STUDY TITLE: **Aspirin use and prostate cancer mortality in men with high-grade prostate cancer: a cohort study**

ENCePP Study Reference Number: ENCEPP/SDPP/3444

AUTHORS AND AFFILIATIONS:

Evelyn M Flahavan[1]

Linda Sharp[2]

Thomas I Barron[1]

Kathleen Bennett[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

SUMMARY RESULTS:

Study Cohort

The study cohort consisted of 912 men who met the inclusion criteria; N=357 used aspirin in the year prior to diagnosis (see Figure 1). Aspirin users were significantly older than aspirin non-users, (73.0 years vs. 71.1 years, p<0.0001) and received more medication in the year prior to diagnosis, (comorbidity score 12.1 vs. 7.5, p<0.0001). Aspirin users were also less likely to be current smokers at diagnosis (12.0% vs. 19.8%, p=0.02). For full characteristics see Table 1. Median patient follow-up for the cohort was 4.6 years.

Survival Analyses

The unadjusted HR for prostate cancer-specific mortality associated with aspirin use was not significant (Table 2: HR=0.99, 95% CI 0.79, 1.24). Similar near-null associations were observed in adjusted analysis (Table 2: HR=1.06, 95% CI 0.81, 1.37). The adjusted HRs of prostate cancer-specific mortality at two, four and eight years after diagnosis were 1.19 (95% CI 0.69, 2.16); 1.01 (95% CI 0.75, 1.36) and 1.05 (95% CI 0.81, 1.37) respectively. The adjusted Cox model satisfied the proportional hazards assumption, p=0.74. Aspirin exposure in this cohort had no association with all-cause mortality (unadjusted HR=1.06, 95% CI 0.89, 1.26; adjusted HR=1.00, 95% CI 0.81, 1.23).

In stratified analyses, non-significantly increased risks of prostate cancer-specific mortality were associated with high aspirin dosing intensity and high aspirin dose (Table 2: HR=1.13 (95% CI 0.82, 1.56) and HR=1.22 (95% CI 0.84, 1.77) respectively). These trends were non-significant. A statistically significant increased HR of prostate cancer-specific mortality was associated with a combination of high aspirin dose and high dosing intensity (Table 2: HR=1.78, 95% CI 1.07, 2.97), however this group was limited by small numbers (N=41).

Effect Modification

Stratification of the analysis by tumour stage suggested a non-significantly reduced risk between aspirin use and prostate cancer-specific mortality in men with stage I-III tumours (Table 3: HR=0.91 95% CI 0.59, 1.40). However men with stage IV prostate cancer had a non-significant increased HR of prostate cancer-specific mortality associated with aspirin exposure (Table 4-10: HR=1.23, 95% CI 0.86, 1.75). The multiplicative interaction for Stage IV versus Stage I-III tumours was non-significant (*p*-interaction=0.26). No association was observed in men with unclassified tumour stage (within-strata HR=0.96, 95% CI 0.57, 1.75).

Sensitivity Analyses

Results of sensitivity analysis which censored aspirin use in the six months preceding diagnosis are presented in Table 4. The characteristics of aspirin exposed (N=314) and unexposed (N=598) men were similar to that of the original analysis. The association between aspirin exposure and prostate cancer specific mortality in this analysis were similar to that of the initial analysis. Sensitivity analyses considering other causes of prostate cancer death did not alter point estimates significantly (Table 5).

DISCUSSION

The strengths of this study include the detailed patient level data and most importantly the accurate aspirin prescribing data. Low-dose aspirin is available only on prescription in the Republic of Ireland; therefore misclassification of aspirin use due to over the counter purchases is likely to be minimal. Protopathic bias, which may occur due to prescription of higher doses of aspirin for analgesia in men who may have had undiagnosed advanced prostate cancer, has been managed by censoring aspirin prescriptions in the six months preceding diagnosis as a sensitivity analysis. The results from this analysis suggest that this bias is not evident. Sensitivity analyses were also undertaken to address the potential for misclassification of prostate cancer death. Some limitations must also be acknowledged. The

sample size was relatively small, as it was limited by the number of patients who met the inclusion criteria. A definitive diagnosis of high-grade cancer was an inclusion criterion; therefore some selection bias may occur as the study is restricted to men who were fit to undergo the prostate biopsy procedure. Some cross-over post-diagnosis occurred, 26.0% of non-users received aspirin during follow-up; however this would be expected to bias results towards the null.

In conclusion, aspirin use appears to be associated with a non-significant reduced risk of prostate cancer-specific mortality in men with localised prostate cancer with Gleason score >7, however, aspirin use does not appear to be associated with survival benefit in men who have metastatic disease at diagnosis.

ACKNOWLEDGEMENTS

We would like to thank the National Cancer Registry Ireland and the Irish Health Services Executive Primary Care Reimbursement Service for providing access to the data upon which this study was based. The interpretation and reporting of these data are the responsibility of the authors and should in no way be seen as the official policy or interpretation of the National Cancer Registry Ireland or the Irish Health Services Executive Primary Care Reimbursement Service.

GRANT SUPPORT

EMF is supported by a PhD studentship from the Irish Cancer Society (CRS10FLA). TIB is supported by the Health Research Board Ireland (HRA-2009-221, ICE-2011-9). The Irish Cancer Society and the Health Research Board Ireland had no role in the study design; collection, analysis, and interpretation of data; or writing of the report.

TABLES

TABLE 1: CHARACTERISTICS OF ASPIRIN USERS AND NON-USERS

Characteristic		Aspirin Non-user (N=555)	Aspirin User (N=357)	
Patient details				
Age /years	Mean (SD)	71.1 (6.2)	73.0 (5.3)	**
Comorbidity Score	Mean (SD)	7.5 (6.0)	12.1 (5.9)	**
Smoking Status - (%)	Never	110 (19.8)	43 (12.0)	*
	Former	180 (32.4)	123 (34.5)	
	Current	109 (19.6)	86 (24.1)	
	Unspecified	156 (28.1)	105 (29.4)	
Tumour details				
Stage - (%)[A]	I	2 (0.4)	0 (0)	
	II	237 (42.7)	139 (38.9)	
	III	50 (9.0)	37 (10.4)	
	IV	129 (23.2)	91 (25.5)	
	Unspecified	137 (24.7)	90 (25.2)	
Tumour Size - (%)[A]	T1,T1a, T1b, T1c	58 (10.5)	34 (9.5)	
	T2, T2a, T2b, T2c	215 (38.7)	129 (36.1)	
	T3, T3a, T3b	68 (12.3)	52 (14.6)	
	T4, T4a	38 (6.8)	23 (6.4)	
	Unspecified	176 (31.7)	119 (33.3)	
Nodal status - (%)[A]	Negative	77 (13.9)	46 (12.9)	
	Positive	24 (4.3)	12 (3.4)	
	Unspecified	454 (81.8)	299 (83.8)	
Metastatic status - (%)[A]	Negative	209 (37.8)	119 (33.3)	
	Positive	105 (19.0)	78 (21.8)	
	Unspecified	239 (43.2)	160 (44.8)	
Treatment details				
Treatment - (%)[B]	Surgery	147 (26.5)	114 (31.9)	
	Radiation	161 (29.0)	109 (30.5)	
	ADT	332 (59.8)	223 (62.5)	
	Chemotherapy	23 (4.1)	16 (4.5)	
Medication Exposures - (%)				
	Beta-blocker	72 (13.0)	141 (39.5)	*
	Statin	86 (15.5)	174 (48.7)	*
	Non-aspirin anticoagulant	49 (8.8)	50 (14.0)	*
	Anti-diabetic	28 (5.0)	56 (15.7)	*
	NSAID	235 (42.3)	183 (51.3)	*
	BPH medicines	159 (28.6)	119 (33.3)	
Aspirin exposure details (1 year pre-diagnosis)				
No of prescriptions dispensed		- -	10,028	
Dosing intensity - (%)	Median (IQR)	- -	86.6% (44.4, 98.4)	
Aspirin exposure details (post-diagnosis)[C]				
Men receiving post-diagnostic aspirin (%)		144 (26.0)	331 (92.7)	

** p-value <0.05.*

***A:** AJCC Staging Manual 5th Ed*

***B:** Received within one year following diagnosis.*

***C:** Receipt of aspirin at any point post-diagnosis.*

TABLE 2: ESTIMATED HAZARD RATIOS OF PROSTATE-CANCER SPECIFIC MORTALITY ASSOCIATED WITH ASPIRIN USE IN THE YEAR PRIOR TO DIAGNOSIS

			Prostate cancer-specific mortality		
Aspirin Use	**N**	**Person Years**	**No. of deaths (rate)[A]**	**Univariate HR (95%CI)**	**Multivariate HR (95%CI)**
Pre-diagnostic aspirin use [B]					
Aspirin non-user in year prior to diagnosis	555	2,447	195 (79.7)	Ref -	Ref -
Aspirin user in year prior to diagnosis	357	1,585	124 (78.3)	0.99 (0.79, 1.24)	1.06 (0.81, 1.37)
Exposure response: dosing intensity					
Low dosing intensity 0%-86% [C]	176	801	60 (74.9)	0.95 (0.71, 1.27)	1.00 (0.73, 1.36)
High dosing intensity 86%-100%	181	784	64 (81.7)	1.03 (0.78, 1.36)	1.13 (0.82, 1.56)
P-trend				*0.94*	*0.49*
Exposure response: dose					
Low dose ≤ 75mg	263	1,204	87 (72.3)	0.91 (0.71, 1.17)	1.00 (0.75, 1.33)
High dose > 75mg	94	381	37 (97.1)	1.25 (0.88, 1.77)	1.22 (0.84, 1.77)
P-trend				*0.58*	*0.41*
Exposure response: dosing intensity & dose					
Low dosing intensity 0%-86%					
Low dose ≤ 75mg	123	579	41 (70.8)	0.90 (0.64, 1.25)	1.03 (0.72, 1.48)
High dose > 75mg	53	222	19 (85.8)	1.10 (0.69, 1.76)	0.94 (0.58, 1.53)
High dosing intensity 86%-100%					
Low dose ≤ 75mg	140	624	46 (73.7)	0.92 (0.67, 1.27)	0.99 (0.70, 1.42)
High dose > 75mg	41	159	18 (112.9)	1.45 (0.90, 2.36)	1.78 (1.07, 2.97)*

* p-value < 0.05.

A: Mortality rate (deaths/1000 person years).

B: All multivariate HRs are adjusted for age at diagnosis, tumour stage (I&II/ III/ IV/ Unspecified), smoking status at diagnosis, comorbidity score, year of incidence, pre-diagnostic exposure to beta-blockers, BPH medicines and statins.

C: Dosing intensity by median

TABLE 3: ASPIRIN USE AND PROSTATE CANCER-SPECIFIC MORTALITY – EFFECT MODIFICATION BY TUMOUR SIZE AT DIAGNOSIS

		Aspirin Non-user		Aspirin User		User Vs Non-user	
Tumour Stage							
I-III	**Death/Censored**	67/222		36/140			
	Multivariate HR[A] (95% CI)	Ref -		0.91 (0.59, 1.40)	p = 0.67	0.91 (0.59, 1.40)	p = 0.67
IV	**Death/Censored**	89/40		63/28			
	Multivariate HR[A] (95% CI)	5.16 (3.73, 7.14)	p < 0.05	6.34 (4.36, 9.22)	p < 0.05	1.23 (0.86, 1.75)	p = 0.25
		Multiplicative scale: rHR (95% CI)		Stage IV Vs. Stage I-III		1.35 (0.80, 2.28)	p = 0.26

A: All multivariate HRs are adjusted for age at diagnosis, tumour stage (I&II/ III/ IV/ Unspecified), smoking status at diagnosis, comorbidity score, year of incidence, pre-diagnostic exposure to beta-blockers, BPH medicines and statins.

TABLE 4: ESTIMATED HAZARD RATIOS OF PROSTATE-CANCER SPECIFIC MORTALITY ASSOCIATED WITH ASPIRIN USE PRIOR TO DIAGNOSIS, CENSORED 6 MONTHS PRIOR TO DIAGNOSIS

			Prostate cancer-specific mortality		
Aspirin Use	**N**	**Person Years**	**No. of deaths (rate)[A]**	**Univariate HR (95%CI)**	**Multivariate HR (95%CI)**
Pre-diagnostic aspirin use [B]					
Aspirin non-user	598	2,631	210 (79.8)	Ref -	Ref -
Aspirin user	314	1,401	109 (77.8)	0.99 (0.78, 1.24)	1.07 (0.82, 1.40)
Exposure response: dosing intensity					
Low dosing intensity 0%-86% [C]	160	730	58 (79.5)	1.02 (0.76, 1.36)	1.07 (0.78, 1.47)
High dosing intensity 86%-100%	154	670	51 (76.0)	0.95 (0.70, 1.30)	1.07 (0.76, 1.50)
P-trend				*0.81*	*0.67*
Exposure response: dose					
Low dose ≤ 75mg	226	1,049	73 (69.6)	0.91 (0.71, 1.17)	1.00 (0.75, 1.33)
High dose > 75mg	88	351	36 (102.5)	1.25 (0.88, 1.77)	1.22 (0.84, 1.77)
P-trend				*0.58*	*0.41*
Exposure response: dosing intensity & dose					
Low dosing intensity 0%-86%					
Low dose ≤ 75mg	105	503	37 (73.6)	0.94 (0.66, 1.33)	1.08 (0.74, 1.58)
High dose > 75mg	55	227	21 (92.7)	1.18 (0.76, 1.86)	1.06 (0.66, 1.69)
High dosing intensity 86%-100%					
Low dose ≤ 75mg	121	546	36 (65.9)	0.82 (0.58, 1.17)	0.92 (0.62, 1.34)
High dose > 75mg	41	125	15 (120.4)	1.55 (0.92, 2.62)	1.80 (1.04, 3.12)*

* p-value < 0.05.

A: Mortality rate (deaths/1000 person years).

B: All multivariate HRs are adjusted for age at diagnosis, tumour stage (I&II/ III/ IV/ Unspecified), smoking status at diagnosis, comorbidity score, year of incidence, pre-diagnostic exposure to beta-blockers, BPH medicines and statins.

C: Dosing intensity by median

TABLE 5: SENSITIVITY ANALYSIS: ESTIMATED HAZARD RATIOS PROSTATE-CANCER SPECIFIC MORTALITY ASSOCIATED WITH ASPIRIN USE IN THE YEAR PRIOR TO DIAGNOSIS

			Prostate cancer-specific mortality		
Sensitivity Analysis 1	**N**	**Person Years**	**No. of deaths (rate)[A]**	**Univariate HR (95%CI)**	**Multivariate HR[B] (95%CI)**
Aspirin unexposed	555	2,447	201 (82.2)	Ref -	Ref -
Aspirin exposed	357	1,585	124 (78.3)	0.96 (0.77, 1.20)	1.03 (0.79, 1.34)
Sensitivity Analysis 2					
Aspirin unexposed	555	2,447	201 (82.2)	Ref -	Ref -
Aspirin exposed	357	1,585	133 (83.9)	1.03 (0.83, 1.28)	1.06 (0.82, 1.37)

A: Mortality rate (deaths/1000 person years).

B: All multivariate HRs are adjusted for age at diagnosis, tumour stage (I&II/ III/ IV/ Unspecified), smoking status at diagnosis, comorbidity score, year of incidence, pre-diagnostic exposure to beta-blockers, BPH medicines and statins.

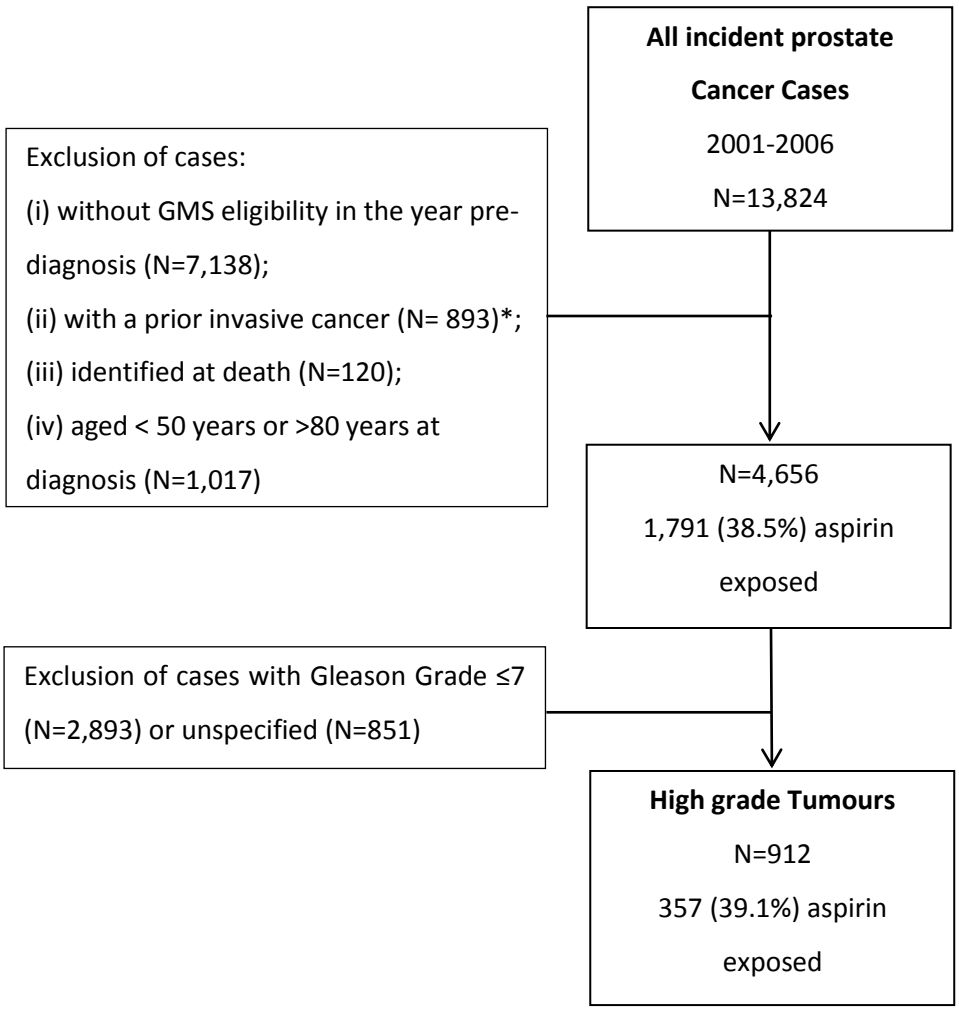

Figure 1: Cohort Selection for Study

* excluding non-melanoma skin cancers