 152 (100.0%)    | 8 (5.3%)  | NR                     |
| Matsuz et al.           | 2010  | Portugal  | Retrospective | 1         | 2003       | 2007     | 95       | NR                  | 62 (66.7%) | 95        | 2       | 2.2%             | 86 (92.9%)      | 0 (0.0%)  | NR                     |
| Meroxan et al.          | 2013  | Poland    | Retrospective | 1         | 1988       | 1998     | 109      | NR                  | 58 (53.2%) | 20        | 1       | 0.9%             | 109 (100.0%)    | 3 (3.0%)  | 37.2                   |
| Ondu et al.             | 1999  | Japan     | Retrospective | 1         | 1993       | 1993     | 95       | NR                  | 1,092 (1.0%) | 1,092     | 19      | 0.2%             | 133 (12.2%)     | 0 (0.0%)  | 37.2                   |
| Ondu et al.             | 2020  | South Korea | Retrospective | 1         | 2009       | 2014     | 139      | NR                  | 53 (39.0%) | 139       | 16      | 11.5%            | 139 (100.0%)    | 80 (57.6%) | NR                     |
| Ondu et al.             | 2020  | South Korea | Retrospective | 1         | 2014       | 2019     | 98       | NR                  | 98 (0.0%)   | 98        | 0       | 0.0%             | 98 (100.0%)     | 0 (0.0%)  | NR                     |
| Ondu et al.             | 2018  | South Korea | Retrospective | 1         | 2008       | 2008     | 689      | NR                  | 1,092 (1.0%) | 689       | 25      | 3.6%             | 109 (25.1%)     | 0.09 (100.0%) | 60                     |
| Ondu et al.             | 2019  | South Korea | Retrospective | 1         | 1995       | 2005     | 1,558    | NR                  | 725 (46.4%) | 1,558     | 34      | 3.6%             | 0 (0.0%)        | 1,508 (100.0%) | 37.2                   |
| Park et al.             | 2015  | South Korea | Retrospective | 1         | 1997       | 2012     | 836      | 47       | 198 (26.3%)          | 836       | 56        | 6.7%             | 836 (100.0%)     | 184 (22.0%) | NR                     |
| Patel et al.            | 2019  | UK        | Retrospective | 1         | 2008       | 2013     | 558      | 52       | 297 (53.2%)          | 558       | 3        | 0.3%             | 89 (15.9%)       | 168 (30.1%) | 23.5                   |
| Author        | Year | Country | Design       | Sites | Start date | End date | Patients | Median age (months) | Female | Polyps | Cancers | Malignancy rate | Cholecystectomy | Monitoring | Median follow-up (months) |
|--------------|------|---------|--------------|-------|------------|----------|----------|------------------|--------|--------|---------|-----------------|----------------|------------|-----------------------------|
| Pedersen et al | 2012 | Denmark | Retrospective | 1    | 2008       | 2009     | 203      | 54              | 114    | 6      | 0       | 0.0%            | 13 (6.4%)     | 31 (15.3%) | 24                          |
| Pickering et al | 2020 | Ireland | Retrospective | 4    | 2013       | 2018     | 134      | 53              | 74     | 6      | 4.5%    | 134 (100.0%)   | 0 (0.0%)     | NR         |                             |
| Rafaelson 18  | 2020 | Denmark | Prospective   | 1    | 2007       | 2009     | 154      | 62              | 100    | 6      | 0.0%    | 0 (0.0%)       | 154 (100.0%) | 120        |                             |
| Salmeron et al | 2018 | Turkey  | Retrospective | 1    | 2008       | 2013     | 159      | NR              | NR     | 8      | 5.0%    | 96 (60.4%)     | 0 (0.0%)     | NR         |                             |
| Sans et al    | 2017 | Turkey  | Retrospective | 1    | 2005       | 2015     | 109      | 45              | 69     | 15     | 2.2%    | 109 (100.0%)   | 60 (50.0%)   | 22.2       |                             |
| Sach et al    | 2013 | Turkey  | Retrospective | 1    | 1996       | 2012     | 138      | 55              | 91     | 21     | 15.2%   | 138 (100.0%)   | 0 (0.0%)     | NR         |                             |
| Shah 60       | 2010 | Nepal   | Retrospective | 1    | 2004       | 2009     | 32       | 40              | 23     | 2      | 6.3%    | 32 (100.0%)    | 0 (0.0%)     | NR         |                             |
| Shan et al    | 2019 | China   | Retrospective | 1    | 2011       | 2018     | 38       | 53              | 23     | 10     | 26.3%   | 38 (100.0%)    | 0 (0.0%)     | NR         |                             |
| Shinkai et al | 2008 | Japan   | Retrospective | 1    | 1990       | 1995     | 60       | NR              | 23     | 1      | 13.8%   | 19 (31.7%)     | 0 (0.0%)     | NR         |                             |
| Spaziani et al| 2019 | Italy   | Retrospective | 1    | 2006       | 2018     | 278      | 83              | 52     | 10     | 5.7%    | 278 (100.0%)   | 0 (0.0%)     | NR         |                             |
| Sugiyama et al| 2020 | Japan   | Retrospective | 1    | 1988       | 1997     | 194      | NR              | 100    | 11     | 5.7%    | 194 (100.0%)   | 0 (0.0%)     | NR         |                             |
| Sun et al     | 2018 | Turkey  | Retrospective | 1    | 2004       | 2012     | 145      | NR              | 105    | 19     | 13%     | 145 (100.0%)   | 91 (62.0%)   | NR         |                             |
| Sun et al     | 2019 | China   | Retrospective | 1    | 2013       | 2016     | 686      | NR              | 383    | 60     | 26.3%   | 686 (100.0%)   | 686 (100.0%) | 24         |                             |
| Sung et al    | 2014 | South Korea | Retrospective | 1   | 2009       | 2011     | 516      | NR              | 133    | 250    | 5.7%    | 250 (100.0%)   | 0 (0.0%)     | NR         |                             |
| Szpakowski et al | 2020 | USA     | Retrospective | Multi | 1995      | 2014     | 3,995    | 50              | 1,964  | 53     | 0.0%    | 19 (31.7%)     | 0 (0.0%)     | NR         |                             |
| Tari et al    | 2010 | Turkey  | Retrospective | 1    | 1998       | 1998     | 100      | NR              | 74     | 26     | 26.0%   | 100 (100.0%)   | 0 (0.0%)     | NR         |                             |
| Tertoglu et al | 2017 | Turkey  | Retrospective | 1    | 2010       | 2016     | 278      | NR              | 187    | 279    | 7.1%    | 279 (100.0%)   | 0 (0.0%)     | NR         |                             |
| Ungaravittayana et al | 2018 | Thailand | Retrospective | 1    | 2017       | 2017     | 85       | NR              | 47     | 85     | 2.9%    | 85 (100.0%)    | 0 (0.0%)     | NR         |                             |
| Veledavudi et al | 2017 | Turkey  | Retrospective | 1    | 2011       | 2012     | 82       | NR              | 48     | 82     | 0.0%    | 82 (100.0%)    | 0 (0.0%)     | NR         |                             |
| Wu et al     | 2019 | China   | Retrospective | 1    | 2011       | 2017     | 1,561    | 495             | 925    | 1561   | 5.9%    | 1561 (100.0%)  | 0 (0.0%)     | NR         |                             |
| Xie et al    | 2017 | China   | Retrospective | 1    | 2008       | 2015     | 1,468    | NR              | 74     | 1468   | 0.2%    | 1468 (98.5%)   | 0 (0.0%)     | NR         |                             |
| Yang et al   | 1992 | China   | Retrospective | 1    | 1982       | 1990     | 172      | 443             | 734    | 172    | 7.6%    | 172 (100.0%)   | 0 (0.0%)     | NR         |                             |
| Yeh 39       | 2011 | Taiwan  | Retrospective | 1    | 1991       | 1999     | 123      | NR              | 63     | 123    | 1.6%    | 123 (100.0%)   | 0 (0.0%)     | NR         |                             |
| Zielinski et al | 2019 | USA     | Retrospective | 1    | 1996       | 2007     | 130      | NR              | 85     | 130    | 7.7%    | 130 (100.0%)   | 25 (19.2%)   | 32         |                             |

* NR not reported. Total percentages of patients treated with cholecystectomy and monitoring may not add up to 100% (total can include patients followed-up before or after cholecystectomy and patients lost to follow-up).
Risk of Malignancy in Gallbladder Polyps: a Systematic Review

Substantial heterogeneity was measured between studies (I² = 99.95%, 95% credible interval 99.86–99.98%). The distribution of included studies at different size thresholds is shown in Figure 2 and demonstrates the heterogeneity across studies, although most studies were concentrated in a region with a probability of cancer of less than 0.03. Data reported at subsequent time points were limited, so malignant risk over time could not be determined.

A Bayesian meta-analysis model was developed to accommodate substantial missing data across the studies. As a result, it was possible to include all 82 studies in the analysis. The model demonstrated an increased risk of cancer as polyp size increased (Figure 3a). For example, a mean polyp size of 13.9 mm had a mean risk of 1 in 100. However, there was considerable uncertainty with this estimate due to study heterogeneity and this uncertainty increased with threshold size, illustrated by the widening credible ranges, which may be explained by increased missing data at higher polyp sizes. Figure 3b shows the 95% prediction region for the predicted risk from the model. This demonstrates the effects of between-study heterogeneity on the uncertainty of the risk estimates. The prediction region is wide and increases with polyp size to around 60% suggesting substantial uncertainty in the model estimates. The addition of associated co-variates (age, gender, presence of gallstones, symptoms, and single or multiple polyps) to the model did not substantially change the Deviance Information Criterion (DIC) of the Bayesian model and therefore were excluded (Supplementary Material 1).

The median cancer risk of polyps measuring 5 mm and 10 mm across all studies was 0.14% (99% credible range 0.08–0.26%) and 0.60% (0.30–1.16%), respectively. Thus, the number of patients with polyps measuring 5 mm and 10 mm or less needed to detect one cancer is 714.3 and 166.7, respectively, equating to 13.2 and 64.4 cancers per 10,000 patients. The point estimates and cumulative cancer risk with 99% credible intervals for incremental polyp size is provided in Table 2. A probability matrix, showing incremental sizes of polyps with corresponding cancer risk, is included in Supplementary Material 1.

Risk of bias assessment

The majority of studies (n = 68, 82.9%) were assessed as having high risk of bias due to their observational nature, and the remaining 14 (17.1%) as moderate risk of bias (Supplementary Material 1). According to the GRADE working group methodology,16 13 studies (15.6%) were graded with very low certainty, 56 studies (68.3%) with low certainty, and 13 studies (15.6%) with moderate certainty (Supplementary Material 1). The overall confidence in the result of the quantitative synthesis was summarised as low.

Sensitivity analysis

The effect of methodological quality on the median cancer risk was tested in sensitivity analysis (Figure 4). Compared with the overall median curve, excluding studies with a very low certainty rating had little effect on the estimated risk. However, confining the analyses to those studies with moderate certainty or higher (13 studies) substantially lowered the median risk curve. This is due to the two largest studies, which reported only 38 cancers in 46,782 patients (0.08%), having substantially lower cancer rates than the other studies in the meta-analysis.
In studies considered moderate quality, the median cancer risk of polyps measuring 5 mm and 10 mm or less reduced considerably to 0.03 and 0.04%, respectively. This increased the number of patients needed to detect one cancer to 2754.8 and 2167.8, equating to 3.6 and 4.6 cancers per 10,000 patients with polyps measuring 5 mm and 10 mm or less, respectively.

**DISCUSSION**

This systematic review and meta-analysis of more than 67,000 patients is the first comprehensive meta-analysis to model the risk of malignancy in gallbladder polyps. The study has shown that the estimated risk of malignancy in patients with gallbladder polyps is lower than previously reported and is extremely low in polyps measuring less than 10 mm.

Presently, studies are mostly low quality which affects the estimates of malignant risk presented in this meta-analysis, however the risk of cancer reported in the two largest and higher quality studies was far lower than the remainder of small, low-quality studies, which were likely to report inflated risk. The findings of this meta-analysis suggest that the risk of malignancy in gallbladder polyps is very low, suggesting that the monitoring of gallbladder polyps, particularly small polyps, may not be clinically or cost-effective in some healthcare systems. However, given the uncertainty introduced by the low quality studies, the clinical and cost effectiveness of monitoring small polyps requires further investigation.

Previous work has attempted to estimate the risk of malignancy in ultrasound detected gallbladder polyps. A large recent study hypothesised that the true risk of gallbladder polyps may not be as great as previously reported. A retrospective study reported outcomes of gallbladder polyps over a 20-year period in a population of more than 600,000. The unadjusted gallbladder cancer
rate per 100,000 person-years was 11.3 (95% confidence intervals 6.2–16.3) and increased with greater polyp size, from 1.3 (95% confidence intervals 0.7–6.5) in polyps less than 6 mm to 128.2 (95% confidence intervals 9.4–217.0) in polyps 10 mm or greater. Additionally, gallbladder cancer rates in this cohort study were similar in patients with and without polyps on initial TAUS (0.053% vs 0.054%, respectively). These data were collected retrospectively, and the proportion of pseudopolyps was not reported. The study demonstrated the apparent benign natural history and slow growth of most polyps, but firm estimates of median cancer risk cannot be extrapolated from this study due to its limitations.

Further, we have confirmed that increasing polyp size is an important prognostic factor for the development of malignancy, but an optimal size threshold for intervention remains uncertain. Gallbladder polyp size is commonly reported at TAUS because the reliability and reproducibility of size measurements is excellent. The decision to intervene in patients with gallbladder polyps is contentious, but important, as many patients undergo cholecystectomy every year for gallbladder polyps. An arbitrary threshold of 10 mm is commonly cited for intervention in the literature, although larger size thresholds have been reported to be more accurate at differentiating benign from malignant polyps. Compliance with existing guidelines may have contributed to the increased detection of cancer above 10 mm in this meta-analysis, as findings were predominately derived from retrospective data, although the results demonstrated a clear continuous association with incremental polyp size without any significant step-change in risk at a particular threshold. Large-scale, prospective, multicentre registries are required to increase statistical power and provide better quality data to improve treatment and monitoring decisions in these patients. Randomised data would improve confidence in specific size thresholds.

There is also conflicting data regarding the cost-effectiveness of monitoring gallbladder polyps. Such analysis is dependent on accurate estimates of median cancer risk to provide meaningful analysis, which this meta-analysis can facilitate. Patel et al have suggested that compliance with polyp monitoring guidelines may be cost-effective. However, it is worthy of further research. We included historical data using older ultrasound technology because this review was designed to assess risk rather than technology evaluation and we wanted to capture as much follow-up data as possible. Whilst measurement error is likely to be present in older cohorts, we suggest a greater number of small polyps with less risk are likely to be detected incidentally using newer ultrasound technology, and thus contribute to a further reduction in overall malignant risk. The methodological quality of the included studies was generally considered low. Suboptimal reporting of duration and frequency of follow-up in many studies prevented meaningful modelling of cancer risk in the subsequent years after detection, which would have better informed guideline recommendations for duration of follow-up. Often, patient and polyp characteristics, including proportions of true vs pseudopolyps, were inadequately reported, meaning sensitivity analyses could not be performed to explore variations on our estimated median cancer risk statistics. We had planned to include high-risk patients with primary sclerosing cholangitis (PSC) as a co-variate, however there were insufficient data to allow this. Only eight patients from two included studies were reported.

Many studies have investigated the risk of malignancy in PSC cohorts, but these can inflate the estimates in general populations and hence were excluded. Attempts were made to gather individual patient data. We received individual data from 558 patients, but the overall response rate was poor, so personalised prediction of which patients eventually developed gallbladder cancer could not be attempted. Potentially important clinical co-variates (including patient age, ethnicity, and sessile morphology) were also sporadically reported in many included studies, but addition of available co-variates in the model did not identify any factors of prognostic significance. Furthermore, any predictions are contingent on the accuracy of the model and whilst the parameter estimates were in the right direction, new trial data may refine or even challenge these. Finally, we found significant heterogeneity between studies which affected our overall confidence in the results of the meta-analysis. Publication bias could not be assessed due to the presence of intra- and inter-study heterogeneity.

However, this study also has limitations. The analysis provides an estimate for the overall cumulative risk of cancer for different polyp sizes and the uncertainty associated with this risk. However, a clinical question not answered here is that of the conditional risk of cancer for a polyp of size greater than 10 mm, for example. This would require a far more complex model and is beyond the scope of this analysis. However, for the same reasons given in the above analysis, it is likely that any estimates of the conditional risk would also be shrouded with considerable uncertainty. As such, there is a need for further research.

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CONCLUSION
This review is the first comprehensive meta-analysis investigating the risk of malignancy in gallbladder polyps. Here, based on the data from 67,837 patients across 82 studies, a de novo Bayesian model was developed to establish the best available estimates concerning the development of cancer risk with polyp size. Malignant risk was extremely low, particularly in polyps measuring less than 10 mm. For polyps greater than 10 mm, estimates of the actual risk were hampered by recommended intervention in this group. However, a step increase of risk in polyps measuring larger than 10 mm is neither likely, nor supported, by the data. This suggests research efforts should be directed at obtaining the full articles for review.

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