ORIGINAL ARTICLE

Prediagnostic use of low-dose aspirin and risk of incident metastasis and all-cause mortality among patients with colorectal cancer

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Aims: Previous studies suggest that the use of low-dose aspirin before a colorectal cancer (CRC) diagnosis may be associated with a decreased risk of CRC progression. Data supporting this association, however, have been inconsistent. We evaluate whether the use of prediagnostic low-dose aspirin is associated with a lower risk of metastases and all-cause mortality in CRC patients.

Methods: Using a large Italian population-based primary care database, we identified a cohort of 7478 patients newly diagnosed with nonmetastatic CRC between 2000 and 2013. Use of prediagnostic low-dose aspirin was compared with no use of low-dose aspirin. Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) of incident metastasis and of all-cause mortality associated with prediagnostic low-dose aspirin use, both overall and by duration of use.

Results: There were 314 incident metastatic events and 2189 deaths during a mean follow-up time of 4.4 and 4.7 years, respectively. Overall prediagnostic use of low-dose aspirin was not associated with a decreased risk of incident metastasis (HR 0.88; 95% CI 0.63–1.22) or all-cause mortality (HR 1.09; 95% CI 0.96–1.22) in CRC patients. Cumulative duration of aspirin use was not associated with a decreased risk of incident metastasis (*P*-trend = .22) or all-cause mortality (*P*-trend = .38). These findings remained consistent in sensitivity analyses.

Conclusion: In this real-world, population-based study, the prediagnostic use of low-dose aspirin was not associated with a decreased risk of incident metastasis or all-cause mortality in CRC patients.

KEYWORDS

aspirin, cohort study, colorectal cancer, diagnosis, metastasis, mortality, pharmacoepidemiology

There is no principal investigator. This study is an analysis of secondary data and did not involve direct intervention of patients. 22 April 2020

1 | INTRODUCTION

Colorectal cancer (CRC) is the fourth most common cancer worldwide, behind lung, breast and prostate cancer, accounting for 1.8 million incident cases in 2018.[1] It is the second leading cause of cancer mortality, representing nearly 10% of all cancer deaths.[1]

The US Preventive Task Force currently recommends the use of low-dose **aspirin** for the primary prevention of CRC in adults aged 50–59 years who have a 10-year risk of cardiovascular disease of 10% or more.[2] This recommendation follows evidence that aspirin use may reduce CRC incidence after 5–10 years of use for that specific patient population. Existing evidence for the role of low-dose aspirin in secondary prevention, however, is less consistent. Indeed, once a patient is diagnosed with CRC, it is unclear whether the use of low-dose aspirin before the diagnosis leads to better cancer-specific outcomes. Observational studies investigating the association between prediagnostic use of low-dose aspirin and cancer prognosis have shown inconsistent findings.[3–8] While some studies have demonstrated an association between prediagnostic use of low-dose aspirin and lower CRC-specific mortality,[3,4] all-cause mortality,[4,5] and incident CRC metastasis,[6] others have found no associations.[7,8] Some of these studies also had methodological shortcomings such as confounding by indication, small sample size, immortal time bias and residual confounding. Thus, use of low-dose aspirin before a CRC diagnosis and its role in cancer progression and mortality is still largely debated. Large, population-based observational studies addressing limitations from previous studies and focusing specifically on the use of low-dose aspirin before a CRC diagnosis and its effect on cancer prognosis are thus needed.

Given the conflicting evidence, the objective of this population-based study is to determine whether the use of low-dose aspirin before a CRC diagnosis is associated with a decreased risk of incident metastasis and a decreased risk of all-cause mortality in CRC patients, both overall and by cumulative duration of use.

What is already known about this subject

- Low-dose aspirin appears effective in the primary prevention of colorectal cancer (CRC) in selected populations.
- Its role in the secondary prevention of metastatic colorectal cancer, however, is still unclear and largely debated.
- Few studies have investigated whether low-dose aspirin is associated with a decreased risk of metastasis and mortality in patients with CRC.

What this study adds

- This large, population-based study indicates that low-dose aspirin use was not associated with overall reduced risk of incident metastasis and all-cause mortality.
- Findings suggest a potentially protective effect after >4 years of cumulative use of low-dose aspirin.
- Additional studies are needed to determine whether long-term use of low-dose aspirin is associated with improved prognosis of CRC.

2 | PATIENTS AND METHODS

2.1 | Data source

This study was conducted using the Health Search Database, a large Italian general practice database established in 1998. The database includes electronic records of over 1.1 million patients registered by approximately 800 general practices uniformly distributed across Italy, whom have met predefined quality standards pertaining to the completeness and consistency of the data recorded as well as the representativeness of the data.[9] The quality and representativeness of the data have been demonstrated through comparison with national cross-sectional surveys.[10–12]

The database includes patient demographic and anthropometric data, medical diagnoses coded according to the International Classification of Diseases, 9th Revision (ICD-9), diagnostic investigations and results, hospital referrals and admissions, drug prescription information coded according to the Anatomical Chemical Classification, which include trade name, dosage form, date of filled prescription and number of days' supply, and date of death. Data are linked with a unique, encrypted patient identifier. The encoding of the ambulatory procedures was conducted in accordance with the Nomenclatore Tariffario, a list of all outpatient specialist medical services and related tariffs, instituted by Ministerial Decree in 1996.[13]

This is an observational, population-based, noninterventional study. According to a by-law on the classification and implementation of observational drug-related research, as issued by the Italian National Drug Agency, the present study does not require approval by an ethics committee in Italy (Italian Drug Agency note, 3 August 2007).

2.2 | Study population

We identified a cohort of all patients ≥18 years and newly diagnosed with CRC as recorded in the outpatient file by the general practitioner (identified using ICD-9 codes; Table S1) between 1 January 2000 and 31 December 2013. Cohort entry was defined as the date of this CRC diagnosis. To be eligible for inclusion in the study, patients were required to have at least 1 year of medical history in the database prior to cohort entry. Patients diagnosed with any cancer at any time before cohort entry were excluded (identified using ICD-9 codes; 140.x-239.x).

Patients who met the study inclusion criteria were followed until the incidence of metastatic CRC (identified using ICD-9 codes; Table S1), death from any cause, a new diagnosis of cancer other than CRC, end of registration with general practice or end of study period (31 December 2013), whichever occurred first.

2.3 | Exposure assessment

Low-dose aspirin was defined as a dose of 1 tablet (100 mg) per day (identified using ATC code; B01AC06). Prediagnostic use was defined as the presence of at least 1 low-dose aspirin prescription at any time before cohort entry (i.e. date of CRC diagnosis).

We also defined use of low-dose aspirin according to cumulative duration of use. Cumulative duration of use was calculated by summing the duration of each prescription given at any time before cohort entry until the cohort entry date. Cumulative duration of use was categorized as ≤1 year, 1.1–2 years, 2.1–3 years, 3.1–4 years or >4 years of use.

2.4 | Statistical analysis

Crude incidence rates of incident CRC metastasis and of all-cause mortality, based on the Poisson distribution, were calculated by dividing the number of cases with the total number of cumulative person-years of follow-up. Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) of incident CRC metastasis and all-cause mortality associated with prediagnostic use of low-dose aspirin *vs* nonuse. This was considered the primary analysis.

The models were adjusted for the following confounders measured at or prior to cohort entry: age, sex, year of cohort entry, body mass index, smoking status (current, former, never), alcohol-related disorders, and diagnoses of hypertension, cardiac arrhythmia, dyslipidaemia, stroke, coronary artery disease, congestive heart failure, peripheral vascular disease, peptic ulcer, chronic obstructive pulmonary disease, asthma, diabetes mellitus, kidney disease and autoimmune disease. Models were also adjusted for the following medications prescribed in the year preceding, or on the date of cohort entry: use of antidiabetic drugs, antihypertensive drugs, antithrombotic drugs, cardiac drug therapy, lipid-lowering agents, systemic corticosteroids, nonsteroidal anti-inflammatory drugs other than aspirin, oral contraceptives and hormone replacement therapy.

2.5 | Secondary analysis

We performed 1 prespecified secondary analysis. To assess possible duration–response relationships, we investigated the association between cumulative duration of use on the risk of incident CRC metastasis and of all-cause mortality. For these analyses, hazard ratios (HRs) were estimated for 5 predefined cumulative duration categories (≤1 year, 1.1–2 years, 2.1–3 years, 3.1–4 years and >4 years). We also modelled cumulative duration of use as a continuous variable using restricted cubic spline.

2.6 | Sensitivity analyses

We performed 5 sensitivity analyses to assess the robustness of our results. First, to assess confounding by indication, we conducted an analysis using an interaction term for cardiovascular disease (e.g. stroke, coronary artery disease, peripheral vascular disease) because confounding by indication would occur when patients indicated for aspirin (i.e. those with cardiovascular disease) would be systematically different than those not indicated for aspirin.[14] Second, as an alternative method to control for confounding, we repeated the primary analysis using a disease risk score (DRS). The DRS estimates the probability of the outcome conditional on being unexposed to low-dose aspirin.[15] For this study, this method is more appropriate than the propensity score method because the exposure to aspirin occurs before the covariates, whereas the propensity score is an individual's probability of receiving treatment conditional on the measured covariates at baseline.[15] The DRS was estimated through a Cox regression model and imputed in the model in place of the aforementioned covariates. Third, for the incident metastasis outcome, we conducted a competing risk analysis by death from any cause using the sub-distribution hazards model proposed by Fine and Gray.[16] Fourth, we repeated the primary analysis using a stricter CRC diagnosis definition, restricting the definition to ICD-9 codes for the colon and rectum only. Fifth, to account for differential look-back periods, we repeated the primary analysis restricting to patients with exposure to low-dose aspirin within 5 years of the CRC diagnosis. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

2.7 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY.

3 | RESULTS

The cohort included 7478 patients newly diagnosed with non-metastatic colorectal cancer (Figure 1) followed for a mean of 4.0 years (standard deviation: 3.6 years) for incident metastases and 4.7 years (standard deviation: 3.9 years) for all-cause mortality. A total of 1509 CRC patients were prescribed low-dose aspirin before their CRC diagnosis. During 30 180 person-years of follow-up, there were 314 incident metastases and 2189 all-cause deaths, for a crude incidence rate of 10.3 (95% CI 9.2–1.5) per 1000 person-years for incident metastases and 57.3 (95% CI 54.7–60.1) per 1000 person-years for all-cause

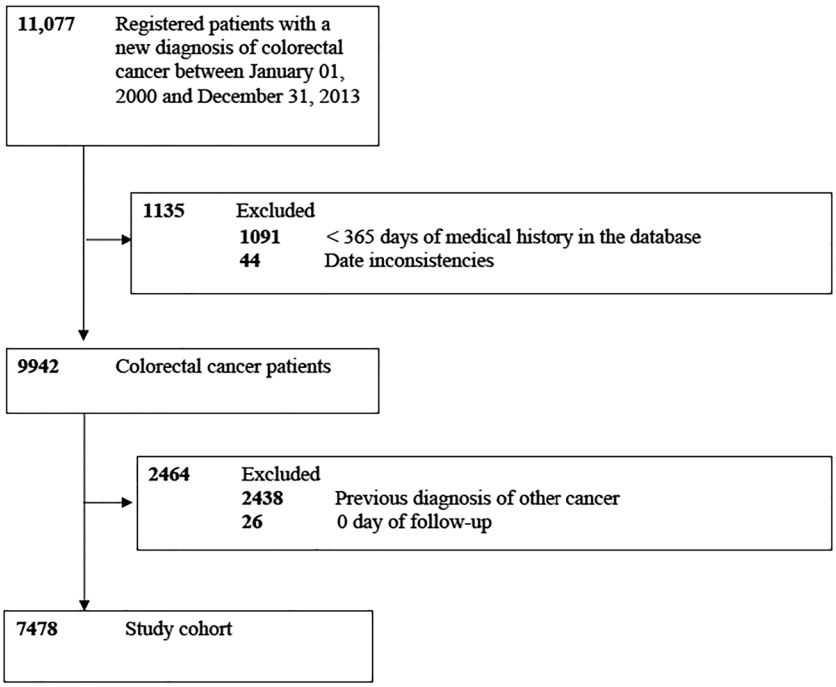

FIGURE 1 Study flow chart of patients included in the cohort

mortality. Most common metastases were of the liver (53.6%) and lungs (24.4%), then to the bone (6.6%), lymph nodes and brain (4.0% each), peritoneum (3.2%), adrenal gland (1.1%), and spleen and ovary (<1% each). The remaining patients were diagnosed with disseminated metastasis without specification of site.

Table 1 presents the baseline characteristics of the entire cohort and stratified by prediagnostic low-dose aspirin users and nonusers at cohort entry. As expected, low-dose aspirin users were older, more likely to be nonsmokers or former smokers, and more likely to be obese (≥25 kg/m^2). Users were also more likely to have comorbidities and use antihypertensive drugs, antithrombotic drugs, cardiac drug therapy, and lipid-lowering agents.

Table 2 presents the results of the primary analysis for risk of incident CRC metastases in users *vs* nonusers of low-dose aspirin. Compared with nonuse of low-dose aspirin, use of low-dose aspirin before a diagnosis of CRC was not associated with a decreased risk of incident metastasis (HR 0.88; 95% CI, 0.63–1.22). The secondary analysis by cumulative duration of use yielded nonsignificant associations (*P*-trend = .22, Table 2 and Figure S1). A hazard ratio below the null was reported in patients with >4 years of cumulative use of low-dose aspirin;, however few events were recorded in that category. Table 3 present the results of the secondary outcome of all-cause mortality. Similarly, compared with nonuse of low-dose aspirin, the use of low-dose aspirin before a diagnosis of CRC was not associated with a decreased risk of all-cause mortality (HR 1.08; 95% CI 0.96–1.22). In the secondary analysis, longer durations of use were not significantly associated with a decreased risk of all-cause mortality (*P*-trend = .38, Table 3 and Figure S2). The 5 sensitivity analyses generated findings that were consistent with those of the primary analysis (Figure 2 and Tables S2–S6).

4 | DISCUSSION

Findings from this large population-based cohort study of patients newly diagnosed with nonmetastatic colorectal cancer shows that the use of low-dose aspirin before a CRC diagnosis is not associated with an overall decreased risk of incident metastasis or of all-cause mortality. Results from the sensitivity analyses were consistent with those of the primary analysis. Although a protective effect was found in patients with >4 years of cumulative use of low-dose aspirin, confidence intervals were wide due to few reported events in that category.

Several observational studies have previously examined the association between prediagnostic use of nonsteroidal anti-inflammatory drugs, including aspirin, and CRC-specific outcomes.[3–5,8,17,18] While some studies have reported risk reductions ranging between 12 and 52%,[3–5,17] others have reported null associations.[8,18] Some of these findings, however, might have been due to selection bias through depletion of susceptibles, immortal time bias[19] or confounding by indication. It is also possible that the survival benefit observed in those studies might have been due to surveillance bias. As an individual regularly taking low-dose aspirin might be more likely to have bleeding and blood in the stools, this might prompt more frequent interactions with the medical system. As a result, CRC might be detected earlier in patients being prescribed low-dose aspirin and thus lead to a better prognosis. As there is some evidence for a protective effect of low-dose aspirin on incident CRC after 5–10 years of use,[2] it is thus possible that individuals using low-dose aspirin have a lower initial risk of incident CRC. We thus conducted a sensitivity analysis restricting to patients with use of low-dose aspirin within 5 years before their CRC diagnosis, thus restricting to a period considered by

TABLE 1 Baseline characteristics of the entire cohort and by exposure status at cohort entry

Characteristic, *n* (%)	Entire cohort	Aspirin use		
		Aspirin	No aspirin	Standardized difference
Total	7478	1509 (20.2)	5969 (79.8)	
Age (y), mean (SD)	70.2 (11.9)	75.6 (9.1)	68.9 (12.1)	0.63
Male	4116 (55.0)	902 (59.8)	3214 (53.8)	0.12
Alcohol-related disorders	47 (0.6)	8 (0.5)	39 (0.7)	0.02
Smoking status				
Current	500 (6.7)	125 (8.3)	375 (6.3)	0.08
Former	924 (12.4)	323 (21.4)	601 (10.1)	0.32
Never	1489 (19.9)	454 (30.1)	1035 (17.3)	0.30
Unknown	4565 (61.1)	607 (40.2)	3958 (66.3)	0.54
Body mass index				
<25 kg/m^2	926 (12.4)	236 (15.6)	690 (11.6)	0.12
≥25.0	1852 (24.8)	633 (42.0)	1219 (20.4)	0.48
Unknown	4700 (62.8)	640 (42.4)	4060 (68.0)	0.53
Medical conditions				
Diabetes mellitus	1005 (13.4)	363 (24.1)	642 (10.8)	0.36
Hypertension [a]	3151 (42.1)	940 (62.3)	2211 (37.0)	0.52
Cardiac arrhythmia	607 (8.1)	235 (15.6)	372 (6.2)	0.30
Dyslipidaemia [b]	2221 (29.7)	677 (44.9)	1544 (25.9)	0.41
Stroke	463 (6.2)	268 (17.8)	195 (3.3)	0.49
Coronary artery disease	646 (8.6)	384 (25.5)	262 (4.4)	0.62
Congestive heart failure	195 (2.6)	77 (5.1)	118 (2.0)	0.17
Peripheral vascular disease	456 (6.1)	210 (13.9)	246 (4.1)	0.35
Kidney disease [c]	1146 (15.3)	391 (25.9)	755 (12.7)	0.34
COPD/asthma	557 (7.5)	174 (11.5)	383 (6.4)	0.18
Autoimmune disease [d]	79 (1.1)	22 (1.5)	57 (1.0)	0.05
Peptic ulcer	1636 (21.9)	471 (31.2)	1165 (19.5)	0.27
Medications				
Antihypertensive drugs	3454 (46.2)	1250 (82.8)	2204 (36.9)	1.06
Antithrombotic drugs	1282 (17.1)	478 (31.7)	804 (13.5)	0.45
Cardiac drug therapy	785 (10.5)	386 (25.6)	399 (6.7)	0.53
Lipid-lowering agents	1014 (13.6)	533 (35.3)	481 (8.1)	0.70
Systemic corticosteroids	549 (7.3)	152 (10.1)	397 (6.7)	0.12
Other NSAIDs	1747 (23.4)	469 (31.1)	1278 (21.4)	0.22
Oral contraceptives	17 (0.2)	*	16 (0.3)	0.05
Hormone replacement therapy	87 (1.2)	9 (0.6)	78 (1.3)	0.07

SD, standard deviation; COPD, chronic obstructive pulmonary disease; NSAIDs, nonsteroidal anti-inflammatory drugs

[a]Hypertension was categorized by either a diagnostic code or a recorded systolic blood pressure >140 mmHg or a diastolic blood pressure >90.

[b]Dyslipidaemia was categorized either by a diagnostic code or a recorded low-density protein >100 mg/dL.

[c]Kidney disease was categorized with both a diagnostic code and a recorded glomerular filtration rate <60 mL/min or recorded transplant or recorded dialysis.

[d]Autoimmune diseases included polyarthritis nodosa and allied conditions (ICD-9 code 446), diffuse diseases of connective tissue (ICD-9 code 710), rheumatoid arthritis and other inflammatory polyarthropathies (ICD-9 code 714), lupus erythematosus (ICD-9 code 695.4), ankylosing spondylitis (ICD-9 code 720.0).

*Numbers <5 are not displayed, as per the confidentiality policies of the Health Search Database.

current evidence to be too short for a risk reduction of incident CRC. Our findings were consistent with our primary analysis, showing no association between the use of low-dose aspirin and risk of incident CRC metastasis. We caution, however, that the number of events after 4 years of use was smaller, thus generating wider confidence intervals.

TABLE 2 Crude and adjusted hazard ratios for the association between the prediagnostic use of low-dose aspirin and the risk of incident metastasis among colorectal cancer patients

Exposure	No. of patients	Events	Person-years	Incidence rate [a] (95% CI)	Crude HR	Adjusted HR (95% CI) [b]
No prediagnostic use	5969	250	26 021	9.6 (8.5–10.9)	1.00 [reference]	1.00 [reference]
Prediagnostic use	1509	64	4159	15.4 (11.9–19.7)	1.29 (0.98–1.69)	0.88 (0.63–1.22)
Duration of aspirin use						
≤1 y	746	29	2357	12.3 (8.2–17.7)	1.09 (0.74–1.60)	0.82 (0.54–1.25)
1.1–2 y	266	16	748	21.4 (12.2–34.7)	1.78 (1.07–2.94)	1.21 (0.70–2.09)
2.1–3 y	160	9	386	23.3 (10.7–44.3)	1.81 (0.93–3.53)	1.09 (0.54–2.22)
3.1–4 y	111	*	235	25.5 (9.4–55.6)	1.92 (0.85–4.32)	1.07 (0.46–2.50)
>4 y	226	*	432	9.3 (2.5–23.7)	0.66 (0.25–1.77)	0.36 (0.13–0.99)
						P-trend: .22

HR, hazard ratio; CI, confidence interval

[a]Per 1000 person-years.

[b]Adjusted for age, sex, year of cohort entry, body mass index, smoking status, alcohol-related disorders, diabetes mellitus, hypertension, cardiac arrhythmia, dyslipidaemia, stroke, coronary artery disease, congestive heart failure, peripheral vascular disease, kidney disease, chronic obstructive pulmonary disease/asthma, autoimmune disease, peptic ulcer, use of antidiabetic drugs, antihypertensive drugs, antithrombotic drugs, cardiac drug therapy, lipid-lowering agents, systemic corticosteroids, nonsteroidal anti-inflammatory drugs, oral contraceptives, hormone replacement therapy.

*Numbers <5 are not displayed, as per the confidentiality policies of the Health Search Database. A second cell was also suppressed to avoid secondary deduction.

TABLE 3 Crude and adjusted hazard ratios for the association between the prediagnostic use of low-dose aspirin and the risk of all-cause mortality among colorectal cancer patients

Exposure	No. of patients	Events	Person-years	Incidence rate [a] (95% CI)	Crude HR	Adjusted HR (95% CI) [b]
No prediagnostic use	5969	1693	30 509	55.5 (52.9–58.2)	1.00 [reference]	1.00 [reference]
Prediagnostic use	1509	496	4920	100.8 (92.1–110.1)	1.60 (1.44–1.77)	1.08 (0.96–1.22)
Duration of aspirin use						
≤1 y	746	264	2775	95.1 (84.0–107.3)	1.56 (1.37–1.78)	1.09 (0.95–1.26)
1.1–2 y	266	88	931	94.5 (75.8–116.5)	1.53 (1.23–1.89)	1.08 (0.86–1.36)
2.1–3 y	160	50	439	113.9 (84.5–150.2)	1.70 (1.28–2.25)	1.00 (0.75–1.35)
3.1–4 y	111	34	289	117.6 (81.5–164.4)	1.75 (1.24–2.45)	1.19 (0.84–1.69)
>4 y	226	60	486	123.5 (94.2–158.9)	1.72 (1.33–2.23)	1.06 (0.80–1.40)
						P-trend: .38

HR, hazard ratio; CI, confidence interval

[a]Per 1000 person-years.

[b]Adjusted for age, sex, year of cohort entry, body mass index, smoking status, alcohol-related disorders, diabetes mellitus, hypertension, cardiac arrhythmia, dyslipidemia, stroke, coronary artery disease, congestive heart failure, peripheral vascular disease, kidney disease, chronic obstructive pulmonary disease/asthma, autoimmune disease, peptic ulcer, use of antidiabetic drugs, antihypertensive drugs, antithrombotic drugs, cardiac drug therapy, lipid-lowering agents, systemic corticosteroids, nonsteroidal anti-inflammatory drugs, oral contraceptives, hormone replacement therapy.

Our study has several strengths. First, our results remained consistent across several sensitivity analyses, including 1 using a stricter CRC diagnosis definition. Second, CRC diagnosis and metastasis using ICD-9 codes have been shown to be of high positive predictive value, sensitivity and specificity in Italian health administrative databases.[20] Third, although we note that information on over-the-counter use of low-dose aspirin was not available and could potentially lead to some exposure misclassification, such bias is unlikely in our study. Low-dose aspirin for the primary prevention of CRC or cardiovascular disease is generally prescribed for long-term rather than short-term use and is covered by insurance plans in Italy. Thus, any use of over-the-counter aspirin would largely be for short-term use and therefore unlikely to affect outcomes of metastasis and mortality.

This study also has some limitations. First, the Health Search Database does not contain information on cancer stage and grade, as well as treatment modality for CRC such as radiotherapy, surgery and chemotherapy. Thus, it was not possible to adjust the models for these variables at cohort entry. Finally, exposure duration of more than 4 years resulted in small sample size, which might have prevented the observation of benefits of long-term low-dose aspirin use.

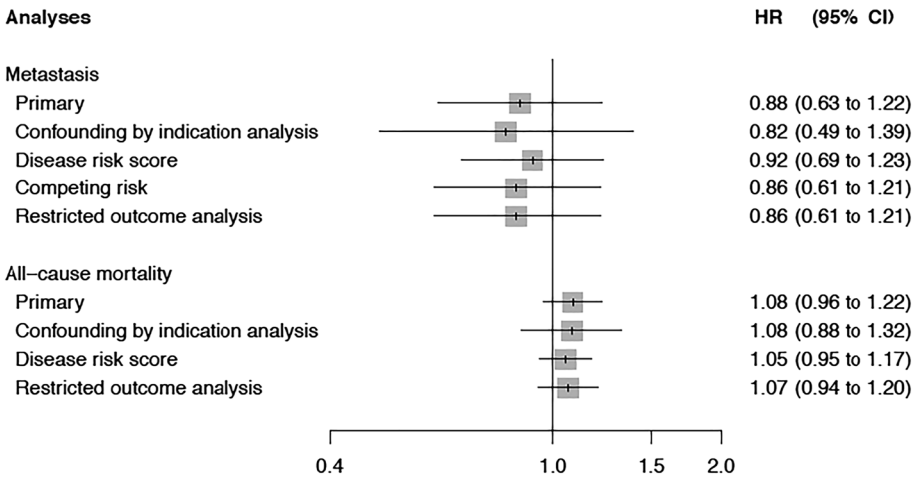

FIGURE 2 Forest plot of primary and sensitivity analyses. CI, confidence interval; HR, hazard ratio

5 | CONCLUSION

In summary, the results of this population-based cohort study indicate that the prediagnostic use of low-dose aspirin before a CRC diagnosis is not associated with a decreased risk of incident metastasis and of all-cause mortality. Additional observational studies with longer follow-up should be conducted to examine the benefits of long-term use.

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COMPETING INTERESTS

J.R. received consulting fees from Biogen for work unrelated to this study. F.L. and C.C. provided consultancies in protocol preparation for epidemiological studies and data analyses for IBSA, Bayer, and Alfa Wassermann. L.A. received consulting fees from Janssen and Pfizer for work unrelated to this study. All other authors have no conflicts to disclose.

CONTRIBUTORS

F.L., C.C. and L.A. acquired the data. All authors conceptualized and designed the study. G.G., J.R., H.Y. and L.A. analysed and interpreted the data. G.G. drafted the manuscript. All authors critically revised and approved the manuscript.

DATA AVAILABILITY STATEMENT

Data not available for sharing due to patient confidentiality.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.