Reply to M. Løberg et al.

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Løberg et al. comment on our paper [1], where we reported on the association of aspirin use

with lower risk of mortality in 23,162 Norwegian patients with colorectal cancer (CRC), of

which 6,102 were regular aspirin users post-diagnosis (>6 months use). With a median

observation time of 3 years after diagnosis, the hazard ratio (HR) from multivariate Cox-

regression analyses was 0.85 and 0.95 for CRC-specific survival (CSS) and overall survival

(OS), respectively.

Løberg et al. [2] focus their criticism on a sub-analysis in our report where we stratified on

aspirin use before and after diagnosis of CRC and only after, and cite our finding that in the

group that did not use aspirin before CRC diagnosis the HR for aspirin use was 1.0. However,

this group was comparably small (1,711 patients that only used aspirin after diagnosis versus

4,391 patents that used aspirin both before and after diagnosis) and with greater uncertainty in

the corresponding effect estimate (HR 1.00 (95% CI 0.87-1.14) versus HR 0.77 (CI 0.71-

0.84)). Furthermore, 2,354 non-users were exposed to aspirin before diagnosis, which may serve to dilute the findings.

We used multivariate Cox-regression analysis where patients dying of other causes were censored, allowing for estimation of interpretable cause-specific hazard ratios while adjusting for confounding factors. The results show that at any point after diagnosis and given the fact that the patients are still alive, the instantaneous risk of dying of colorectal cancer is 15% lower for regular aspirin users compared to non-aspirin users. Estimating cause-specific HRs is a valid and correct approach even in the presence of competing risks [3], and is in our opinion the best way to answer the research question. Estimating Fine-Gray regressions as suggested by Løberg et al. are appropriate if the aim is to compare cumulative incidences, but is not a good approach when comparing risk between groups since such models would incorporate, rather than account for, the potential differences in risk of cardiovascular deaths between aspirin users and non-users. The presence of competing risks may, as stated [1], question the validity of estimated survival curves, as such curves are only interpretable under the assumption of independence between competing causes after conditioning on other covariates. The assumption of independence is untestable but we believe it is reasonable in our material.

We find the alternative interpretations of our data by Løberg et al. to be speculative. The assumption that the majority of deceased CRC patients that used aspirin is more likely to be misclassified as dying of cardiovascular diseases (CVD) is unfounded. All patients in Norway treated for CRC undergo regular clinical controls and surveillance with CT-scan every 6 months for 5 years to determine signs of recurrence or metastases, thus relapsed CRC almost never goes unnoticed. The suggestion that aspirin users are healthier or selected, meaning that

they are less likely to die of CVD than the non-aspirin users is entirely based on speculation. Unfortunately, it is not possible to control for healthy user bias as we do not have data to characterize health-seeking or healthy life style behavior. However, if the aspirin users were more health-conscious, this would only counteract the effect that leads to the alleged misclassification of death as proposed by Løberg et al. We thus disagree with their unfounded claim that CRC-specific mortality is an invalid end-point. Our observation that CSS is comparable for all AJCC stages of CRC further supports the fact that misclassified cause-of-death does not differ significantly between the aspirin users and non-users [1]. Furthermore, analysis of the validity of cancer as cause of death supports use of CSS as an end-point [4].

The two meta-analyses referred by Løberg et al. support our conclusion that post-diagnosis aspirin use increases OS in CRC patients. However, they did not find a significant reduction in cause-specific mortality. Interestingly, the meta-analyses included almost the same primary publications (6 of 8 studies overlap in [5] and [6]) but report somewhat different conclusions. The aggregated cohort size in the meta-analyses is 30,397 patients for OS and 10,923 for CSS, the latter less than half the number of patients in our report as only some of the studies included CSS as primary endpoint. Among five primary studies that have analyzed CSS, four found a significant effect of aspirin [7-10] (Table 1).

In summary, we disagree with the speculations by Løberg et al. and think that it is an accumulated effect of aspirin use that provides potential patient benefit in the secondary preventive setting and not only use prior to diagnosis.

References

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Table 1: Overview of studies of post-diagnosis aspirin use included in meta-analyses [5] and [6][a]

Year	Authors	n	Outcome	HR/OR*/RR**	95% CI
Studies of post-diagnosis aspirin use included in meta-analyses by both Ye et al [5] and Li et al [6]					
2009	Chan et al.	1279	OS	0.79	0.65 - 0.97
			CSS	0.71	0.53 - 0.95
2012	Bastiaannet et al.	4481	OS	0.77**	0.63 - 0.95
2012	Walker et al.	13994	OS	0.91	0.82 - 1.00
2013	McCowan et al.	2990	OS	0.67	0.57 - 0.79
			CSS	0.58	0.45 - 0.75
2014	Cardwell et al.	4794	OS	1,06*	0.94 - 1.19
			CSS	1,06*	0.92 - 1.24
2014	Reimers et al.	999	OS	0.53**	0.38 -0.74
Study of post-diagnosis aspirin use included in meta-analysis by Ye et al [5] only					
2012	Liao et al.	964	OS	0.18[b]	0.06 - 0.61
			CSS	0.54[b]	0.31 - 0.94
Study of post-diagnosis aspirin use included in meta-analysis by Li et al [6] only					
2013	Domingo et al.	896	OS	0.29[b]	0.04 - 2.31
			CSS	0.11[b]	0.001 - 0.832
Study subject to discussion					
2016	Bains et al.	23162	OS	0.95	0.90 - 1.01
			CSS	0.85	0.79 - 0.92

OS, overall survival; CSS, cancer specific survival

a Space limitations prevents us from citing the primary reports, see [5] and [6] for references

[b] In subset of patients with mutated-PI3K colorectal cancers