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Review

The prevalence of human papillomavirus in colorectal adenomas and adenocarcinomas: A systematic review and meta-analysis

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Abstract ***Background:*** The role of human papillomavirus (HPV) in colorectal cancer has been widely studied with conflicting results. We performed a systematic review and a meta-analysis to estimate the prevalence of HPV in colorectal adenocarcinomas and adenomas, and test the potential association.

Methods: The pooled HPV prevalence was estimated using a random effects model and the I^2 statistic was used to describe the amount of heterogeneity. Potential sources of heterogeneity were evaluated by meta-regression and stratified analyses. For the studies on adenocarcinomas including control tissue, random effects estimates of odds ratios (ORs) and 95% confidence intervals (CIs) were calculated.

Results: Thirty-seven studies were included. Among the 2630 adenocarcinomas, the pooled HPV prevalence was 11.2% (95% CI, 4.9–19.6%) with substantial between-study heterogeneity ($I^2 = 97.2\%$). The HPV prevalence varied by geographical region with highest prevalence in South America (45.1%, 95% CI, 21.9–69.4%), Asia (39.2%, 95% CI, 20.3–60.0%) and the Middle East (32.2%, 95% CI, 1.1–79.3%), and by detection method with the highest HPV prevalence in PCR-based studies. In the eight case–control studies, the pooled HPV prevalence was 36.8% (95% CI, 21.3–53.8%) in adenocarcinomas and 1.6% (95% CI, 0.0–9.6%) in controls giving an OR of 6.0 (95% CI, 2.0–17.9%) for the association between HPV and colorectal cancer. Among the 415 adenomas, the pooled HPV prevalence was 5.1% (95% CI, 0.0–17.8%; $I^2 = 93.7\%$).

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Conclusions: HPV may be associated with a subset of colorectal cancers. Future large-scale multicenter case–control studies with data on risk factors such as lifestyle and sexual behaviour are needed.

1. Introduction

Colorectal cancer is the fourth most common cancer worldwide with an estimated 1,360,602 new cases and 693,881 deaths annually [1]. Approximately 95% of colorectal cancers are adenocarcinomas [2], and the main precursor lesions are the adenomas [2].

The progression of adenomas to adenocarcinomas is influenced by genetic and environmental factors [3]. One environmental factor which may be associated with colorectal cancer is human papillomavirus (HPV) [4–6]. HPV is a necessary cause of cervical cancer [7] and is also associated with a subset of other anogenital cancers (e.g. vulvar, vaginal, anal and penile cancer) and head and neck cancers [8]. However, the association between HPV and colorectal cancer remains inconclusive.

HPV could potentially infect the colorectum by an ascending infection from anogenital sites [9,10], or through haematogen or lymphogen spread [11–13]. Since the first reports in the late 1980s [14–17], an accumulating amount of studies have investigated the prevalence of HPV in colorectal cancer with prevalence estimates ranging from 0% [14,16–30] to 84% [31]. Although two previous reviews [4,5] and one meta-analysis [6] on the association between HPV and colorectal cancer have been published, they had weaknesses such as non-exhaustive literature search; inclusion of conference abstracts without peer-review; limited statistical analysis; or inclusion of studies with potential overlapping study populations or immunosuppressed patients [4–6]. Furthermore, new data on the HPV prevalence in colorectal cancer have been published recently [11,30,32,33] including one large study with 555 cases [33]. These studies were not included in the previous reviews and meta-analyses.

We systematically searched the literature and performed an updated review and meta-analysis of all studies of the HPV DNA prevalence in colorectal adenocarcinomas and adenomas. Meta-regression and stratified analyses were applied to investigate variables potentially related to the HPV prevalence and finally, we tested the association between HPV infection and colorectal adenocarcinomas by pooling studies with colorectal control tissue.

2. Materials and methods

2.1. Search strategy

We searched PubMed and Embase up to 22 March, 2013 for all studies of the HPV DNA prevalence in colorectal adenocarcinomas and adenomas. Combinations of search terms for HPV and carcinoma, adenoma, or polyps of the colon or rectum were used (Supplementary, Table 1). We identified 1267 records in PubMed and 1785 records in Embase (Fig. 1). After removal of duplicates ($n = 882$), all abstracts ($n = 2170$) were reviewed independently by two authors (LB and LTT). Full-text copies of potentially relevant papers ($n = 114$) were obtained and reviewed independently by two authors (LB and LTT). Inconsistencies in the identification of relevant papers were discussed to reach consensus. We also reviewed reference lists of retrieved publications to identify other relevant studies.

2.2. Eligibility criteria

We included studies that reported the prevalence of HPV DNA in human colorectal adenocarcinoma or adenoma tissue samples. Only peer-reviewed studies published in English and with explicit information on HPV DNA detection method were included. We did not include studies detecting HPV in serum or cytology samples or in metastatic tissue; studies with less than five cases; studies of colorectal tumours of other histology than adenocarcinomas (e.g. squamous cell carcinomas); and studies of immunosuppressed patients.

The study was conducted in accordance with the "preferred reporting items for systematic reviews and meta-analyses" (PRISMA) guidelines [34].

2.3. Data extraction

Data were extracted independently by two authors (LB and, LTT or TBO) with disagreements resolved by consensus. For each study we extracted information on: first author and publication year; country; year of sample collection; type of tissue; HPV DNA detection method; HPV types detected; number of colorectal adenocarcinoma and adenoma cases; number of colorectal controls (tumour-adjacent control tissue or colorectal tissue from cancer-free controls); specific anatomical origin of adeno-