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Distinct effects of anti-inflammatory and anti-thrombotic drugs on cancer characteristics at diagnosis

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Abstract ***Background:*** A previous study showed that regular use of low-dose aspirin was associated with smaller tumour size and fewer metastases for colorectal and lung cancer. We aim to explain these distinct effects in terms of the anti-inflammatory and anti-thrombotic properties of aspirin.

Methods: From the Swedish Cancer Register, we identified patients diagnosed with colorectal and lung cancers between 1st October 2006 and 31st December 2009; each cancer was assessed in terms of tumour size/extent (T), lymph-node (N) and metastatic (M) status. Linkage with the Swedish Prescribed Drug Register was performed to obtain information on the use of low-dose aspirin, anti-inflammatory and anti-thrombotic drugs prior to cancer diagnosis.

Results: We identified 14,743 individuals with colorectal cancer and 5888 with lung cancer. For low-dose aspirin users we observed a statistically significant association with smaller tumour size and fewer metastases. For both cancers, the use of non-aspirin anti-inflammatory drugs was associated with smaller tumour size in all categories T2–T4 odds ratio (OR = 0.76, 95% confidence interval (CI) 0.63–0.92 for T2 versus T1 in colorectal cancer), but not with metastatic status (OR = 0.94, 95% CI 0.84–1.06 in colorectal cancer). In contrast, anti-thrombotic drug use was associated with fewer metastases, but not with tumour categories T2 and T3.

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Conclusions: The results suggest that the use of anti-inflammatories is associated with tumour-growth inhibition at the primary site, while the use of anti-thrombotics is associated with restriction of cancer-cell metastasising capability. These have clinical implications on the potential use of these drugs for chemoprevention or chemotherapy.

1. Introduction

Long-term regular use of low-dose aspirin has been shown to be associated with lower cancer mortality, notably for colorectal and lung cancers [1], however, the exact biological mechanisms are not fully understood. It is now commonly accepted that chronic inflammation increases susceptibility to cancer, and there is experimental evidence for how anti-inflammatory drugs might stop certain cancers from developing [2,3]. Hence, as an anti-inflammatory agent, aspirin may suppress cancer-cell growth by inhibiting or modifying prostaglandin-endoperoxide synthase 2 (PTGS2), also known as cyclo-oxygenase-2 (COX-2), which in turn down-regulates phosphatidylinositol 3-kinase (PI3K) signalling activity, thereby inducing apoptosis [4]. Liao et al. [5] showed strong evidence that the survival benefit of aspirin was seen only among patients with PIK3CA-mutated colorectal cancer. However, aspirin has multiple known properties, and it is not immediately clear how each contributes to the overall benefit. In fact, Midgley et al. [6] and Domingo et al. [7] found no evidence of a survival benefit for colorectal patients from the use of the anti-inflammatory drug rofecoxib (also known as VIOXX), a selective COX-2 inhibitor. This means that the survival benefit of aspirin cannot be explained by its anti-inflammatory property alone.

Our previous study [8] showed that the pre-diagnosis use of low-dose aspirin was associated with smaller tumour extent/size (T) and fewer metastases (M) for colorectal and lung cancers. Assuming that tumour size in its primary site and metastasis in distant organs represent the early and later stages of cancer progression, respectively, the result indicates that the effects of aspirin span the different stages of the disease process. In addition to its anti-inflammatory effects, aspirin is a potent anti-platelet agent, and there is substantial pre-clinical evidence that platelets are involved in cancer metastasis [9,10]. Thus the multiple effects of aspirin could be due to its distinct properties; specifically, the tumour-growth inhibitory effect on the primary site is due to its anti-inflammatory property, while the anti-metastatic effect is due to its anti-thrombotic property. Our aim was to investigate this by assessing the association between the pre-diagnosis use of non-aspirin anti-inflammatory agents and the TNM status of cancer at diagnosis, and similarly for the use of anti-thrombotic agents.

2. Methods

2.1. Cancer incidences and TNM values

The Swedish Cancer Register, established in 1958, includes histologically verified cancer incidences and has approximately 95 percent of coverage [11]. Since 2004 the Register includes stage information in terms of tumour extent/size (T), nodal involvement (N) and metastatic status (M). We focused on two cancers where we previously observed significant effects of aspirin, namely colorectal and lung cancers [8]. Between 2006-07-01 and 2009-12-31, using only biopsy-confirmed diagnoses, we identified 14,743 patients with colorectal cancer and 5888 patients with lung cancer. Since inhibition of prostaglandin synthesis by aspirin and anti-inflammatory drugs has a strong effect on epithelial glandular cells, the lung cancers were further classified as 2627 non-small cell adenocarcinoma and 1243 as non-small cell squamous-cell carcinoma; there were too few in other sub-categories of lung cancer for further analyses. All of these reports referred to primary cancers, while individuals with previous cancers were excluded. These numbers were lower than those reported in Jonsson et al. [8], because we have now included only cases with available TNM values. Our study was approved by the Ethics Committee of the Karolinska Institutet.

2.2. Prescription of low-dose aspirin, anti-inflammatory and anti-thrombotic agents

The Swedish Prescribed Drug Register was established in 1999, but information on personal identification was included only since 1st July 2005 [12]. The register contains data on drugs prescribed and dispensed in ambulatory care. It includes substance name, ATC-code, brand name, formulation, package information, amount and defined daily dose (DDD), which according to World Health Organisation (WHO) is the 'assumed average maintenance dose per day for a drug used for its main indication in adults'. Also, there is administrative information such as the date of dispensing. The Register does not include data on prescription-free medications or drugs used in hospitals, and only partially includes drugs used in ambulatory care. The Register is also incomplete with regard to vaccines and drugs