TITLE: Aspirin use and prostate cancer mortality in men with high grade prostate cancer

ENCePP Study Reference Number: ENCEPP/SDPP/3444

Authors and Affiliations:

Evelyn M. Flahavan[1]

Kathleen Bennett[1]

Linda Sharp[2]

Thomas I Barron[1]

1 Department of Pharmacology & Therapeutics, Trinity College, University of Dublin, Dublin, Ireland.

2 National Cancer Registry Ireland, Cork, Ireland.

Corresponding Author:

Kathleen Bennett PhD.

Address: Department of Pharmacology & Therapeutics,

Trinity Centre for Health Sciences,

St James's Hospital, Dublin 8, Ireland.

Email: bennettk@tcd.ie

Phone: +353 1 896 1303

Fax: +353 1 453 9033

Background & Research Question

Aspirin exposure has been associated with reduced incidence of prostate cancer[1,2] and less advanced prostate tumours at diagnosis.[3] More recently, large meta-analysis and observational studies have reported associations between aspirin use and reduced mortality from cancer.[4,5] In particular, aspirin use in men with localised prostate cancer, has been reported to be most significantly associated with reduced mortality from prostate cancer in both meta-analysis[6] and observational studies.[7] In the latter study the most significant findings were in men with high-risk disease i.e. larger tumours, high PSA and high Gleason Score.

The hypothesis for the present study has evolved from this evidence and the findings of another study by the authors assessing associations between aspirin exposure and prostate cancer mortality in men with localised prostate cancer. The results suggested aspirin exposure to be associated with a modest non-significant reduction in prostate cancer-specific mortality (HR=0.90, 95% CI 0.68, 1.20) with high dose (>75mg) of aspirin having a more pronounced association with reduced mortality (HR=0.59, 95% CI 0.35, 1.00).

The mechanism attributed to aspirin's anticancer activity which has been investigated most extensively is the inhibition of cyclo-oxygenase enzyme 2 (COX-2). COX-2 expression in cancerous prostate cells is associated with higher Gleason Score,[8,9] distant metastasis,[10] biochemical failure and treatment failure.[11] It is biologically plausible that there is a stronger association between aspirin use and reduced prostate cancer mortality in men with high-grade prostate cancer. The vasculature close to the tumour and the newly generated tumour vasculature have been shown to express COX-2.[12] Another mechanism of proposed anti-cancer activity is the anti-platelet property of aspirin, which may inhibit the spread of tumour cells through the vasculature.[13] Considering these mechanisms through which aspirin may mediate an effect on prostate tumours, it is of interest to examine whether associations between aspirin use and prostate cancer mortality differ depending on if the cancer is localised or has progressed beyond the prostate to lymph nodes or other sites.

This cohort study will be carried out in men aged 50-80 years diagnosed with high-grade prostate cancer in Ireland using the linked database of the National Cancer Registry Ireland (NCRI) and the Primary Care Reimbursement Services (PCRS) pharmacy claims database. The study aims to assess whether there is an association between aspirin use and mortality, in men with high-grade prostate cancer and whether there is a difference in the association between aspirin use and mortality in men with localised compared to advanced disease.

Methods

Setting and Data Sources:

The National Cancer Registry Ireland (NCRI) database, which has been linked to Ireland's Health Services Executive (HSE) – Primary Care Reimbursement Services (PCRS) pharmacy claims database, will be used to conduct this study. The NCRI database is nationally representative. Detailed data on all incident cancers in the population of the Republic of Ireland is complied, with five-year tumour registration of prostate cancer estimated to be in excess of 96% complete.[14] Hospital-based tumour registration officers collect information on patient characteristics, tumour details and treatment received from hospital medical records. Tumours are recorded using the ICD-O system (Prostate neoplasm, C61).[15] The national death certificate register, which includes patient cause of death, coded as ICD-9 or ICD-10, is linked to the data at the NCRI.

The general medical services (GMS) scheme, provided by the HSE-PCRS, delivers state-funded universal healthcare, including prescription medicines, to approximately one third (1.4 million) of the Irish population. GMS scheme eligibility is assessed through means test and age; all persons over the age of 70 years were entitled to the GMS scheme prior to January 2009. The GMS database contains claims for all prescription drugs dispensed from community pharmacies to GMS patients. Drugs are coded according to the WHO Anatomical Therapeutic Chemical Classification (ATC) system.[16]

Linkage of various files is by an identifier generated by the NCRI. Cancer cases diagnosed from January 1st 2001 to December 31st 2006 have had prescription claims have been linked using probabilistic matching techniques. Follow-up of vital status is until December 31st 2010. This linked database has been used for similar studies before.[17]

The use of data held by the NCRI for research purposes is covered by the Health (Provision of Information) Act 1997. Data utilisation agreements have been established with the NCRI. All potential patient identifiers are removed from the datasets prior to use. The data is to be stored on an encrypted drive on a desktop computer available only to the researcher.

Study cohort

Men aged 50-80 years at the time of prostate cancer diagnosis (ICD-O, C61),[15] diagnosed as having a tumour with Gleason Score histology > 7,[18] between 1st January 2001 and 31st December 2006 will be included in the study. Continuous eligibility for the GMS scheme for a full year prior to diagnosis is also required for inclusion. Men who received a prostate cancer

diagnosis at death or autopsy only and men with a prior invasive tumour other than non-melanoma skin cancer will be excluded.

Sample size will depend on the number of cases in the dataset which meet the inclusion criteria i.e. all men in the population who meet the inclusion criteria will be included. Formal power calculations have not carried out *a priori*.

Exposure definition

Prescriptions for aspirin and aspirin combinations dispensed to eligible men will be identified from the GMS database using WHO-ATC codes (see Appendix 1).[16] Aspirin users will be defined as men who have a supply of aspirin available in the year prior to prostate cancer diagnosis. The date, dose and number of days' supply on each prescription are recorded and will be used to stratify pre-diagnostic aspirin use by: (i) dosing intensity (high/low) split on the median proportion of days covered (PDC) with a supply of aspirin available in the year prior to diagnosis;[19] (ii) dose prescribed (low: only received dose ≤75mg / high: any received dose > 75 mg).

As low-strength aspirin indicated for anti-platelet activity is licensed as a prescription only medicine in Ireland, very low levels of misclassification of aspirin use due to over the counter purchases are anticipated. New aspirin use in the six months prior to diagnosis will be censored as a sensitivity analysis to guard against bias introduced by new aspirin users receiving aspirin for pain which may be due to cancer progression.

Outcome Definitions

Information from death certificates, provided by the General Register Office to the NCRI, will be used to identify the date and primary cause of death. Primary outcome: prostate cancer death (ICD 9 185; ICD 10 C61); Secondary outcome: any cause death. All men will be followed from the date of diagnosis to death or the end of follow-up (31st December 2010).

Study Covariates

The following patient demographics and tumour characteristics at diagnosis will be identified from the NCRI database: patient age (years); smoking status (current/ former/ non-smoker/ unspecified); and AJCC tumour stage (tumour size, nodal status, metastases).[18] Treatment type and date received in the year post-diagnosis is also captured in the NCRI data: prostate surgery (yes/no), radiation (yes/no) androgen deprivation therapy (ADT) (yes/no) or chemotherapy (yes/no). Where data is missing for a covariate it will be retained in the analysis and classified as unspecified.

The prescription claims data will be used to determine a medication-based comorbidity score, based on the sum of distinct medication classes (as defined by the 5 character ATC code) received by each man in the year prior to diagnosis.[20] Prescription dispensing data will be used to identify exposure (yes/no) to other, potentially confounding, medication in the year prior to prostate cancer diagnosis: anti-diabetic agents, statins, non-aspirin anti-coagulants, non-aspirin NSAIDs, medication for the treatment of Benign Prostatic Hypertrophy (BPH). See Appendix 1 for WHO-ATC codes.

Statistical Analyses

Cohort characteristics will be tabulated to assess univariate differences between aspirin users and non-users. Cox proportional hazards models will be used to estimate hazard ratios (HR) with 95% confidence intervals (CI) for prostate cancer-specific mortality associated with aspirin use. Covariates are to be considered for inclusion in multivariate models based on prior knowledge of clinical and demographic predictors of prostate cancer mortality: age;[21] comorbidity score;[20] smoking status;[22,23] tumour size;[21] diabetes;[24] and exposure to beta-blockers,[17] statins,[25] non-aspirin anti-coagulants,[7,26] non-aspirin NSAIDS[25] and drugs used in BPH.[27] Also considered for inclusion in the model will be the year of prostate cancer diagnosis (continuous) and treatment received in the year following diagnosis: prostate surgery / radiation / androgen deprivation therapy (time-varying). A backward deletion method, with a 10% maximum change in the effect component of the fully adjusted HR will be used to select the final multivariate model.[28] The proportionality of hazard functions will be assessed by testing for the interaction between aspirin use and the logarithm of person-time (Wald test for product term).

Effect Modification

Analyses will be stratified by tumour stage to assess the potential for modification of the association between aspirin use and prostate cancer mortality according to whether the tumour has progressed to involve lymph nodes or metastases. Multiplicative interactions across strata of tumour stage will be determined (ratio of hazard ratios, rHR) with 95%CI.

Sensitivity Analyses

Due to the potential for misclassification of prostate cancer death on death certificates, sensitivity analyses are to be carried out. Firstly other cancer causes of death by which prostate cancer may reasonably be misclassified will considered as prostate cancer deaths (See appendix 2);[29] and secondly death certificates where prostate cancer is recorded as a secondary or contributory cause of death will be considered as prostate cancer deaths.

Sensitivity analyses around aspirin exposure will also be examined to guard against the potential for protopathic bias which may occur as a result of men being prescribed aspirin as an analgesic for pain prior to the diagnosis of cancer.

Limitations

Although the cancer registry captures population-based cancer cases, the subset of men for whom data on medication exposure exists are those men eligible for the GMS scheme. As eligibility for the scheme is based on means test and age, older men and men of lower socioeconomic status are likely to be over-represented. However this is unlikely to confound the potential association between aspirin and prostate cancer mortality. It should be noted that only medicines dispensed on the GMS scheme have been linked, and medicines dispensed under other community drugs schemes are not captured. This is not considered to differ greatly between aspirin users and non-users. As the data is based on medicines dispensed, it does not necessarily mean men were adherent, however determining (high/low) dosing intensity does stratify men on their level of exposure.

Although measures have been taken to account, as far as possible, for confounding by comorbidities using a medication-based comorbidity score, there may be some unmeasured confounding associated with comorbidity. The comorbidity score to be used has been validated as a medication-based means of prediction of mortality, hospitalisation and long-term care admissions.[20]

There may be selection bias based on the selection of only men who had a histologically graded prostate biopsy, thus men who were not deemed fit for a biopsy may have been excluded, which may affect external validity

Time-frame, planning and dissemination

The analysis is to commence in February 2013 with write-up anticipated to be complete by April 2013. Further amendments to the data in this time frame are not anticipated.

This work is to be disseminated as an original research article in a peer-reviewed journal and conference presentations.

References

1. Veitonmaki T, Tammela TL, Auvinen A, Murtola TJ. Use of aspirin, but not other non-steroidal anti-inflammatory drugs is associated with decreased prostate cancer risk at the population level. Eur J Cancer 2012.
2. Bosetti C, Rosato V, Gallus S, Cuzick J, La Vecchia C. Aspirin and cancer risk: a quantitative review to 2011. Ann Oncol 2012;23:1403-15.
3. Dhillon PK, Kenfield SA, Stampfer MJ, Giovannucci EL. Long-term aspirin use and the risk of total, high-grade, regionally advanced and lethal prostate cancer in a prospective cohort of health professionals, 1988-2006. Int J Cancer 2011;128:2444-52.
4. Rothwell PM, Fowkes FG, Belch JF, Ogawa H, Warlow CP, Meade TW. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. Lancet 2011;377:31-41.
5. Jacobs EJ, Newton CC, Gapstur SM, Thun MJ. Daily Aspirin Use and Cancer Mortality in a Large US Cohort. J Natl Cancer Inst 2012;104:1208-17.
6. Rothwell PM, Wilson M, Price JF, Belch JF, Meade TW, Mehta Z. Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials. Lancet 2012;379:1591-601.
7. Choe KS, Cowan JE, Chan JM, Carroll PR, D'Amico AV, Liauw SL. Aspirin Use and the Risk of Prostate Cancer Mortality in Men Treated With Prostatectomy or Radiotherapy. J Clin Oncol 2012.
8. Shappell SB, Manning S, Boeglin WE, et al. Alterations in lipoxygenase and cyclooxygenase-2 catalytic activity and mRNA expression in prostate carcinoma. Neoplasia 2001;3:287-303.
9. Jia RP, Xu LW, Su Q, et al. Cyclooxygenase-2 expression is dependent upon epidermal growth factor receptor expression or activation in androgen independent prostate cancer. Asian J Androl 2008;10:758-64.
10. Richardsen E, Uglehus RD, Due J, Busch C, Busund LT. COX-2 is overexpressed in primary prostate cancer with metastatic potential and may predict survival. A comparison study between COX-2, TGF-beta, IL-10 and Ki67. Cancer Epidemiol 2010;34:316-22.
11. Khor LY, Bae K, Pollack A, et al. COX-2 expression predicts prostate-cancer outcome: analysis of data from the RTOG 92-02 trial. Lancet Oncol 2007;8:912-20.
12. Masferrer JL, Leahy KM, Koki AT, et al. Antiangiogenic and antitumor activities of cyclooxygenase-2 inhibitors. Cancer Res 2000;60:1306-11.
13. Jain S, Harris J, Ware J. Platelets: linking hemostasis and cancer. Arterioscler Thromb Vasc Biol 2010;30:2362-7.
14. Data Quality and Completeness at the Irish National Cancer Registry: National Cancer Registry Ireland; 2012.
15. Fritz AG, Jack A, Percy C, et al. International classification of diseases for oncology : ICD-O. 3rd ed. Geneva: World Health Organization; 2000.
16. ATC/DDD Index 2012. WHO collaborating centre for drug statisitcs methodology, 2012. (Accessed 13/03/2012, 2012, at http://www.whocc.no/atc_ddd_index/.)
17. Barron TI, Connolly RM, Sharp L, Bennett K, Visvanathan K. Beta blockers and breast cancer mortality: a population- based study. J Clin Oncol 2011;29:2635-44.
18. Fleming I, Cooper J, Henson D, et al. American Joint Committee on Cancer: AJCC cancer staging manual. 5 ed. Philidelphia, PA, USA: Lippincott-Raven; 1997.
19. Peterson AM, Nau DP, Cramer JA, Benner J, Gwadry-Sridhar F, Nichol M. A checklist for medication compliance and persistence studies using retrospective databases. Value Health 2007;10:3-12.
20. Schneeweiss S, Seeger JD, Maclure M, Wang PS, Avorn J, Glynn RJ. Performance of comorbidity scores to control for confounding in epidemiologic studies using claims data. Am J Epidemiol 2001;154:854-64.

21. Buhmeida A, Pyrhonen S, Laato M, Collan Y. Prognostic factors in prostate cancer. Diagn Pathol 2006;1:4.
22. Kenfield SA, Stampfer MJ, Chan JM, Giovannucci E. Smoking and prostate cancer survival and recurrence. JAMA 2011;305:2548-55.
23. Warren GW, Kasza KA, Reid ME, Cummings KM, Marshall JR. Smoking at diagnosis and survival in cancer patients. Int J Cancer 2012.
24. Onitilo AA, Engel JM, Glurich I, Stankowski RV, Williams GM, Doi SA. Diabetes and cancer I: risk, survival, and implications for screening. Cancer Causes Control 2012;23:967-81.
25. Katz MS, Carroll PR, Cowan JE, Chan JM, D'Amico AV. Association of statin and nonsteroidal anti-inflammatory drug use with prostate cancer outcomes: results from CaPSURE. BJU Int 2010;106:627-32.
26. Choe KS, Correa D, Jani AB, Liauw SL. The use of anticoagulants improves biochemical control of localized prostate cancer treated with radiotherapy. Cancer 2010;116:1820-6.
27. Fleshner NE, Lucia MS, Egerdie B, et al. Dutasteride in localised prostate cancer management: the REDEEM randomised, double-blind, placebo-controlled trial. Lancet 2012;379:1103-11.
28. Rothman KJ, Greenland S, Lash TL. Modern Epidemiology. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2008.
29. Trends in Cancer Survival in Scotland 1971-1995. Edinburgh: Scottish Cancer Intelligence Unit; 2000.

Appendix 1

WHO ATC[16] Drug codes for medication exposures

Drug Exposure	WHO ATC Code
Aspirin & Combinations	B01AC06, M01BA03, N02BA01, N02BA51, N02BA71
Anti-diabetic medication	A10
Statins	C10AA
Non-aspirin anti-coagulants	B01A, excluding B01AC06
Non-aspirin NSAIDS	M01A
Benign Prostatic Hypertrophy	G04C

Appendix 2

Table S2.1: Potential other cancer sites which prostate cancer death may be misclassified:[29]

Cancer Site	ICD 9 Code	ICD 10 Code
Malignant neoplasm of prostate	185	C61
Malignant neoplasm of other male genital organs, site unspecified	187.9	C63.9
Malignant neoplasm of pelvis	195.3	C41.4
Secondary malignant neoplasm	196-198	C76-C80
Malignant neoplasm without specification of site	199	C80.9
Benign neoplasm of prostate	222.2	D29.1
Benign neoplasm of male genital organs, site unspecified	222.9	D29.9
Neoplasm of uncertain behaviour of prostate	236.5	D40.0
Neoplasm of uncertain behaviour of other and unspecified male genital organs	236.6	D40.9
Neoplasm of uncertain behaviour, site unspecified	238.9	D48.9
Neoplasm of unspecified nature of other genitourinary organs	239.5	D40.7, D41
Neoplasm of unspecified nature, site unspecified	239.9	D48.9