Original Investigation

Association Between Oral Fluoroquinolone Use and Retinal Detachment

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IMPORTANCE A recent study of ophthalmologic patients found a strong association between fluoroquinolone use and retinal detachment. Given the prevalent use of fluoroquinolones, this could, if confirmed in the general population, translate to many excess cases of retinal detachment that are potentially preventable.

OBJECTIVE To investigate if oral fluoroquinolone use is associated with an increased risk of retinal detachment.

DESIGN, SETTING, AND PARTICIPANTS A nationwide, register-based cohort study in Denmark from 1997 through 2011, using linked data on participant characteristics, filled prescriptions, and cases of retinal detachment with surgical treatment (scleral buckling, vitrectomy, or pneumatic retinopexy). The cohort included 748 792 episodes of fluoroquinolone use (660 572 [88%] ciprofloxacin) and 5 520 446 control episodes of nonuse.

MAIN OUTCOMES AND MEASURES Poisson regression was used to estimate rate ratios (RRs) for incident retinal detachment, adjusting for a propensity score that included a total of 21 variables. The risk windows were classified as current use (days 1-10 from start of treatment), recent use (days 11-30), past use (days 31-60), and distant use (days 61-180).

RESULTS A total of 566 cases of retinal detachment occurred, of which 465 (82%) were rhegmatogenous detachments; 72 in fluoroquinolone users and 494 in control nonusers. The crude incidence rate was 25.3 cases per 100 000 person-years in current users, 18.9 in recent users, 26.8 in past users, and 24.8 in distant users compared with 19.0 in nonusers. Compared with nonuse, fluoroquinolone use was not associated with a significantly increased risk of retinal detachment: the adjusted RRs were 1.29 (95% CI, 0.53 to 3.13) for current use; 0.97 (95% CI, 0.46 to 2.05) for recent use; 1.37 (95% CI, 0.80 to 2.35) for past use; and 1.27 (95% CI, 0.93 to 1.75) for distant use. The absolute risk difference, estimated as the adjusted number of retinal detachment cases per 1 000 000 treatment episodes, was 1.5 (95% CI, −2.4 to 11.1) for current use.

CONCLUSIONS AND RELEVANCE In this cohort study based on the general Danish population, oral fluoroquinolone use was not associated with increased risk of retinal detachment. Given its limited power, this study can only rule out more than a 3-fold increase in the relative risk associated with current fluoroquinolone use; however, any differences in absolute risk are likely to be of minor, if any, clinical significance.

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Supplemental content at jama.com

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JAMA. 2013;310(20):2184-2190. doi:10.1001/jama.2013.280500

Retinal detachment, an acute eye disorder that may lead to loss of visual acuity despite prompt surgical intervention, is classified as rhegmatogenous, exudative, or tractional according to the underlying pathogenetic mechanism.[1,2] Rhegmatogenous detachment is by far the most common type with an annual incidence of 6 to 18 per 100 000 persons.[3,4]

A recent case-control study nested within a cohort of nearly 1 million ophthalmologic patients found that use of fluoroquinolones was strongly associated with retinal detachment, reporting a 4.5-fold significantly increased risk for ongoing exposure.[5] The possible mechanism was suggested to involve drug effects on connective tissue, whereby the breakdown of collagen promotes posterior vitreous detachment, which in turn leads to the detachment of the retina.[5] Fluoroquinolone use is associated with tendinopathy and rupture of the Achilles tendon,[6-8] and mechanistic studies indicate fluoroquinolone-induced tendon degeneration with up-regulation of proteolytic enzymes, decreased collagen production, and inhibition of cell proliferation, as well as apoptosis.[9-12] Therefore, a similar mechanism involving connective tissue of the eye may be plausible. Additionally, based on spontaneous reports to the Adverse Events Reporting System, the US Food and Drug Administration recently identified a potential safety signal of retinal detachment following fluoroquinolone exposure.[13]

Given the prevalence of fluoroquinolone use,[14,15] a 4.5-fold increase in risk would, if confirmed, give rise to many excess cases of retinal detachment that could have been prevented had another antibiotic been used. Indeed, the nested case-control study reported a number needed to harm of 2500 for fluoroquinolone use within the last year[5]; this should be interpreted in context of the fact that nearly 100 fluoroquinolone prescriptions per 1000 persons were dispensed in the United States in the year 2010.[14] However, before any changes to antibiotic prescribing policies are implemented, these findings need to be confirmed. For that reason, we conducted a nationwide, register-based cohort study in Denmark to investigate whether oral fluoroquinolone use was associated with increased risk of retinal detachment compared with no use.

Methods

This study was approved by the Danish Data Protection Agency. In Denmark, ethics approval and informed consent are not required for register-based studies. We conducted a nationwide study from January 1, 1997, through December 31, 2011, using health care and administrative registries that were linked on the individual level by the use of a unique personal identifier. We assessed the risk of incident retinal detachment in a cohort of episodes of oral fluoroquinolone use and nonuse, adjusting for a propensity score that incorporated potential confounders. The risk windows were classified as current (days 1-10, starting on the first day of treatment), recent (days 11-30), past (days 31-60), and distant use (days 61-180). The reference category was a 180-day period of nonuse. Given previous findings,[5] current use was defined as the risk window of primary interest. This classification of risk windows allowed us to assess the risk associated with fluoroquinolone use in periods incorporating the standard treatment duration of 10 days (recommended treatment duration is typically 7-14 days) and up to 170 days after treatment had ended. An increase in risk with current use that later disappeared, similar to the results reported in the Canadian study,[5] would suggest an acute toxic mechanism; conversely, an increase in risk in all time windows with no clear pattern of temporality would reflect unmeasured confounding or an effect that both had an acute onset and was very long lasting. Oral fluoroquinolone treatment was assumed to commence on the day the prescription was filled. The actual length of the fluoroquinolone prescription was not available; instead, current use was assumed to have a duration of 10 days.

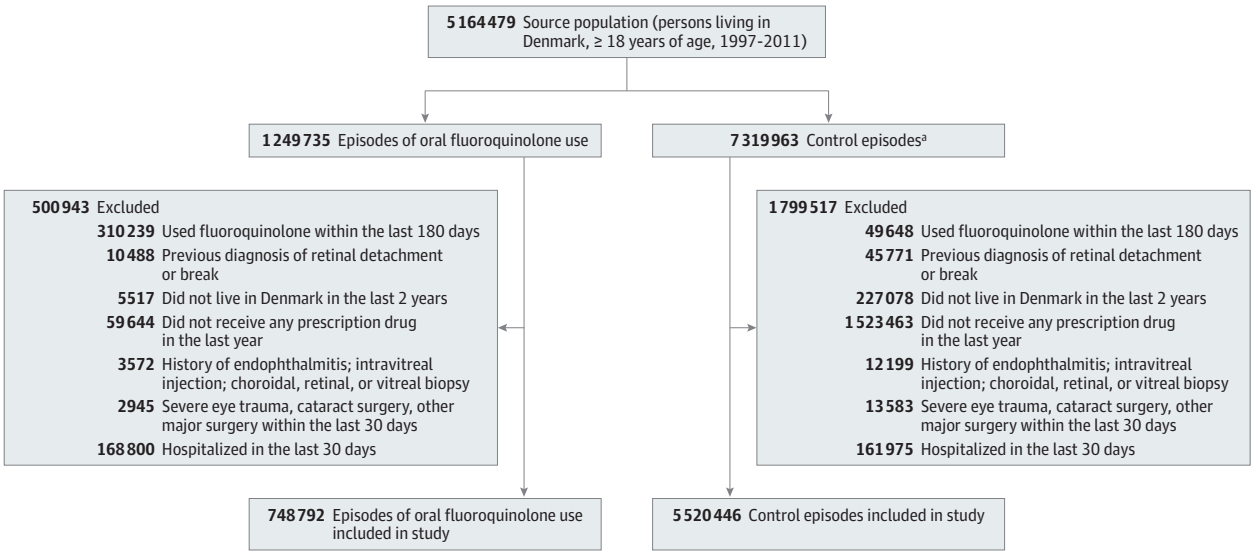
Sources of Data

The Central Person Register,[16] which is Denmark's main administrative register and includes information on date and place of birth, migration, and vital status (updated daily), was used to identify the source population for the cohort. The National Prescription Registry holds information on all prescriptions filled at all Danish pharmacies since 1995 and is considered near to complete; each new prescription generates an electronic file that is automatically transferred to this registry within minutes.[17] Data include the Anatomic Therapeutic Chemical (ATC) code of the drug and the date the prescription was dispensed. We used this register to identify prescriptions for any oral fluoroquinolone (ATC code, J01MA) and for concomitantly used drugs. The Danish National Patient Register holds records of individual-level information from all hospitals in Denmark (inpatient admissions, emergency department visits, and outpatient visits), including physician-assigned diagnoses classified according to the *International Classification of Diseases, Eighth Revision* (*ICD-8*; between 1977 and 1993) and *International Classification of Diseases, 10th Revision (ICD-10;* since 1994), as well as data on surgical procedures, classified according to the Nordic Medico-Statistical Committee Classification of Surgical Procedures (NCSP).[18,19] This register was used to identify concurrent medical conditions and cases of retinal detachment.

Cohort

From the source population of persons living in Denmark aged 18 years or older during the study period, we included in the cohort episodes of oral fluoroquinolone use in persons who had no previous diagnosis of retinal detachment or break (data available from 1977 onward); did not use oral fluoroquinolones in the last 180 days; had lived in Denmark for a minimum of 2 years (to ensure adequate assessment of covariates); had filled at least 1 prescription for any medication in the last year (to ensure some degree of activity in the health care system); and had not been hospitalized within the last 30 days (information on in-hospital antibiotic exposure was not available) (**Figure 1**). We excluded persons with a history of endophthalmitis, intravitreal injection, or choroidal, retinal, or vitreal biopsy; and persons who had cataract surgery, other major eye surgery, or were diagnosed with severe eye trauma within the last 30 days (to minimize the influence of potential confound-

Figure 1. Enrollment of Episodes of Fluoroquinolone Use and Nonuse, Denmark, 1997-2011



The numbers for individual exclusion criteria do not sum to the totals because some episodes were excluded for more than 1 reason.

[a] Each fluoroquinolone episode randomly assigned up to 10 control episodes in individuals with the same sex and birth date, and not using fluoroquinolone.

ers in which the sequence of events would be challenging to disentangle; both ocular surgery and trauma are known to increase the risk of retinal detachment and a postoperative or posttraumatic infection could prompt fluoroquinolone treatment; simultaneously, it would likely take time before a retinal detachment is detected in a postoperative or posttraumatic setting complicated by an infection, and the detachment would hence erroneously appear as occurring after fluoroquinolone exposure). Details on eligibility criteria are summarized in eTable 1 (in the Supplement).

Included were also control episodes of nonuse. From the source population, we randomly assigned each eligible fluoroquinolone episode up to 10 control episodes in persons with the same sex and date of birth, thereby creating a pool of potential controls for subsequent inclusion in the cohort. These control episodes were assigned the same index date as the corresponding fluoroquinolone episode and had to fulfill the same eligibility criteria. A single person could contribute with multiple treatment episodes to the cohort and could also contribute with episodes of nonuse; these episodes were all unique and never overlapped in time, thereby fulfilling statistical assumptions of independence.

Propensity Score

To control for a range of potential confounders, we used propensity score methods.[20] A propensity score was estimated for each episode of fluoroquinolone use and nonuse in the cohort using logistic regression as the probability of exposure given the following 21 variables at baseline: age, sex, calendar period, country of birth; history of severe eye trauma, chorioretinitis, retinopathy and other retinal disorders, retinal vascular occlusion, disorders of vitreous body, disorders of orbit, cataract surgery, other major eye surgery; diabetes, cardiovascular disease, renal disease; oral corticosteroid use, recent use of antibiotic eyedrops, recent use of oral antibiotics; and number of hospitalizations and emergency department visits in last year, number of drugs used in last year, and any ophthalmologic visit in last year (details in eTable 2 in the Supplement).

Retinal Detachment

The outcome was defined as an incident diagnosis of retinal detachment in combination with a surgical procedure for retinal detachment within 14 days following the date of diagnosis. The specific types of retinal detachment included rhegmatogenous (*ICD-10*: H330), exudative (H332), tractional (H334), other (H335), and unspecified (H33; general category of retinal detachment without specification of type). The surgical procedures were scleral buckling surgery (NCSP code: KCKC60, KCKC70), vitrectomy (KCKD60, KCKD65), and pneumatic retinopexy (KCKD10, KCKD15).

Statistical Analyses

Participants contributed person-time from the date a prescription for a fluoroquinolone was filled or the corresponding control index date and censored at the date of an outcome event, loss to follow-up (emigration or disappearance), death, a diagnosis of retinal detachment but no surgery within 14 days of diagnosis, a surgical procedure but no diagnosis, filling a fluoroquinolone prescription (ie, any prescription among nonusers and new prescription among fluoroquinolone users), hospitalization, 181 days following start of follow-up, or end of the study period, whichever occurred first.

Poisson regression was used to estimate rate ratios (RRs) with 95% CIs, comparing the incidence rates between fluoroquinolone users and nonusers (SAS version 9.3). The propensity score, categorized in deciles, was used as an adjustment

variable in the statistical models. Assuming that propensity score matching may provide more robust confounder control than adjustment for propensity score, we did a post hoc sensitivity analysis; episodes of fluoroquinolone use and nonuse were matched in a 1:2 ratio on the basis of the propensity score. The greedy 5→1 digit matching algorithm was applied[21,22] (ie, for each fluoroquinolone user, matching was first attempted on the first 5 digits of the propensity score; if no match was found, matching was attempted on the first 4 digits, and so on, until the first digit). Standardized differences between groups were estimated to assess the balance achieved by matching; a baseline characteristic was considered to be well balanced if the standardized difference was less than 10%. The adjusted absolute risk difference was estimated as (adjusted RR − 1) × I, for which I was the crude incidence rate among the unexposed; and reported as the number of cases per 1 000 000 treatment episodes. Results were considered statistically significant when the 95% CIs did not overlap 1.0.

Results

From the source population of 5 164 479 persons, 1 249 735 episodes of oral fluoroquinolone use and 7 319 963 control episodes of nonuse were identified. The eligibility criteria were met for 748 792 episodes of fluoroquinolone use and 5 520 446 control episodes (Figure 1). Baseline characteristics of the cohort are shown in **Table 1**. Fluoroquinolone users were more often men and residents of the greater Copenhagen region, and were somewhat younger; had a higher prevalence of diabetes, cardiovascular disease, and renal disease; more often had a history of cataract and other major eye surgery; were more often users of oral corticosteroids and antibiotic eyedrops, as well as oral antibiotics in the last 30 days; had used a higher number of prescription drugs in the last years; had more often visited an emergency department or been hospitalized in the last year; and more often had had an ophthalmologic visit in the last year.

The majority of treatment episodes with fluoroquinolones were with ciprofloxacin (660 572 [88.2%]), followed by ofloxacin (68 609 [9.2%]), fleroxacine (8731 [1.2%]), moxifloxacin (5670 [0.8%]), and other fluoroquinolones (5210 [0.7%]). In total, 566 cases of retinal detachment occurred, corresponding to an incidence rate of 19.5 per 100 000 person-years. Of the retinal detachment cases, 465 (82%) were rhegmatogenous detachments. The mean age at diagnosis of retinal detachment was 66.1 years (SD, 12.5) and 56% were women. There was a median of 1 day (interquartile range, 1-3) between diagnosis and surgical treatment.

Table 2 shows the propensity score–adjusted analyses of retinal detachment risk associated with use of oral fluoroquinolones. Of 72 fluoroquinolone-exposed cases, 5 occurred during current use, 7 during recent use, 14 during past use, and 46 during distant use. In nonuser controls, 494 cases occurred. Current fluoroquinolone use compared with nonuse was not associated with significantly increased risk of retinal detachment (adjusted RR, 1.29 [95% CI, 0.53 to 3.13]). There was no significantly increased risk of retinal detachment with

Table 1. Baseline Characteristics of Cohort of Episodes of Oral Fluoroquinolone Use and Nonuse, Denmark, 1997-2011

Characteristics	No. (%)[a]	
	Fluoroquinolone (n = 748 792)	No Fluoroquinolone (n = 5 520 446)
Age, mean (SD), y	57.7 (19.9)	59.0 (19.1)
Men	281 816 (38)	1 865 343 (34)
Calendar year		
1997-1999	123 830 (17)	893 455 (16)
2000-2002	90 775 (12)	658 732 (12)
2003-2005	130 035 (17)	951 495 (17)
2006-2008	185 100 (25)	1 370 723 (25)
2009-2011	219 052 (29)	1 646 041 (30)
Country of birth		
Denmark	703 967 (94)	5 177 072 (94)
Other European	17 822 (2)	131 910 (2)
Other	27 003 (4)	211 464 (4)
Region of residence		
Greater Copenhagen	240 435 (32)	1 642 645 (30)
Zealand	92 413 (12)	840 363 (15)
Southern Denmark	176 833 (24)	1 232 970 (22)
Central Denmark	168 953 (23)	1 196 157 (22)
Northern Denmark	70 158 (9)	608 311 (11)
Ophthalmologic history		
Chorioretinitis	116 (<0.1)	733 (<0.1)
Retinopathy and other retinal disorders	11 318 (2)	70 841 (1)
Retinal vascular occlusion	1004 (0.1)	6977 (0.1)
Disorder of vitreous body	1498 (0.2)	9010 (0.2)
Disorder of orbit	255 (<0.1)	1534 (<0.1)
Severe eye trauma[b]	1096 (0.1)	6519 (0.1)
Cataract surgery[b]	55 440 (7)	369 094 (7)
Other major eye surgery[b]	30 191 (4)	190 472 (4)
Other medical history		
Diabetes[c]	52 554 (7)	293 155 (5)
Cardiovascular disease	141 523 (19)	801 017 (15)
Renal disease	9660 (1)	27 421 (0.5)
Use of oral corticosteroid in last year	74 161 (10)	319 085 (6)
Use of antibiotic eyedrops in last 30 d	12 774 (2)	62 995 (1)
Use of oral antibiotics in last 30 d	257 820 (34)	301 923 (6)
No. of prescription drugs used in last year		
1-2	144 024 (19)	1 884 081 (34)
3-5	195 505 (26)	1 753 564 (32)
6-9	178 050 (24)	1 134 698 (21)
≥10	231 213 (31)	748 103 (14)
No. of hospitalizations/emergency department visits in last year		
0	512 259 (68)	4 309 744 (78)
1-2	183 918 (25)	1 044 191 (19)
≥3	52 615 (7)	166 511 (3)
Any ophthalmologic visit in last year	19 367 (3)	125 965 (2)

[a] Percentages may not add to 100 because of rounding.

[b] Because individuals who were diagnosed with severe eye trauma or who underwent cataract or other major eye surgery within 30 days before cohort entry were excluded, these numbers refer to the period prior to 30 days before cohort entry.

[c] Defined by the use of insulin or oral antidiabetic drug.

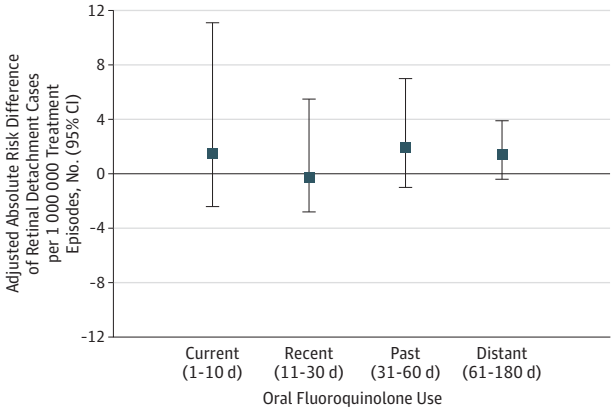
Table 2. Risk of Retinal Detachment in Propensity Score–Adjusted Analyses Comparing Oral Fluoroquinolone Use With Nonuse

	No Fluoroquinolone Use	Fluoroquinolone Use[a]			
		Current	Recent	Past	Distant
Person-years, No.	2 602 472	19 797	37 015	52 207	185 590
Events, No.	494	5	7	14	46
Crude rate per 100 000 person-years	19.0	25.3	18.9	26.8	24.8
Crude rate ratio (95% CI)	1 [Reference]	1.33 (0.55-3.21)	1.00 (0.47-2.10)	1.41 (0.83-2.40)	1.31 (0.97-1.77)
Adjusted[b] rate ratio (95% CI)	1 [Reference]	1.29 (0.53-3.13)	0.97 (0.46-2.05)	1.37 (0.80-2.35)	1.27 (0.93-1.75)

[a] Fluoroquinolone exposure was classified in fixed risk windows as current use (days 1-10 from start of treatment), recent use (days 11-30), past use (days 31-60), and distant use (days 61-180).

[b] Adjusted for propensity score (variables included in propensity score are listed in Table 1).

Figure 2. Adjusted Absolute Risk Difference of Retinal Detachment in the Comparison of Treatment Episodes of Oral Fluoroquinolone Use and Episodes of Nonuse



recent, past, or distant use of fluoroquinolones (Table 2). The absolute risk difference for current use, estimated as the adjusted number of retinal detachment cases per 1 000 000 treatment episodes, was 1.5 (95% CI, -2.4 to 11.1; **Figure 2**).

In sensitivity analyses, we tested assumptions related to exposure and outcome definitions as well as confounder control. Given that a retinal detachment case occurring on the same day as the prescription was filled could have occurred before or after drug intake, the temporality of events on this day could not be determined and reverse causation was possible. When this day was removed, the adjusted RR for current use, compared with nonuse, was 0.86 (95% CI, 0.28-2.69). In the primary analysis, the outcome was defined as the combination of diagnosis and surgical procedure, which might have been too conservative. When defining the outcome by diagnosis alone, the incidence rates were substantially higher in both fluoroquinolone users and nonusers; the adjusted RRs, however, were similar to those in the primary analysis (**Table 3**). In a post hoc sensitivity analysis with propensity score matching, fluoroquinolone users and nonusers were well balanced on baseline characteristics (eTable 3 in the Supplement). The RRs were very similar to those in the primary analysis. Compared with nonuse, current fluoroquinolone use was not associated with increased risk of retinal detachment (RR, 1.22 [95% CI, 0.50-2.99]), and neither was recent, past, or distant use (Table 3).

Discussion

This nationwide cohort study in Denmark found no significantly increased risk of retinal detachment associated with use of oral fluoroquinolone antibiotics. In terms of absolute risk, the upper limit of the CIs indicates that current use of fluoroquinolones would, in the worst-case scenario, account for no more than 11 additional cases of retinal detachment per 1 000 000 treatment episodes.

Our study was prompted by the findings of a recent nested case-control study,[5] which was the first and only study so far to investigate this potential association. Using Canadian databases, the study reported that retinal detachment was strongly associated with oral fluoroquinolone use. Their assessment of current use, defined as a prescription with a duration that overlapped with the date of diagnosis of retinal detachment, had an approximated RR of 4.50 (95% CI, 3.56-5.70). No significant association was observed with recent use (RR, 0.92 [95% CI, 0.45-1.87]), defined as a prescription that had ended within 7 days prior to the date of detachment diagnosis. These findings were interpreted as evidence of an acute adverse event. A potential mechanism was suggested to involve toxic fluoroquinolone effects on connective tissue in the vitreous body, thereby inducing posterior vitreous detachment, which in turn precipitated retinal detachment. Our findings are inconsistent with these data and provide no evidence of a temporal pattern to support the possibility of an acute toxic mechanism. Despite the size of our study, including more than 748 000 treatment episodes with fluoroquinolones, only 5 cases of retinal detachment occurred during current use; while this is reassuring, it limited the precision of the estimates for this risk window. Still, for the exposure category of current use, the upper limit of the CIs in our study (95% CI, 0.53-3.13) was below the lower limit of the CIs in the Canadian study (95% CI, 3.56-5.70).[5] Thus, there is a high degree of certainty that our data are inconsistent with the association reported in the Canadian study.

Although the Canadian study had a nested case-control design and we used a cohort approach, the 2 studies are comparable given the use of similar database information and identical case definitions. However, there are also a few major differences in their designs. First, while the Canadian study was restricted to ophthalmologic patients, our cohort was de-

Table 3. Sensitivity Analyses of Association Between Oral Fluoroquinolone Use and Risk of Retinal Detachment

	No Fluoroquinolone Use	Fluoroquinolone Use[a]			
		Current	Recent	Past	Distant
Outcome defined by diagnosis alone[b]					
Person-years, No.	2 609 978	19 862	37 130	52 362	186 096
Events, No.	853	9	10	22	73
Crude rate per 100 000 person-years	32.7	45.3	26.9	42.0	39.2
Crude rate ratio (95% CI)	1 [Reference]	1.39 (0.72-2.67)	0.82 (0.44-1.54)	1.29 (0.84-1.96)	1.20 (0.95-1.52)
Adjusted rate ratio (95% CI)[c]	1 [Reference]	1.31 (0.67-2.53)	0.78 (0.42-1.46)	1.22 (0.79-1.87)	1.14 (0.89-1.46)
Propensity score–matched cohort[d,e]					
Person-years, No.	600 998	19 323	36 187	51 115	182 134
Events, No.	127	5	7	14	44
Rate per 100 000 person-years	21.1	25.9	19.3	27.4	24.2
Rate ratio (95% CI)	1 [Reference]	1.22 (0.50-2.99)	0.92 (0.43-1.96)	1.30 (0.75-2.25)	1.14 (0.81-1.61)

[a] Fluoroquinolone exposure was classified in fixed risk windows as current use (days 1-10 from start of treatment), recent use (days 11-30), past use (days 31-60), and distant use (days 61-180).

[b] In contrast to the primary analysis, for which the outcome was defined as a diagnosis of retinal detachment in combination with a surgical procedure for retinal detachment, the outcome in this sensitivity analysis was defined as a diagnosis of retinal detachment alone.

[c] Adjusted for propensity score (variables included in propensity score are listed in Table 1).

[d] Episodes of fluoroquinolone use and nonuse were matched in a 1:2 ratio on the basis of propensity scores (variables included in the propensity score are listed in Table 1).

[e] Outcome defined as a diagnosis of retinal detachment in combination with a surgical procedure for retinal detachment.

rived from the entire adult population of Denmark. The Canadian study was therefore enriched with patients who were at higher risk of retinal detachment. Indeed, with 1 682 305 person-years of follow-up (calculated from 989 591 patients and median 1.7 years' follow-up[5]) and 4384 events, the incidence rate was approximately 260 per 100 000 person-years; this far exceeds the incidence reported in population-based studies including ours (ranging between 6 and 18 per 100 000 person-years for rhegmatogenous retinal detachment in other studies and 19 per 100 000 for retinal detachment overall in our study).[3,4] Second, the control of potential confounders was more comprehensive in our study; through adjustment for propensity score and application of specific eligibility criteria, we controlled for variables such as severe eye trauma, retinopathy, disorders of the vitreous, and major eye surgery. These variables were not accounted for in the Canadian study. Thus, failure to control for important risk factors for retinal detachment, especially in a population enriched with such risk factors, may explain the findings of the Canadian study. An alternate interpretation of the divergent results in the 2 studies is that the risk of retinal detachment is increased with current fluoroquinolone use in a population at very high baseline risk of this disorder, but that this has no effect on the level of the general population.

Our study has strengths and limitations. The use of registries with nationwide coverage and a cohort design allowed the study period to extend over 15 years and minimized concern about important sources of bias, such as those related to sampling and recall. To maximize specificity of the register-based case ascertainment, our case definition required both a diagnosis and a surgical procedure. In support of the validity of this approach, the incidence rates were similar to those from other population-based studies.[3,4] Additionally, when the outcome was defined by registered diagnosis alone in a sensitivity analysis, similar RRs as in the primary analysis were observed.

Our exposure definition implied that a dispensed prescription was equivalent to drug use. Some individuals may not have used the drugs; this would bias results toward the null. Most participants in this study used ciprofloxacin and results are therefore primarily applicable to this specific fluoroquinolone. Although this is comparable with the Canadian study, in which 83% of the fluoroquinolone-exposed cases used ciprofloxacin,[5] some of the other fluoroquinolones might be associated with retinal detachment.

A key issue in observational studies is the possibility of unmeasured confounding. The RRs were slightly above 1.0 in 3 out of 4 risk windows. In the absence of a clear temporal pattern (ie, in the presence of an acute toxic mechanism, the RR would be expected to be increased for current use and decrease thereafter), this observation may suggest some degree of residual or unmeasured confounding toward increased risk. Although we controlled for a number of potential confounders, we did not have data on some recognized risk factors for retinal detachment, such as myopia, smoking, and high body mass index; these could represent a source of unmeasured confounding. On the other hand, the primary concern in this study would be confounders obscuring a true association. We find no reason to believe that factors such as smoking and high body mass index would be more prevalent in nonusers than in fluoroquinolone users, thereby masking a true risk conferred by fluoroquinolones. Similarly, although data on the specific indications for fluoroquinolone treatment were not available, it is unlikely that any infection, irrespective of its anatomic location and severity, in patients treated with fluoroquinolones would be associated with a decreased risk of retinal detachment thereby masking a true risk conferred by these medications.

Conclusion

In contrast to a recent nested case-control study from Canada,[5] this nationwide, population-based cohort study in Denmark found no significant association between fluoroquinolone use and retinal detachment. Given limited power, this study can only rule out more than a 3-fold relative increase in the risk of retinal detachment associated with current fluoroquinolone use. However, any differences in absolute risk are likely to have limited, if any, clinical significance.

ARTICLE INFORMATION

Author Contributions: Dr Pasternak had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: All authors.
Acquisition of data: Svanström.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: Pasternak.
Critical revision of the manuscript for important intellectual content: Svanström, Melbye, Hviid.
Statistical analysis: Svanström.
Obtained funding: Pasternak.
Administrative, technical, or material support: Melbye.
Study supervision: Melbye, Hviid.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Funding/Support: This study was supported by The Danish Medical Research Council.

Role of the Sponsor: The Danish Medical Research Council had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES

1. D'Amico DJ. Clinical practice: primary retinal detachment. *N Engl J Med*. 2008;359(22):2346-2354.

2. Kang HK, Luff AJ. Management of retinal detachment: a guide for non-ophthalmologists. *BMJ*. 2008;336(7655):1235-1240.

3. Mitry D, Charteris DG, Fleck BW, Campbell H, Singh J. The epidemiology of rhegmatogenous retinal detachment: geographical variation and clinical associations. *Br J Ophthalmol*. 2010;94(6):678-684.

4. Mitry D, Chalmers J, Anderson K, et al. Temporal trends in retinal detachment incidence in Scotland between 1987 and 2006. *Br J Ophthalmol*. 2011;95(3):365-369.

5. Etminan M, Forooghian F, Brophy JM, Bird ST, Maberley D. Oral fluoroquinolones and the risk of retinal detachment. *JAMA*. 2012;307(13):1414-1419.

6. van der Linden PD, Sturkenboom MC, Herings RM, et al. Increased risk of achilles tendon rupture with quinolone antibacterial use, especially in elderly patients taking oral corticosteroids. *Arch Intern Med*. 2003;163(15):1801-1807.

7. Wise BL, Peloquin C, Choi H, Lane NE, Zhang Y. Impact of age, sex, obesity, and steroid use on quinolone-associated tendon disorders. *Am J Med*. 2012;125(12):1228.

8. van der Linden PD, Sturkenboom MC, Herings RM, et al. Fluoroquinolones and risk of Achilles tendon disorders: case-control study. *BMJ*. 2002;324(7349):1306-1307.

9. Sendzik J, Shakibaei M, Schäfer-Korting M, et al. Synergistic effects of dexamethasone and quinolones on human-derived tendon cells. *Int J Antimicrob Agents*. 2010;35(4):366-374.

10. Shakibaei M, Stahlmann R. Ultrastructure of Achilles tendon from rats after treatment with fleroxacin. *Arch Toxicol*. 2001;75(2):97-102.

11. Tsai WC, Hsu CC, Tang FT, Wong AM, Chen YC, Pang JH. Ciprofloxacin-mediated cell proliferation inhibition and G2/M cell cycle arrest in rat tendon cells. *Arthritis Rheum*. 2008;58(6):1657-1663.

12. Corps AN, Harrall RL, Curry VA, et al. Ciprofloxacin enhances the stimulation of matrix metalloproteinase 3 expression by interleukin-1β in human tendon-derived cells: a potential mechanism of fluoroquinolone-induced tendinopathy. *Arthritis Rheum*. 2002;46(11):3034-3040.

13. US Food and Drug Administration. Potential signals of serious risks/new safety information identified by the Adverse Event Reporting System (AERS) between April-June 2012. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm324020.htm. Accessed September 9, 2013.

14. The Center for Disease Dynamics, Economics, and Policy. Antibiotic use overview. http://www.cddep.org/ResistanceMap/use. Accessed April 22, 2013.

15. Zhang Y, Steinman MA, Kaplan CM. Geographic variation in outpatient antibiotic prescribing among older adults. *Arch Intern Med*. 2012;172(19):1465-1471.

16. Pedersen CB, Gøtzsche H, Møller JO, Mortensen PB. The Danish Civil Registration System: a cohort of 8 million persons. *Dan Med Bull*. 2006;53(4):441-449.

17. Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health*. 2011;39(7)(suppl):38-41.

18. Andersen TF, Madsen M, Jørgensen J, et al. The Danish National Hospital Register: a valuable source of data for modern health sciences. *Dan Med Bull*. 1999;46(3):263-268.

19. Nordic Medico-Statistical Committee. NOMESCO classification of surgical procedures. http://nomesco-eng.nom-nos.dk/filer/publikationer/NCSP%201_15.pdf. Accessed October 9, 2012.

20. Glynn RJ, Schneeweiss S, Stürmer T. Indications for propensity scores and review of their use in pharmacoepidemiology. *Basic Clin Pharmacol Toxicol*. 2006;98(3):253-259.

21. Parson LS. Reducing bias in a propensity score matched-pair sample using greedy matching techniques. Poster presented at: 26th Annual SAS Users Group International Conference; April 22-25, 2001; Long Beach, CA. http://www2.sas.com/proceedings/sugi26/p214-26.pdf. Accessed October 18, 2013.

22. Austin PC. Primer on statistical interpretation or methods report card on propensity-score matching in the cardiology literature from 2004 to 2006: a systematic review. *Circ Cardiovasc Qual Outcomes*. 2008;1(1):62-67.