**Annex 1.** Methods of the systematic review and meta-analysis.

***Search strategy***

**In a first step, we conducted an umbrella review on smoking and the risk of cancer at any site. Umbrella reviews provide syntheses of existing evidence on a specific topic, systematically searching and evaluating all systematic reviews and/or meta-analyses on all health outcomes associated with a specific exposure (1). Thus, through a comprehensive literature search on various databases (PubMed/MEDLINE, Embase, Institute for Scientific Information Web of Science, and the Cochrane Database of Systematic Reviews), we identified all meta-analyses, pooled analyses, and reviews on the association between cigarette smoking and the risk of cancer at any site published up to 27th April 2017 (2). We identified seven systematic reviews/meta-analyses (3-9) and three pooled analyses (10-12) on the association between cigarette smoking and the risk of colorectal cancer (Supplementary Figure 1). We also considered two monographs of the IARC on tobacco smoking (13,14) and two reports from the Centers for Disease Control and Prevention (CDC) (15,16). We screened the 14 above-mentioned reports and identified a total of 184 non-duplicate publications on tobacco smoking and the risk of CRC.**

**In a second step we carried out a literature search to identify all original studies published between January 2008 (i.e. the publication date of the last and most comprehensive review available on the topic (3)**) **and September 2018 (Box 1). After exclusion of duplicate publications and ineligible articles and the inclusion of 13 additional relevant publications identified from other sources (e.g., reference list of relevant publications), the update of the scientific literature resulted in 119 original publications on cigarette smoking and the risk of CRC. Combining original articles identified in the umbrella review (step 1) and in the updated literature search (step 2), we retrieved 290 relevant original study publications (Supplementary Figure 1) that were screened on the basis of their full text using the eligibility criteria described below.**

***Eligibility criteria***

**Studies were included in the present meta-analysis if they satisfied all of the following eligibility criteria: i) they were either case-control studies (including nested case-control studies or pooled analyses of case-control studies) or cohort studies (including case-cohort studies or pooled analyses of cohort studies); ii) they were published as original articles in English; iii) they provided data on the general population; iv) they provided information on cigarette smoking; v) they reported risk estimates, including risk ratios, odds ratios, hazard ratios or mortality rate ratios – all referred to as relative risk (RR) – for at least one variable among smoking status (current, former and/or ever smoking), intensity, duration, and time since quitting, compared to never or current cigarette smokers, and corresponding 95% confidence intervals (CI), or providing sufficient information to compute them. Moreover, we considered only original articles that reported findings on malignant CRC or colon or rectal cancers, thus excluding articles on colorectal polyps and adenomas.**

**Eligibility was independently evaluated by two investigators (Borroni and Santucci). Of 290 original publications, 65 were excluded because they did not meet the above-mentioned eligibility criteria (Supplementary Table 1 and Supplementary Figure 1).**

**When results of the same study were provided in more than one original publication, we considered data published in the most recent and/or more complete publication.**

***Data extraction***

**For each eligible study, we collected general information on the publication (e.g., first author, year of publication and journal), study (e.g., country, study name, calendar period, study design, outcome and sample size), the model used for RR estimates (including covariates allowed for), and RRs with the corresponding 95% CIs and, when available, the number of cases and controls (or subjects at risk/person years for cohort studies) for various exposure categories.**

**Where necessary, we used the method for pooling non-independent estimates described by Hamling and colleagues (17) to change the reference category or to collapse the RRs of two or more categories when the reference group was the same. Where RRs were reported for colon and rectal cancer separately, we used the method described by Rucker and colleagues (18) to obtain a single RR for colorectal cancer.**

**Box 1.** Literature search strings for the update of the last available comprehensive review on the association between smoking and colorectal cancer risk used in MEDLINE and Embase.

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| **MEDLINE**((((colon OR rectum OR rectal OR colorectum OR colorectal OR “colon-rectum”) AND (cancer OR neoplasm OR carcinoma OR Neoplasms [MeSH Terms]) AND (cigarette OR cigarettes OR tobacco OR smoking OR smokers OR smoking [MeSH Terms]))) AND English[Language]) AND ("2008"[Date - Publication] : "2020"[Date - Publication]) |
| **Embase**cigarette:ti OR cigarettes:ti OR tobacco:ti OR smoking:ti OR smokers:ti AND (colon:ab,ti OR rectum:ab,ti OR rectal:ab,ti OR colorectum:ab,ti OR colorectal:ab,ti) AND (cancer:ab,ti OR neoplasm:ab,ti OR carcinoma:ab,ti) AND (article:it OR review:it) AND [english]/lim AND [2008-2020]/py NOT [medline]/lim |

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