ASPICAN study

(ASPIrin use and colorectal CANcer risk)

Background

Colorectal cancer (CRC) is a major cause of illness and death worldwide. In 2012, the worldwide incidence of colorectal cancer rose to an estimated 1.4 million new cases per year, and colorectal cancer deaths rose to approximately 0.7 million [1]. In Italy, it has been estimated that there were 31,000 incident cases of colorectal cancer and 11,000 deaths due to colorectal cancer in 2012 [2].

Aspirin has been associated with a reduced risk of colorectal and possibly of a few other cancers [3-6].

The use of low-dose aspirin (LDA) for the primary prevention of colorectal cancer has been debated for a long time [7]. Recently, the United States Preventive Services Task Force (USPSTF) recommended low-dose aspirin use for the primary prevention of cardiovascular diseases (CVD) and colorectal cancer among "adults [aged] 50 to 59 years who have a 10% or greater 10-year CVD risk [that] are not at increased risk for bleeding, have a life expectancy of at least 10 years and are willing to take low-dose aspirin daily for at least 10 years" (USPTF, 2016). This recommendation has been released as a level B recommendation because there is "high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial" [8].

Two meta-analysis published on 2012 analyzed almost 40 observational studies published till the year 2011 that studied the association between aspirin use and CRC risk, showed the protective effect of aspirin use and CRC risk with an overall protective effect of about 30% [9,10]. The stronger effect has been found when the data were stratified by duration and frequency. In particular daily aspirin users for at least five years had a CRC risk reduction of about 40% [10].

A more recent meta-analysis of published cohort studies showed a dose-risk and duration-risk relationship between aspirin and CRC. In particular, the authors suggested the existence of a threshold effect between aspirin intake and the risk of CRC, suggesting that the recommended dose of aspirin for prevention of CRC is 75–325 mg daily and 2–7 times per week. In addition, linear dose-response relationship was observed between duration of use and cancer protection, so long-term (>5 years) consistent use of aspirin appears necessary to achieve a protective effect [11].

In 2016 Cea Soriano conducted a study in which they performed three case-control analyses nested in three different study cohorts, to evaluate the protective effect of low-dose aspirin against CRC. The authors concluded that a daily dose of 75 mg/day was effective in reducing CRC risk [12].

Recently we conducted a cohort study comparing CRC mortality between subjects who received prescriptions of LDA for the whole year and subjects who did not have any prescriptions over the same period in the Florence district. We found that CRC mortality was reduced by almost 30% (HR = 0.71, 95% CI: 0.52-0.97) [13].

CRC is associated with several risk factors. People with a history of colorectal cancer in a first-degree relative (parent, sibling, or child) are at increased risk. The risk is even higher if that relative was diagnosed with cancer when they were younger than 45, or if more than one first-degree relative is affected [14]. About 5% to 10% of people who develop CRC have inherited gene mutations that can cause family cancer syndromes and lead to them getting the disease. The most common inherited syndromes linked with CRC are familial adenomatous polyposis and Lynch syndrome [15-16]. Type 2 (usually non-insulin dependent) diabetes is also associated to an increased risk of colorectal cancer. Both type 2 diabetes and colorectal cancer share some of the same risk factors [17]. In addition to the latter, modifiable risk factors are also know and may present opportunities for primary prevention of CRC. These includes: long-term cigarette smoking [118-20], increased body mass (regardless of the measure of adiposity) [21] and alcohol consumption [22] which are all associated with an increased risk of CRC, while vegetarian and pescovegetarians diets[23]., as well as physical activity[24] are associated with a lower incidence of CRC.

To date, different populations and study designs have been used to minimize the effect of possible residual and/or uncontrolled confounders with respect to the association between LDA use and the risk of CRC [12]. To the best of our knowledge, no study addressed this issue by comparing the risk of CRC between different categories of LDA exposure within a population of patients for which LDA use should be expected, i.e. in secondary cardiovascular prevention.

Objectives

The aim of this study is to investigate the association between LDA use and the risk of developing CRC in patients in secondary cardiovascular prevention.

Materials and methods

Data source

This study will be based on the analysis of data from different administrative data sources that record information on healthcare assistance delivered to Tuscany Region inhabitants and reimbursed by the National Healthcare Service (NHS). In particular, the regional administrative database collect anonymized person-level information from different archives which can linked through a unique regional identifier code. These include the inhabitant registry, hospital discharge records (HDR), dispensing of prescription drugs for outpatients use (PDO) and the mortality registry (MR), For each subject, demographic characteristics (e.g. gender, date of birth, date of death), information on outpatient drug utilization (e.g. dispensing date, active principle, ATC code, dose and pharmaceutical formulation) and hospital admission (e.g. discharge diagnoses, date of admission, date of discharge) will be available.

Selection of study population

Since Italy has universal public healthcare assistance, the source population will correspond to the entire Tuscan regional population. The study cohort will be drawn from patients with a first hospitalization for cardiovascular disease (CVD) during the period 2005-2010. CVD events will be identified through ICD9CM code (see appendix 1 for the entire list of code and selection criteria). The date of hospitalization for CVD will correspond to the patient cohort entry date. Only those patients with ≥5 years of follow-up and ≥2 years of look-back period in the Inhabitant Registry will be retained in the study cohort. Patients with ≥1 prescription of LDA or a cancer diagnosis (ICDCM code 140*-239* in HDR) prior cohort entry will be excluded. Moreover, patients will be excluded if they experienced one of the following events during the first 5 years from cohort entry: exit from the Inhabitant Registry (i.e. death or emigration from Tuscany) or occurrence of any cancer.

Study design

We will conduct a case control analysis nested in the selected study cohort. The 5th anniversary after the index hospital discharge will be the start of the period at risk for the occurrence of CRC. Each patient will be followed until the occurrence of the study outcome, i.e an incident CRC, or a censoring event among: any cancer other than CRC, death, exit from the Inhabitant Registry, end of study period (31 December 2016), whichever came first. The date of occurrence of CRC will be

the case index date. Per each case, up to 5 controls will be selected from the case's risk set and matched by sex, age and year of cohort entry.

Exposure

The exposure will be defined according to utilization of low-dose aspirin (LDA) prior to index date. With aim of describing the pattern of prescription of different LDA formulation in the study cohort users will be categorised according to the amount of active principle contained in the formulation received: 75 mg, 100 mg, 150 mg, 300mg or mixed in case users received prescriptions of different dosages during follow-up.

Since the outcome of the study (colon cancer) has a long latency period there is no chance that any exposure in the year before diagnosis has a causal relationship with the onset outcome. For this reason, we will not measure exposure in the year before outcome. Moreover, the year before the diagnosis is a period when the outcome is likely to have already happened, and possible associations with exposure or any other factor may be biased or even inverse. [25,26], LDA dispensing recorded within 1 year before the index date will be disregarded. We will define "ever use" of low-dose aspirin as 2 or more dispensings filled on separate dates and "nonuse" as fewer than 2 dispensings. We will than model the exposure within the ever use category according to recency, continuity and duration of use, as well as the prescribed daily dose (i.e LDA formulation prescribed) and the average amount of aspirin received per day of follow-up daily.

Ever users will be divided into recent users (≥1 dispensings during year 2 or 3 before index before the index date) and former users (no dispensings during the recent use period).

We will assume that patients treated with LDA are expected to take one posologic unit (tablet or sachets) per day, we will define the duration of each dispensing as the number of tablets dispensed. In recent users of LDA, *continuous use* will be defined as no treatment interruption (i.e. >90 days between the end of the duration of a LDA dispensing and the date of the following dispensing, if any) until 1 year before the index date. Along with continuity, *duration of use* will be defined as the difference between the first dispensing date and the end of the last dispensing. Recent users will be then categorised as

- continuous use for >5 years
- continuous use between 3 and 5 years
- continuous use <3 years

In a second analysis, the duration of separate treatment periods will be added to measure the cumulative duration of LDA use in recent users. The duration of use will be categorized according to the tertiles of the distribution of the duration of use observed in the control group.
Finally, recent users will be categorized on the basis of the intensity of use intended as the total amount of active principle dispensed during follow-up dived by number of days of follow-up.

Covariates

The following covariates will be measured at cohort entry: age, sex, pharmacotherapies, comorbidities and procedures (see appendix 2 for more details). In particular, we will consider the following pharmacotherapies that could represent a risk factor for CRC or a proxy of a risk factor (e.g. diabetes, chronic inflammatory bowel disease):

1. 'cardiovascular system': C01DA, organic nitrates; C02, antihypertensive agents; C03, diuretics; C04, peripheral vasodilators; C05, vasoprotective agents; C07, β blocking agents; C08, calcium channel blockers; C09, agents acting on the renin–angiotensin system, C10, lipid modifying agents;
2. 'blood and blood forming': B01, antithrombotic agents (excluding B01AC06);
3. 'alimentary tract and metabolism': A10, drugs used in diabetes.
4. Others: metformin, NSAID, hormone replacement therapy, antidepressants, Immunosuppressive, non aspirin anticoagulant.

Comorbidities:

1. Inflammatory bowel disease
2. Chronic obstructive pulmonary disease or asthma
3. Hypertension
4. Coronary heart disease
5. CVD at entry (i.e. stroke, IHD, CHF…)
6. Diabetes mellitus

Procedures:

1. Colonscopy

Others:

1. Deprivation index [27]

Outcome

The study outcome will correspond to all incident CRC cases occurred after the fifth year from cohort entry up to the end of the available follow-up time. CRC cases will be identified through principal hospital discharge diagnoses by using the ICD9CM codes 153.0-154.1, 154.8.

Statistical analysis

Use of LDA in the study cohort will be described during the first 5 years from cohort entry according to the exposure categories defined above.

Characteristics of the full study cohort will be described at cohort entry and at start of at risk period.

The incidence rate of CRC will be calculated using the number of observed cases as the numerator and the total amount of person-time cumulated during the "period at risk" as the denominator, stratified by sex and age group. Multivariable conditional regression will applied to estimate odds ratio and 95% confidence intervals for the association between LDA use and CRC.

References

1. IARC web site: http://globocan.iarc.fr (accessed February 25, 2016).
2. Rossi S, Crocetti E, Capocaccia R, Gatta G, AIRTUM Working Group. (2013). Estimates of cancer burden in Italy. Tumori. 99:416-424.
3. Bosetti C, Rosato V, Gallus S, Cuzick J, La Vecchia C. (2012). Aspirin and cancer risk: a quantitative review to 2011. Ann Oncol 23:1403-1415.
4. Friis S, Riis AH, Erichsen R, Baron JA, Sørensen HT. (2015). Low-dose aspirin or nonsteroidal anti-inflammatory drug use and colorectal cancer risk: a population-based, case-control study. Ann Intern Med 163: 347–355.
5. Nan H, Hutter CM, Lin Y, Jacobs EJ, Ulrich CM, White E, et al. (2015). Association of aspirin and NSAID use with risk of colorectal cancer according to genetic variants. JAMA 313:1133–1142.

6. Cao Y, Nishihara R, Wu K, Wang M, Ogino S, Willett WC, et al. (2016) Population-wide Impact of Long-term Use of Aspirin and the Risk for Cancer. JAMA Oncol. [Epub ahead of print] doi:10.1001/jamaoncol.2015.6396.
7. Whitlock EP, Williams SB, Burda BU, Feightner A, and Beil T. (2015). Aspirin Use in Adults: Cancer, All-Cause Mortality, and Harms. A Systematic Evidence Review for the U.S. Preventive Services Task Force. Evidence Synthesis No. 132. AHRQ Pubblication No: 13-05193-EF-1, Kaiser Permanente Center for Health Research.
8. USPSTF web site: http://www.uspreventiveservicestaskforce.org/Page/Document/draftrecommendation-statement/aspirin-to-prevent-cardiovascular-disease-and-cancer (accessed February 25, 2016).
9. Bosetti C, Rosato V, Gallus S, Cuzick J, La Vecchia C. (2012). Aspirin and cancer risk: a quantitative review to 2011. Ann Oncol 23:1403-1415.
10. Algra AM, Rothwell PM. Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials. Lancet Oncol. 2012 May;13(5):518-27. doi: 10.1016/S1470-2045(12)70112-2. Epub 2012 Mar 21.
11. Ye X, Fu J, Yang Y, Chen S. Dose-risk and duration-risk relationships between aspirin and colorectal cancer: a meta-analysis of published cohort studies. PLoS One. 2013;8(2):e57578. doi: 10.1371/journal.pone.0057578. Epub 2013 Feb 25.
12. Cea Soriano L, Soriano-Gabarró M, García Rodríguez LA. The Protective Effect of Low-Dose Aspirin against Colorectal Cancer Is Unlikely Explained by Selection Bias: Results from Three Different Study Designs in Clinical Practice. PLoS One. 2016 Jul 18;11(7):e0159179. doi: 10.1371/journal.pone.0159179. eCollection 2016.
13. Ventura L, Miccinesi G, Barchielli A, Manneschi G, Puliti D, Mantellini P, Orso F and Zappa M. Does low-dose aspirin use for cardiovascular disease prevention reduce colorectal cancer deaths? A comparison of two cohorts in the Florence district, Italy. Eur J Cancer Prev. 2016
14. American Cancer Society (2016). Detailed guide: colon and rectum cancer. Available at: http://www.cancer.org/Cancer/ColonandRectumCancer/DetailedGuide/index.

15. Arends MJ. Pathways of colorectal carcinogenesis. Appl Immunohistochem Mol Morphol. 2013;21(2):97-102.
16. Jasperson KW, Tuohy TM, Neklason DW, Burt RW. Hereditary and familial colon cancer. Gastroenterology. 2010;138(6):2044-58. PMCID: PMC3057468.
17. Yang YX, Hennessy S, Lewis JD. Type 2 diabetes mellitus and the risk of colorectal cancer. Clin Gastroenterol Hepatol. 2005 Jun;3(6):587-94
18. Newcomb PA, Storer BE, Marcus PM. Cigarette smoking in relation to risk of large bowel cancer in women. Cancer Res. 1995;55(21):4906-9.
19. Chao A, Thun MJ, Jacobs EJ, Henley SJ, Rodriguez C, Calle EE. Cigarette smoking and colorectal cancer mortality in the cancer prevention study II. J Natl Cancer Inst. 2000;92(23):1888-96.
20. Paskett ED, Reeves KW, Rohan TE, Allison MA, Williams CD, Messina CR, Whitlock E, Sato A, Hunt JR. Association between cigarette smoking and colorectal cancer in the Women's Health Initiative. J Natl Cancer Inst. 2007;99(22):1729-35.
21. Moore LL, Bradlee ML, Singer MR, Splansky GL, Proctor MH, Ellison RC, Kreger BE. BMI and waist circumference as predictors of lifetime colon cancer risk in Framingham Study adults. Int J Obes Relat Metab Disord. 2004;28(4):559-67.
22. Ferrari P, Jenab M, Norat T, et al. Lifetime and baseline alcohol intake and risk of colon and rectal cancers in the European prospective investigation into cancer and nutrition (EPIC). Int J Cancer. 2007;121(9):2065-72.
23. Orlich MJ, Singh PN, Sabaté J. Vegetarian dietary patterns and the risk of colorectal cancers. JAMA Intern Med. 2015 May;175(5):767-76.
24. Giovannucci E, Ascherio A, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Physical activity, obesity, and risk for colon cancer and adenoma in men. Ann Intern Med. 1995;122(5):327-34.
25. Rothman KJ, Greenland S, Lash TL. Modern Epidemiology. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2008.
26. Jørgensen TL, Herrstedt J, Friis S, Hallas J. Polypharmacy and drug use in elderly Danish cancer patients during 1996 to 2006. J Geriatr Oncol. 2012;3:33-40.
27. Caranci N, Biggeri A, Grisotto L, Pacelli B, Spadea T, Costa G. The Italian deprivation index at census block level: definition, description and association with general mortality. Epidemiol Prev. 2010 Jul-Aug;34(4):167-76.

Appendix 1. Definition of events for cohort entry

1. ISCHEMIC HEART DISEASE
The selection algorithm for cohort definition includes the following ICD9CM codes in either primary or secondary diagnosis fields:
410.* Acute myocardial infarction
411.* Other acute and subacute forms of ischemic heart disease

Appendix 2. Definition of covariates

Index admission (secondary diagnosis) and admissions in 2 years before Index admission (primary and secondary diagnosis).

Diseases and ICD9CM codes

DIABETES
250.* Diabetes mellitus
OR
ATC code A10* - Drugs used in diabetes

COPD
491.* Chronic bronchitis
492.* Emphysema
493.* Asthma
496 Chronic airway obstruction not elsewhere classified
OR
Primary diagnosis = codes compatible** with a diagnosis of COPD and secondary diagnosis = 491.*, 492.*, 493.*, 496
**Codes compatible with diagnosis of COPD
518.81 Acute respiratory failure
518.83 Chronic respiratory failure
518.84 Acute and chronic respiratory failure
416.8 Other chronic pulmonary heart diseases
416.9 Chronic pulmonary heart disease unspecified

GASTROINTESTINAL DISEASES
530.11 Reflux esophagitis
530.81 Esophageal reflux
531.4* Chronic or unspecified gastric ulcer with hemorrhage
531.5* Chronic or unspecified gastric ulcer with perforation
531.6* Chronic or unspecified gastric ulcer with hemorrhage and perforation
531.7* Chronic gastric ulcer without mention of hemorrhage or perforation
531.9* Gastric ulcer unspecified as acute or chronic without mention of hemorrhage or perforation
532.4* Chronic or unspecified duodenal ulcer with hemorrhage
532.5* Chronic or unspecified duodenal ulcer with perforation
532.6* Chronic or unspecified duodenal ulcer with hemorrhage and perforation
532.7* Chronic duodenal ulcer without mention of hemorrhage or perforation
532.9* Duodenal ulcer unspecified as acute or chronic without mention of hemorrhage or perforation
533.4* Chronic or unspecified peptic ulcer of unspecified site with hemorrhage
533.5* Chronic or unspecified peptic ulcer of unspecified site with perforation
533.6* Chronic or unspecified peptic ulcer of unspecified site with hemorrhage and perforation
533.7* Chronic peptic ulcer of unspecified site without mention of hemorrhage or perforation

533.9* Peptic ulcer of unspecified site unspecified as acute or chronic without mention of hemorrhage or perforation
534.4* Chronic or unspecified gastrojejunal ulcer with hemorrhage
534.5* Chronic or unspecified gastrojejunal ulcer with perforation
534.6* Chronic or unspecified gastrojejunal ulcer with hemorrhage and perforation
534.7* Chronic gastrojejunal ulcer without mention of hemorrhage or perforation
534.9* Gastrojejunal ulcer unspecified as acute or chronic without mention of hemorrhage or perforation
535* Gastritis and duodenitis
553.3 Diaphragmatic hernia without obstruction or gangrene

DISORDERS OF THYROID GLAND
240* Simple and unspecified goiter
241* Nontoxic nodular goiter
242* Thyrotoxicosis with or without goiter
243* Congenital hypothyroidism
244* Acquired hypothyroidism
245* Thyroiditis
246* Other disorders of thyroid

HYPERTENSION
401.* Essential hypertension
OR ATC C02*, C03*, C07*, C08*, C09* (at least two prescription before cohort entry)

HYPERCHOLESTEROLEMIA
272.0 Pure hypercholesterolemia
HYPERTRIGLYCERIDEMIA
272.1 Pure hyperglyceridemia
DYSLIPIDEMIA
272.2 Mixed hyperlipidemia
OR ATC: C10* (at least two prescription in the year before the cohort entry)

RENAL FAILURE
584.* Acute renal failure
585.* Chronic kidney disease

OTHER FACTORS RELATED TO SEVERITY OF DISEASE
Cardiovascular procedures

CORONARY ARTERY BYPASS SURGERY
36.1* Bypass anastomosis for heart revascularization
V45.81 Postsurgical aortocoronary bypass status
PTCA
00.66 Percutaneous transluminal coronary angioplasty [ptca] or coronary atherectomy
36.0* Removal of coronary artery obstruction and insertion of stent(s)
V45.82 Percutaneous transluminal coronary angioplasty status
CEREBRAL REVASCULARIZATION
00.61 Percutaneous angioplasty or atherectomy of precerebral (extracranial) vessel(s)
00.62 Percutaneous angioplasty or atherectomy of extracranial vessel(s)
38.11 Endarterectomy, intracranial vessels
38.12 Endarterectomy, other vessels of head and neck
38.31 Resection of vessel with anastomosis, intracranial vessels
38.32 Resection of vessel with anastomosis, other vessels of head and neck
OTHER HEART SURGERY PROCEDURES

35.* Operations On Valves And Septa Of Heart
37.0 Pericardiocentesis
37.1* Cardiotomy and pericardiotomy
37.3* Pericardiectomy and excision of lesion of heart
37.4* Repair of heart and pericardium
37.5* Heart replacement procedures
37.6* Implantation of heart assist system
37.9* Other operations on heart and pericardium

Statin (ATC code):
atorvastatin (C10AA05), rosuvastatin (C10AA07), lovastatin (C10AA02), simvastatin (C10AA01), pravastatin (C10AA03) and fluvastatin (C10AA04).

NSAID (ATC code):
diclofenac (M01AB05), sulindac (M01AB02), indomethacin (M01AB01), acemetacin (M01AB11), aceclofenac (M01AB16), meloxicam (M01AC06), ibuprofen (M01AE01), naproxen (M01AE02), ketoprofen (M01AE03), mefenamic acid (M01AG01).