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L'EXPOSITION AUX ANTI-INFLAMMATOIRES NON STEROÏDIENS ET AUX ANTIHYPERTENSEURS ET LE RISQUE DE CANCER DE LA PROSTATE

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Résumé

Des études suggèrent que les anti-inflammatoires non stéroïdiens (AINS) et les antihypertenseurs préviendraient peut-être le développement du cancer de la prostate. La confirmation de ces observations pourrait conduire à l'élaboration de mesures de chimioprévention de ce cancer.

Pour vérifier si l'usage de ces médicaments est associé au risque de développer un cancer de la prostate, nous avons réalisé une étude cas-témoins avec appariement sur l'âge. La population participante comportait 2221 cas et 11 105 témoins. La durée rétrospective d'observation s'étendait sur huit ans. Les renseignements sur la maladie et l'exposition médicamenteuse provenaient des banques de données informatisées de la Régie de l'assurance maladie du Québec et du Fichier des tumeurs du Québec.

Nous avons observé que ceux recevant 80 mg ou plus d'acide acétylsalicylique (AAS) quotidiennement, depuis 8 ans, avaient 18 % moins de risque de développer un cancer de la prostate que les non-exposés (rapport de cotes (RC) = 0,82, intervalle de confiance à 95 % (IC) = 0,71-0,95). L'association entre l'AAS et le cancer de la prostate démontrait des gradients durée-réponse et dose-réponse consistants. Par ailleurs, nous avons observé que l'effet protecteur de l'AAS s'estompait rapidement lorsque cessait l'exposition. Ceci laisse croire que l'AAS pourrait retarder plutôt que prévenir le développement du cancer de la prostate. Le risque de néoplasie prostatique était indépendant de l'usage des AINS autres que l'AAS. Un biais de classification explique peut-être cette dernière constatation.

Par ailleurs, par rapport aux non-exposés, le risque de cancer de la prostate chez les exposés aux antihypertenseurs était de 0,98 (IC, 0,88-1,08). Lorsque analysé par classe, seule l'exposition aux bêta-bloquants s'est avérée associée au risque de néoplasie prostatique (RC=0,86, IC=0,77-0,96). Par rapport aux non-exposés, le risque était de 0,89 (0,75-1,05), 0,91 (0,75-1,09), et 0,82 (0,69-0,96) chez ceux ayant cumulé moins d'un an, un à quatre ans et plus de quatre ans d'exposition aux bêta-bloquants, respectivement. De plus, les hommes exposés pendant au moins quatre ans à l'AAS et à un bêta-bloquant présentaient 31 % (RC=0,69, IC=0,50-0,97) moins de cancer de la prostate que les non-exposés.

L'usage d'AAS de même que l'usage de bêta-bloquants serait donc, selon nos résultats, associé à une réduction du risque de survenue d'un cancer de la prostate.

Avant-Propos

De nombreuses personnes ont participé à la réalisation de cette recherche. C'est François Meyer et Isabelle Bairati qui ont rédigé la demande de subvention d'où provenaient les fonds de l'étude tandis que Lynne Moore et François Meyer ont procédé à la constitution initiale de la banque de données. Subséquemment, j'ai pris en charge la validation de cette banque, la planification des analyses, la revue de la littérature, l'analyse des données et la rédaction des articles présentés aux chapitres II et III de la thèse. Le premier article a été publié dans la revue International Journal of Cancer alors que le second a été soumis pour publication à la revue Cancer causes and control.

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Enfin, je veux exprimer une reconnaissance particulière à mon conjoint, Marc, pour sa compréhension et ses encouragements tout au long de ce projet.

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1.1   Le cancer de la prostate

Le cancer de la prostate est le cancer le plus souvent diagnostiqué chez les hommes canadiens. En 2002, il y représentait 26 % de l'ensemble des nouveaux cancers[1]. On estime qu'un Canadien sur 8,3 en souffrira au cours de sa vie[1]. En terme de mortalité, le cancer de la prostate se classe au second rang, derrière le cancer du poumon. Au Canada, en 2002, la probabilité à vie pour un homme d'en mourir se chiffrait à 3,6 %, soit 1 Canadien sur 27,7[1]. Par ailleurs, durant cette même année, ce cancer dérobait 33 000 années potentielles de vie, ce qui en faisait la troisième cause d'années potentielles de vie perdues par cancer chez les hommes, derrière le cancer du poumon et le cancer colorectal [1].

Au Canada, le taux d'incidence du cancer de la prostate augmente progressivement depuis le début des années 1970. Entre 1973 et 1998, il est passé de 60 à 114 cas par 100 000 personnes-année[1]. L'adoption par les médecins de méthodes de détection précoce du cancer de la prostate comme le toucher rectal, la résection transuréthrale de la prostate, l'échographie transrectale et le dosage de l'antigène prostatique spécifique (APS) explique en grande partie cette hausse[1]. Ces pratiques ont permis d'identifier de plus en plus de carcinomes prostatiques asymptomatiques. L'introduction du dosage des APS, tout particulièrement, s'est traduite par une élévation abrupte de l'incidence entre les années 1989 et 1993[1]. Cependant, comme le taux d'incidence commença à s'élever avant l'avènement des pratiques de détection précoce, plusieurs soutiennent que des changements dans l'exposition à certains facteurs de risque contribuent également à expliquer la tendance[2]. Entre le début des années 1970 et le milieu de la dernière décennie, le taux de mortalité par cancer de la prostate a également progressé, passant de 25 à 31 décès par 100 000 personnes-année[1]. Depuis 1995 toutefois, on observe une légère tendance dans la direction inverse[1]. Un biais d'attribution pourrait rendre compte, du moins en partie, de l'apparente hausse de la mortalité par cancer de la prostate[3]. Le biais d'attribution correspond à la probabilité accrue d'attribuer faussement un décès au cancer de la prostate par le simple fait de l'accroissement de la prévalence de ce cancer dans la population. Par ailleurs, l'amélioration des traitements et une meilleure utilisation de l'hormonothérapie expliquent vraisemblablement le récent fléchissement du taux de mortalité[4, 5]. Certains prétendent toutefois que ce déclin résulterait plutôt d'un biais d'attribution dans le sens opposé à celui décrit précédemment puisque, depuis le milieu des années 1990, la tendance

à la hausse de l'incidence du cancer de la prostate a passablement ralenti par rapport à ce qu'elle était entre 1989 et 1993[6]. Enfin, compte tenu du vieillissement de la population canadienne, le nombre absolu de cas de cancer de la prostate augmentera au cours des prochaines décennies[7].

À l'échelle mondiale, le cancer de la prostate est la troisième cause de cancer chez les hommes. Avec un demi-million de nouveaux cas par année, il représente 10 % de tous les cancers incidents dans ce groupe[6]. Bien qu'à la hausse partout dans le monde, l'incidence standardisée pour l'âge du carcinome prostatique varie énormément d'un pays à l'autre. Aux États-Unis, il est diagnostiqué 3 fois plus souvent qu'en Europe et 10 fois plus souvent qu'en Asie[6]. Le taux de mortalité ajusté pour l'âge montre des variations internationales beaucoup moins frappantes. Aux États-Unis et dans les pays d'Europe, les taux sont à peu près identiques[6]. Dans les pays d'Extrême-Orient, par contre, on enregistre des taux de mortalité par cancer de la prostate beaucoup plus faibles[6].

L'étiologie du cancer de la prostate demeure méconnue mais il s'agit vraisemblablement d'une pathologie d'origine multifactorielle. L'âge, les antécédents familiaux de cancer de la prostate et l'origine ethno-raciale (les hommes de race noire sont plus affectés que ceux de race blanche, qui eux, le sont davantage que les Asiatiques) constituent les facteurs les plus fortement associés au risque de développer ce cancer[8]. Les variations internationales dans l'incidence et la mortalité par cancer de la prostate ainsi que les observations faites auprès des populations migrantes suggèrent toutefois que des facteurs environnementaux participent aussi au développement de cette néoplasie[8]. La consommation de gras d'origine animale représente le risque environnemental de cancer de la prostate le mieux documenté[8]. La sédentarité[9], l'obésité[8, 10], le degré d'activité sexuelle[11], les antécédents de maladies transmissibles sexuellement[11], le fait d'avoir subi une vasectomie[8, 12], la consommation d'alcool[13] et l'exposition à certaines substances toxiques[8] sont autant d'autres facteurs environnementaux suspectés. De même, divers micronutriments sur lesquels nous reviendrons plus tard affecteraient le développement et l'évolution de ce cancer[8, 14].

La carcinogenèse du cancer de la prostate reste assez mal connue également[15]. À l'instar des autres cancers, ce processus comporte de nombreuses étapes et s'étale sur plusieurs années. En fait, la carcinogenèse du cancer de la prostate s'échelonne sur 30 à 40 ans[16]. Ainsi, beaucoup de temps sépare l'apparition des lésions prénéoplasiques et la survenue

d'un cancer cliniquement apparent. De plus, seulement une faible proportion des hommes qui ont un cancer de la prostate latent développe des symptômes cliniques[15]. Pour les autres, la maladie demeurera silencieuse toute la vie. Cette forme latente est extrêmement fréquente. À l'autopsie, jusqu'à 80 % des hommes de 80 ans et plus en sont atteints[15]. On ne connaît pas les causes du passage de la forme latente à la forme cliniquement symptomatique ni le mécanisme par lequel ce passage s'effectue[15]. Plusieurs éléments permettent de croire que les androgènes circulants jouent un rôle important dans la carcinogenèse du cancer de la prostate[8]. Des hormones de croissance, dont principalement la famille des facteurs de croissance insulinomimétiques (*Insulin-like growth factors)*, moduleraient également le développement et la croissance des cellules prostatiques néoplasiques[8]. Aussi, le polymorphisme génétique expliquerait que certains hommes et certains groupes raciaux sont plus sensibles que les autres aux effets hormonaux[8]. Enfin, bien que l'histoire familiale soit un facteur de risque, la majorité des cancers de la prostate ne peut être attribuée à un profil génétique spécifique[8].

1.2   Les stratégies de lutte contre le cancer de la prostate

La lutte contre le cancer de la prostate repose essentiellement sur le traitement des cas symptomatiques et des cas détectés fortuitement ou lors d'un examen de dépistage. L'arsenal thérapeutique inclut la surveillance (*watchful waiting*), la prostatectomie radicale, la radiothérapie, la cryothérapie et l'hormonothérapie[17]. Hormis la surveillance, toutes les modalités thérapeutiques peuvent provoquer des effets iatrogènes sérieux dont les plus courants sont l'incontinence urinaire et l'impuissance[17]. Le choix du traitement dépend du niveau sérique d'APS, du grade histologique des tumeurs, du stade de la maladie, du nombre de biopsies positives, de l'âge du patient et de ses antécédents médicaux[17]. Les préférences du patient et du médecin traitant guident aussi ce choix, car il n'existe pas de consensus absolu sur la ligne de conduite à suivre dans le traitement du cancer de la prostate, particulièrement pour les stades très précoces de la maladie[17]. Après traitement, les hommes dont le cancer est diagnostiqué aux stades T_1, T_{2a} ou T_{2b} (Stades TNM[18]) survivent en moyenne plus de 10 ans[19]. Ceux diagnostiqués au stade T_{2c} survivent en moyenne 10 ans et ceux diagnostiqués au stade T_3, de 5 à 10 ans[19]. Les patients qui présentent déjà un envahissement ganglionnaire lors de la découverte du cancer survivent

en moyenne cinq ans tandis que ceux qui ont des métastases, deux ans[19]. Lors d'une rechute consécutive à une hormonothérapie, la survie moyenne est de 6 à 12 mois[19].

Le détection précoce par le toucher rectal, l'analyse histologique de tissu réséqué par voie transuréthrale ou le dosage sérique des APS est une autre composante de la lutte contre le cancer de la prostate. Vers la fin des années 1980, avec l'avènement du test de dosage sérique des APS, est apparue l'idée d'implanter des programmes systématiques de dépistage du cancer de la prostate. Ceci a soulevé un important débat. Les principaux arguments en faveur de tels programmes incluent la simplicité et l'acceptabilité du test de dosage des APS, la prévalence élevée de la maladie, sa longue phase de latence et son pronostic favorable lorsque traitée tôt[20]. Par contre, la faible validité du test, la méconnaissance de l'évolution naturelle de la maladie, l'absence de preuves quant à l'efficacité des traitements et l'importance de leurs effets indésirables militent contre le dépistage systématique[20, 21]. Pour l'instant, le débat reste ouvert. En principe, les résultats (attendus pour 2010) des essais randomisés en cours devraient le résoudre, mais plusieurs doutent que ces études apportent des réponses définitives aux questions soulevées. Dans ce contexte et à l'instar d'autres chercheurs[22-26], nous avons réalisé, en parallèle aux travaux présentés dans cette thèse, une étude écologique afin d'apporter un certain éclairage sur le sujet. Nous avons donc mesuré la corrélation entre l'ampleur du dépistage auquel chaque région du Québec était soumise, entre 1989 et 1993, et l'évolution de leur taux de mortalité par cancer de la prostate, entre 1995 et 1999[27]. Les résultats suggèrent que le dépistage par le dosage des APS n'est pas responsable de la baisse récente des taux de mortalité par cancer de la prostate observée dans la plupart des régions du Québec. Le lecteur intéressé peut consulter cette étude à l'annexe 1. La majorité des autres études d'observation faites à date sur ce sujet arrivent à la même conclusion que nous[22-25].

Le fardeau sanitaire et économique que représente le cancer de la prostate malgré la disponibilité de traitements curatifs et palliatifs ainsi que les incertitudes qui entourent le dépistage de cette maladie sont autant de facteurs qui soulignent l'urgence de développer des interventions de prévention[28, 29]. Malheureusement, en dépit des nombreuses recherches menées sur l'étiologie du cancer de la prostate, on n'a pas identifié de relation causale permettant d'entrevoir des mesures potentiellement valables de prévention primaire[7]. En effet, parmi les facteurs environnementaux modifiables suspectés d'être liés au cancer de la

prostate aucun ne possède les caractéristiques propres à générer des mesures d'impact intéressantes, advenant qu'il ferait l'objet d'un programme de prévention primaire. Par conséquent, et peut-être aussi en raison des valeurs médicales actuellement dominantes dans les pays industrialisés, on met beaucoup d'espoir du côté de la chimioprévention du cancer de la prostate[7, 14, 16, 28-30].

1.3   La chimioprévention du cancer de la prostate

La chimioprévention des cancers réfère à l'usage d'agents naturels ou synthétiques pour empêcher, arrêter ou retarder le processus de la carcinogenèse et, ainsi, éviter ou différer l'apparition de lésions prénéoplasiques et néoplasiques[29]. Bien que cette stratégie de lutte paraisse nouvelle en oncologie, on l'utilise couramment en cardiologie pour prévenir les troubles cardiovasculaires chez les hypertendus et les hypercholestérolémiques. Aux États-Unis, le National Cancer Institute démarrait récemment un important programme de recherche sur la chimioprévention des cancers. Il élabora du même coup, en collaboration avec la Food and Drug Administration, un protocole d'investigation destiné à toutes les substances présentant un potentiel de chimioprévention, potentiel généralement mis en évidence par des études épidémiologiques[16]. Ce protocole d'investigation comprend des études de phase I, II et III semblables à celles qui précèdent l'homologation de tout agent pharmaceutique[31, 32]. Par contre, dans ce cas-ci, la réalisation des études, surtout celles de phase III, présente des défis de taille[31-33]. En effet, puisqu'il s'agit de vérifier la toxicité et l'efficacité d'agents destinés à être administrés à des populations saines afin d'empêcher ou de retarder l'apparition d'une maladie rare, et caractérisée par une très longue période de latence, on doit prévoir des tailles d'échantillon fort considérables et de très longues périodes d'observation[31-33]. Ces études s'avèrent donc extrêmement coûteuses et difficiles à réaliser.

Actuellement, on investigue au-delà d'une douzaine d'agents potentiels de chimioprévention du cancer de la prostate[16]. Les plus importants sont :

- la finastéride (médicament utilisé dans le traitement de l'hypertrophie bénigne de la prostate et de la calvitie);
- le sélénium (un minéral);
- l'alpha-tocophérol (une forme de la vitamine E);
- le lycopène (un agent de la grande classe des caroténoïdes qui sont des provitamines A);

- le rétinol (une forme de la vitamine A);
- des analogues synthétiques du calcitriol (un métabolite actif de la vitamine D);
- la génistéine (une isoflavone du soya);
- les polyphénols (des composantes du thé vert);
- le sulindac, le flurbiprofen et le célécoxib (des anti-inflammatoires non stéroïdiens);
- et le difluorométhylornithine (une substance pharmacologique généralement désignée sous l'acronyme DFMO).

Comme tout agent de chimioprévention des cancers, ces substances peuvent agir sur l'une ou l'autre des trois phases de la carcinogenèse que sont l'initiation, la promotion et la progression[29]. Leurs modes d'action anticancérigène sont divers et dans bien des cas seulement partiellement compris[14]. La Finastéride, par exemple, bloque la transformation de la testostérone en dihydrotestostérone. Ce faisant, elle réduit la disponibilité du plus puissant stimulant de la prolifération des cellules prostatiques cancéreuses [29]. Le Sélénium, l'alpha-tocophérol, le rétinol et le lycopène possèdent des propriétés antioxydantes. Ils interviendraient dans la carcinogenèse principalement en prévenant les dommages oxydatifs à l'ADN prostatique[14, 16, 30, 34]. La génistéine modulerait le développement du cancer de la prostate par l'intermédiaire de ses propriétés antiandrogéniques et antioxydantes[14, 16, 30, 34]. Les anti-inflammatoires non stéroïdiens, sur lesquels nous reviendrons au chapitre II, influenceraient la carcinogenèse prostatique par l'inhibition d'un système enzymatique impliqué dans la synthèse des prostaglandines[35]. Enfin, le DFMO en bloquant la synthèse d'une enzyme clé impliquée dans la croissance et la prolifération cellulaire interromprait l'effet promoteur des oncogènes[14, 34]. Quant aux polyphénols du thé vert et au calcitriol, on a proposé plusieurs mécanismes d'action pour expliquer leur effet anti-cancérigène[14, 16, 30, 34]. Sans être exhaustive, cette énumération des agents candidats et de leurs modes d'action potentiels illustre la diversité des pistes actuellement explorées en chimioprévention du cancer de la prostate.

On a proposé différentes populations susceptibles de bénéficier de la chimioprévention du cancer de la prostate. Ces groupes cibles, définis en fonction de leur risque de développer la maladie, comprennent :

- les hommes de 55 ans et plus, asymptomatiques, dont le niveau sérique d'APS est normal et le toucher rectal négatif;
- les hommes avec des antécédents familiaux de cancer de la prostate;
- les hommes avec un niveau sérique d'APS qui est à la limite de la normale;

- les hommes avec un niveau sérique d'APS anormalement élevé mais une biopsie négative;
- les hommes avec des lésions prénéoplasiques à la biopsie;
- les hommes avec un cancer de la prostate précoce chez qui on aurait normalement privilégié la surveillance à toutes autres formes de traitement;
- les hommes avec un risque élevé de récidive après avoir subi un traitement pour un cancer de la prostate[16].

L'observance d'une population cible à une mesure préventive dépend de la perception de son risque à développer la maladie et de l'acceptabilité de la mesure proposée. Ainsi, en chimioprévention des cancers, le choix d'un groupe cible découlera en bonne partie de la toxicité du ou des agents à administrer. Plus une substance présente un potentiel de toxicité élevé, plus la population ciblée doit être vulnérable à la maladie que l'on tente de prévenir.

Pour l'instant, aucune des substances potentielles de chimioprévention du cancer de la prostate n'a franchi toutes les étapes d'évaluation préalables à son homologation. Cependant, deux essais cliniques randomisés de phase III sont en cours. L'étude *Prostate Cancer Prevention Trial* a recruté 18 000 hommes, entre 1993 et 1997, pour examiner l'effet de la finastéride sur l'incidence des néoplasies prostatiques détectées à la biopsie[30]. Nous attendons les résultats de cette étude pour la fin de l'année 2004. Par ailleurs, l'étude *Selenium and Vitamin E comparison Trial* (SELECT) mesure l'effet du sélénium et de l'alpha-tocophérol sur la survenue du cancer de la prostate[30]. L'étude commencée en 2001 prévoit enrôler 32 000 hommes et les suivre pendant 12 ans.

1.4   Les objectifs de l'étude

Dans la présente recherche, nous nous sommes intéressés à deux classes de médicaments qui font l'objet de controverses quant à leur capacité à prévenir le développement du cancer de la prostate. Il s'agit des anti-inflammatoires non stéroïdiens (AINS) et des médicaments employés dans le traitement de l'hypertension artérielle. Ceux-ci sont généralement désignés sous le vocable antihypertenseurs.

Au cours des années 1990, des études épidémiologiques démontrèrent que l'exposition régulière et prolongée aux AINS réduisait le risque de cancer colorectal[35]. Des travaux en laboratoire sont rapidement venus appuyer ces observations en proposant des mécanismes d'action plausibles à cet effet anticancérigène[35-38]. Subséquemment, des nombreuses équipes de recherche ont entrepris de mesurer et comprendre l'association entre

l'exposition aux AINS et le risque de cancer à divers autres sites anatomiques[35]. Dans cette foulée, plusieurs études *in vitro* et chez l'animal démontrèrent que les AINS freinaient la prolifération de lignées cancéreuses de cellules prostatiques humaines[39-48]. Par contre, la dizaine d'études épidémiologiques publiées sur l'association entre les AINS et le cancer de la prostate n'a pas permis de confirmer cet effet protecteur chez l'homme[49-58]. Des divergences méthodologiques expliquent probablement en grande partie pourquoi les résultats de ces études se contredisent. Afin d'apporter un éclairage supplémentaire sur le sujet, nous avons entrepris une première étude pour évaluer si l'exposition aux AINS et à l'acide acétylsalicylique (AAS) (nom de marque, Aspirine), pendant une période de huit années, affectait le risque de développer un cancer de la prostate. De plus, nous avons mesuré l'effet du dosage, de la durée et du patron d'exposition aux AINS, et à l'AAS, sur le risque de survenue du cancer de la prostate. Le prochain chapitre présente les résultats de cette étude.

Par ailleurs, au milieu des années 1990, deux études épidémiologiques montrent une association positive entre le cancer et l'exposition à certaines classes d'antihypertenseurs[59, 60]. Ceci donne le coup d'envoi à la recherche épidémiologique sur l'effet oncogène des antihypertenseurs. Aujourd'hui, les revues de littérature concluent que l'usage des différentes classes d'antihypertenseurs n'augmente pas le risque de cancer, sauf pour l'association entre les diurétiques et le carcinome rénal[61-64]. Ces recensions constatent même que certains antihypertenseurs pourraient réduire la probabilité de survenue des cancers. Dans la littérature scientifique, nous trouvons deux études traitant spécifiquement de l'association entre l'exposition aux antihypertenseurs et le cancer de la prostate[65, 66]. L'une observe une réduction du risque chez ceux exposés aux bêta-bloquants seulement tandis que l'autre note une importante baisse du risque avec chacune des classes d'antihypertenseurs. Selon les auteurs de la seconde étude, les antihypertenseurs pourraient abaisser le risque de cancer de la prostate en interférant sur la sécrétion d'androgène[65]. À noter qu'aucune des deux études ne disposait d'effectifs suffisants pour établir des estimés statistiquement précis. Par ailleurs, plusieurs travaux de laboratoire ont récemment démontré que les alpha-bloquants, des médicaments utilisés pour traiter l'hypertension artérielle et l'hypertrophie bénigne de la prostate, stimulaient l'apoptose et inhibaient l'angiogenèse dans des souches cancéreuses de cellules prostatiques humaines[67-70]. À notre connaissance, personne n'a encore analysé, par l'intermédiaire d'études cliniques ou

épidémiologiques, cet effet antinéoplasique chez l'homme. Dans ce contexte, nous souhaitions, dans la deuxième étude de cette recherche, vérifier si l'exposition aux antihypertenseurs en général ou l'exposition à l'une ou l'autre des classes d'antihypertenseurs affectait le risque de survenue d'un cancer de la prostate. Nous avons également estimé dans quelle mesure l'usage chronique d'AAS modifiait la relation entre les antihypertenseurs et le cancer de la prostate. Comme pour la première étude, nous avons tenu compte de l'exposition sur une période de huit années. Le troisième chapitre de la thèse relate les résultats de cette étude.

1.5 Éléments clés de la méthodologie

1.5.1 Le devis des études

Nous avons employé un même devis d'étude cas-témoins appariés dans une population dynamique (*Population based matched case-control study*) pour les deux études de la recherche. Cinq témoins ont été appariés à chaque cas sur la base de la date de naissance et du statut vital au moment du diagnostic de cancer de la prostate chez le cas. Tous les membres d'un sextuple partagent donc la même date de naissance. Également, le jour du diagnostic de cancer chez le cas, nous savons que les cinq témoins vivaient. Puisque sans antécédent de cancer de la prostate au moment de la sélection, les témoins étaient donc des individus non malades, mais à risque de le devenir. D'ailleurs, certains sujets qui participaient à l'étude à titre de témoin y participent ultérieurement à titre de cas.

Compte tenu des caractéristiques du devis, les rapports de cotes calculés estiment des rapports de densités d'incidence, et ce, sans qu'aucune condition particulière n'intervienne. Il en est ainsi parce que nous avons sélectionné les témoins alors qu'ils pouvaient encore développer la maladie (échantillonnage dit par densité d'incidence)[71]. Ils fournissent, par conséquent, la distribution d'exposition (le personne-temps des exposés par rapport à celui chez des non-exposés) de la population entière d'où émanent les cas, et non seulement des non-malades comme dans une étude cas-témoins classique.

1.5.2 Les populations source et participante

Pour circonscrire la population source et sélectionner la population participante, décrites aux chapitres II et III, nous avons croisé la base de données de la Régie de l'assurance-

maladie du Québec (RAMQ) et celle du Fichier des tumeurs du Québec (FTQ). Nous avons utilisé, pour ce faire, le numéro d'identification personnel (NIP) de la RAMQ.

La base de données de la RAMQ est très fiable au regard du recensement des individus. En effet, hormis les immigrants illégaux, tous les résidents du Québec sont admissibles au régime universel d'assurance-maladie de la RAMQ. L'inscription se fait dès la naissance ou au cours des procédures d'immigration. Les personnes qui auraient échappé à cette inscription ont tout avantage à la réclamer dès que possible afin de pouvoir bénéficier de la couverture qu'offre la RAMQ au regard de la plupart des frais médicaux.

L'exhaustivité du FTQ soulève davantage d'interrogations. Ce registre répertorie les nouveaux cas de cancer survenus chez des individus ayant séjourné en centre hospitalier de soins de courte durée ou ayant été admis pour une chirurgie d'un jour. Il comprend les carcinomes *in situ* et les tumeurs malignes, mais ne fournit rien sur le stade du cancer au moment du diagnostic. Ce sont des archivistes d'hôpital qui y inscrivent les informations à partir, principalement, de la feuille résumée d'hospitalisation, mais aussi des protocoles chirurgicaux et des rapports histopathologiques. Des ententes interprovinciales permettent l'enregistrement des nouveaux cas de cancer de résidents québécois hospitalisés à l'extérieur du Québec. Les résultats préliminaires d'une étude suggèrent que jusqu'à 30 % des cas de cancer de la prostate échapperaient au FTQ (Jacques Brisson, Université Laval, communication personnelle). Par conséquent, la fiabilité de ce registre pour l'identification des cas pourrait être source de biais dans notre recherche. Nous y reviendrons en détail au chapitre IV. Quant aux renseignements qu'il contient sur l'identité, l'âge, le sexe et le diagnostic des patients, sa validité serait tout à fait satisfaisante selon les résultats d'une petite étude pilote (Jacques Brisson, Université Laval, communication personnelle). La date de diagnostic du cancer, par contre, serait sujette à davantage d'erreurs. Celles-ci découleraient principalement du fait que, dans ce registre, on considère comme date de diagnostic, la date de congé de la première hospitalisation où l'on mentionne la néoplasie.

1.5.3 Les variables d'exposition

C'est par l'intermédiaire du registre des réclamations pharmaceutiques de la RAMQ que nous avons mesuré l'exposition médicamenteuse. Ce registre recense toutes les demandes de remboursement que les pharmaciens ont adressées à la RAMQ depuis le 1er janvier

1981. Entre 1975 et 1997, la RAMQ remboursait aux pharmaciens le coût des ordonnances dispensées aux personnes non hospitalisées de 65 ans et plus. Le régime universel d'assurance-médicament de l'époque couvrait tous les Québécois de 65 ans et plus, incluant les nouveaux arrivants. Les émigrants perdaient l'accès au programme six mois après leur départ du Québec. Les seules personnes âgées inadmissibles étaient les membres des premières nations, les vétérans de l'armée canadienne et les détenus des prisons fédérales. Pour chaque ordonnance ayant fait l'objet d'une réclamation, le registre compte, entre autres variables, le NIP du patient, la date du service, les trois codes permettant d'identifier le médicament et la dose par unité, le nombre de doses prescrites et la durée recommandée du traitement. Robin Tamblyn *et al.* ont évalué la validité et l'exhaustivité de ce registre à partir d'un échantillon de 1 917 214 demandes de remboursement adressées à la RAMQ en 1990. Dans cet échantillon, moins de un pour cent des champs comportaient des données manquantes ou incongrues [72]. À partir d'un sous-échantillon de 723 prescriptions, ils ont aussi examiné la similitude entre les informations inscrites sur l'ordonnance papier et celles colligées au registre. Il s'avéra que l'identité du patient, du médicament et du prescripteur étaient identiques dans 83 % des cas[72]. Toutefois, compte tenu des caractéristiques de l'étude, il s'agit vraisemblablement là d'un estimé de validité très conservateur[72]. Ils observèrent, de plus, que les renseignements sur le nombre de doses et la durée de la prescription étaient exacts dans 69,1 % et 72,1 % des cas, respectivement[72]. Ici encore, ils sous-estimaient vraisemblablement la validité du registre, qui pourrait être plutôt de l'ordre de 90 %[72]. Le lecteur désireux d'en savoir plus peut consulter l'étude précitée à l'annexe 2.

Nous avons reconstitué l'histoire des dispensations pharmaceutiques des participants du jour de leur 65ème anniversaire jusqu'à la date de référence. Pour chaque membre d'un sextuple (un cas et ses cinq témoins appariés), la date de référence est la date du diagnostic de cancer chez le cas. Pour ceux qui atteignirent 65 ans avant le 1er janvier 1981, l'historique débute le 1er janvier 1981. Ainsi, selon la date de naissance des sujets, nous disposions d'entre 8 et 14 années de données. Cependant, afin d'avoir des tailles d'échantillon acceptables pour toutes les analyses, nous n'avons exploité que les données des huit dernières années d'observation. Par exemple, si nous avions prolongé la période d'observation à 10 ans, limitant ainsi la population participante aux 75 à 79 ans, nous aurions sérieusement compromis la reproductibilité des analyses des tableaux 5, 6 et 12. Par ailleurs, c'est par souci de prévenir le biais protopathique (biais de causalité inversée) que

nous avons ignoré les prescriptions des trois mois précédant immédiatement la date de référence. Toutes les ordonnances d'AAS, d'AINS autres que l'AAS et d'antihypertenseurs dispensées entre huit ans et trois mois avant la date de référence nous ont servis pour construire, respectivement, les variables d'exposition à l'AAS, aux AINS et aux antihypertenseurs. Nous avons aussi créé des variables d'exposition spécifiques pour chaque classe d'antihypertenseurs.

Nous avons défini l'exposition de quatre façons différentes : en terme dichotomique, en terme de durée cumulative, en terme de dose quotidienne moyenne et, finalement, en terme de profil d'exposition. Ci-dessous, nous décrivons brièvement chacune de ces mesures.

La catégorisation dichotomique
Pour l'exposition définie en terme dichotomique, nous avons considéré comme étant exposés tous ceux chez qui on avait dispensé au moins une ordonnance durant la période d'observation de huit ans à trois mois avant la date de référence.

La durée cumulative d'exposition
La durée cumulative d'exposition reflète le nombre total de jours sous médication, à la lumière des renseignements fournis par le registre des réclamations pharmaceutiques de la RAMQ. Pour chaque sujet, nous avons donc additionné les durées (nombre de jours de traitement prescrit) de toutes les ordonnances d'intérêt dispensées durant la période d'observation. Subséquemment, nous avons transformé l'unité de cette variable en années et établi des catégories mutuellement exclusives.

La dose quotidienne moyenne
La dose quotidienne moyenne exprime la quantité de milligrammes de médicament consommés en moyenne à chaque jour, entre le moment de la première dispensation d'intérêt - trouvée durant la période de huit ans à trois mois avant la date de référence - et la fin de la période d'observation. Pour l'AAS, nous avons tout simplement divisé la dose totale reçue, durant cette période, par le nombre de jours de ladite période. La dose totale d'AAS reçue est la somme des teneurs totales de chaque ordonnance soit : ($\sum$ (nombre de comprimés * dose unitaire)). Nous avons ensuite transformé cette variable quantitative continue en catégories mutuellement exclusives.

Comme les puissances thérapeutiques des différentes classes d'AINS autres que l'AAS varient, il n'est pas possible d'additionner les doses brutes d'AINS. Cent milligrammes d'Ibuprofène n'équivalent pas à 100 milligrammes d'Indométhacine! Nous avons donc procédé à une standardisation des teneurs des médicaments avant de calculer la dose quotidienne moyenne d'AINS. Comme facteur de standardisation, nous avons utilisé les *Defined Daily Doses* (DDD) que l'Organisation mondiale de la santé (OMS) émet annuellement pour chaque médicament[73]. La DDD d'un médicament correspond à la dose quotidienne habituellement prise par un adulte pour l'indication la plus courante. À titre d'exemple, la DDD de l'Ibuprofène est de 1200 mg et celle de l'Indométhacine, de 100 mg. Pour chaque ordonnance d'AINS, nous avons divisé le nombre total de milligrammes dispensés par la DDD de la classe respective d'AINS. Un sujet qui aurait reçu 400 mg d'Ibuprofène aux 6 heures pendant 10 jours aurait accumulé une dose totale de 16 000 mg et une dose totale standardisée de 13,3. Ainsi standardisées, les doses des différentes classes d'AINS deviennent comparables. Ensuite, nous avons procédé comme pour l'AAS, mais en remplaçant la dose totale par la dose totale standardisée. La dose quotidienne moyenne standardisée s'interprète comme un pourcentage de la dose quotidienne habituellement nécessaire pour induire un effet anti-inflammatoire. Dans l'exemple précédent, en supposant une durée d'observation de 100 jours (la première et unique ordonnance d'AINS aurait été prescrite 100 jours avant la fin de la période d'observation) la dose quotidienne moyenne standardisée serait de 0,13, soit 13,3 % de la DDD de l'Indométhacine. À noter que, dans nos analyses, nous n'avons pas exprimé l'exposition aux antihypertenseurs en terme de dose quotidienne moyenne.

Le profil d'exposition

En dernier lieu, nous avons bâti une variable pour rendre compte du profil d'exposition. Cette variable comprend quatre catégories mutuellement exclusives soit les non-exposés, les « utilisateurs récents », les « utilisateurs chroniques » et les « autres » dont le profil d'utilisation ne correspond à aucune des trois catégories précédentes. Nous avons défini comme « utilisateurs récents » ceux exclusivement (ou presque, dans le cas de l'exposition aux antihypertenseurs) exposés entre quatre ans et trois mois avant la date de référence et comme « utilisateurs chroniques » ceux dont l'utilisation s'est étendue sur toute la période d'observation de huit ans à trois mois avant la date de référence. Pour l'AAS, nous avons considéré exposés ceux dont la dose quotidienne moyenne égalait ou dépassait 80 mg; pour

les AINS, ceux dont la dose quotidienne moyenne égalait ou dépassait 10 % de la dose quotidienne habituellement nécessaire pour induire un effet anti-inflammatoire, selon l'OMS; et pour les antihypertenseurs, ceux dont la dose quotidienne moyenne égalait ou dépassait 50 % de la dose quotidienne habituellement prescrite, selon l'OMS. Nous avons calculé les doses quotidiennes moyennes comme décrit précédemment, à une différence près : dans ce cas-ci le dénominateur était constant. Il était de 1371 jours (4 ans moins 3 mois) pour la première période et de 1461 jours (4 ans) pour la seconde période. Les non-exposés n'avaient d'exposition à la classe de médicament d'intérêt ni à la première ni à la deuxième période. Les « utilisateurs récents » étaient ceux qui respectaient la condition d'exposition à la première période, mais qui avaient une exposition nulle (ou presque dans le cas de l'exposition aux antihypertenseurs) à la deuxième période. Les « utilisateurs chroniques » respectaient la condition d'exposition à la première et la deuxième période. Cette variable nous a permis d'évaluer dans quelle mesure la persistance dans le temps d'une exposition significative influençait le risque de développer la maladie.

1.5.4 Le contrôle des biais de confusion

De façon générale, les hommes exposés à l'une ou l'autre des substances pharmaceutiques étudiées (AAS, AINS et antihypertenseurs) reçoivent plus de médicaments d'ordonnance que les non-exposés. Ceci pourrait signifier qu'ils visitent plus souvent un médecin et, par ricochet, ont davantage de chances de se voir administrer un test de dépistage du cancer de la prostate. Puisque chez les hommes de 73 à 79 ans, le cancer de la prostate est généralement asymptomatique et seulement mis en évidence par des tests de dépistage, cette situation pourrait induire un biais de confusion important. Afin de contrôler ce biais potentiel, nous avons introduit dans toutes les analyses une variable dichotomique appelée *recent medical contacts*. Cette variable reflète l'existence de consultations médicales durant la période de un à trois mois avant la date de référence. Nous avons mesuré l'existence des contacts médicaux en comptant le nombre de jours différents où au moins une ordonnance de n'importe quel médicament avait été dispensée. Subséquemment, nous avons catégorisé la variable suivant qu'il y ait eu ou non au moins un contact médical durant cette courte période de temps. Nous postulons que le fait d'avoir eu ou non un contact médical récent traduit l'intensité de la surveillance médicale à laquelle les sujets étaient soumis, durant la

période d'observation de notre étude. La variable a été construite à partir des données du fichier des réclamations pharmaceutiques de la RAMQ.

Par ailleurs, lorsque pertinent, nous avons contrôlé pour l'exposition concomitante à d'autres médicaments que ceux étudiés. Nous les présentons aux chapitres II et III. Nous considérions qu'une variable introduisait de la confusion si sa présence dans un modèle de régression logistique modifiait de plus de 10 % la valeur du ou des paramètres de la variable d'exposition d'intérêt. À noter que nous avons contrôlé la confusion potentielle de la variable âge *a priori* par l'appariement.

1.5.5 Le contrôle du biais protopathique

Un biais protopathique résulte d'une confusion dans la séquence temporelle entre la cause et l'effet. Il se produit lorsque ce sont les premiers symptômes de la maladie d'intérêt qui entraînent la consommation du médicament à l'étude[76, 77]. Dans notre recherche, il adviendrait si la consommation des médicaments d'intérêt, pendant la période d'observation, était motivée par des symptômes ou signes cliniques d'un cancer de la prostate non encore diagnostiqué. Pour évaluer la présence de ce biais, nous avons fait des analyses qui sont décrites au chapitre II.

1.5.7 Les analyses statistiques

Nous avons estimé les risques relatifs (rapports de densités d'incidence) de cancer de la prostate pour l'exposition à l'AAS, aux AINS autres que l'AAS, aux antihypertenseurs et à chacune des classes d'antihypertenseurs. Pour ce faire, nous avons calculé des rapports de cotes par régression logistique conditionnelle. Nous avons employé la régression logistique conditionnelle plutôt que la régression logistique non conditionnelle afin de contrôler le biais parfois induit par l'appariement des témoins aux cas, dans les études cas-témoins[78]. Pour toutes les analyses, la catégorie de référence comprend les sujets non exposés à la classe de médicament respective. Nous avons calculé des intervalles de confiance à 95 % (hypothèse de recherche bilatérale) pour toutes les mesures d'association.

Pour documenter les différentes facettes de l'exposition médicamenteuse, nous avons réalisé différentes analyses. Le premier niveau d'analyse consistait à estimer l'effet de l'exposition lorsque exprimée de façon dichotomique. À un second niveau d'analyse, nous

mesurions l'effet de la durée cumulative d'exposition. En troisième lieu, par une analyse stratifiée, nous nous sommes intéressés à l'effet de la dose quotidienne moyenne pour des niveaux déterminés de durée cumulative d'exposition. Quatrièmement, nous avons examiné l'effet du profil d'exposition qui tient compte simultanément de la dose quotidienne moyenne, de la durée cumulative d'exposition et de la régularité d'utilisation. Enfin, nous avons évalué l'interaction entre deux classes de médicaments.

Le prochain chapitre présente l'étude sur la relation entre l'exposition à l'AAS et aux AINS, autres que l'AAS, et le risque de cancer de la prostate. L'étude sur la relation entre l'exposition aux antihypertenseurs et le cancer de la prostate est présenté subséquemment au chapitre III.

Chapitre II : Dosage, duration, and timing of nonsteroidal anti-inflammatory drug use and the risk of prostate cancer

Linda Perron, Isabelle Bairati, Lynne Moore, François Meyer

Résumé

Nous avons mesuré l'association entre le risque de cancer de la prostate et l'exposition aux anti-inflammatoires non stéroïdiens (AINS) dans une étude cas-témoins appariés. L'exposition était définie en terme de dose quotidienne moyenne, durée cumulative d'exposition et profil d'exposition. La durée rétrospective d'observation s'étendait sur huit années. Les renseignements sur la maladie et l'exposition médicamenteuse provenaient de deux registres nationaux informatisés. Nous avons contrôlé pour le biais de détection et estimé l'effet du biais protopathique. Aussi, l'effet de l'AAS a été analysé séparément de l'effet des autres AINS. La population participante comportait 2221 cas et 11 105 témoins. Nous avons observé une tendance négative entre la durée cumulative d'exposition à l'AAS et le risque de cancer de la prostate (valeur p = 0,0009). De même, l'exposition à une dose quotidienne moyenne d'AAS d'au moins 80 mg pendant les huit années d'observation était associée à une diminution de 18 % du risque de cancer de la prostate (RC = 0,82, IC = 0,71-0,95). Toutefois, aucun effet protecteur ne persistait une année après l'interruption d'un usage régulier de sept ans de l'AAS. Par ailleurs, le risque de cancer de la prostate s'est avéré indépendant de l'exposition aux AINS autres que l'AAS.

Abstract

Experimental studies suggest that nonsteroidal anti-inflammatory drugs (NSAIDs) could reduce prostate cancer risk. Results of observational studies on the relation between NSAIDs and prostate cancer risk have, however, been inconsistent. Moreover, none have addressed the issues of dosage, duration and timing of exposure. In a population based age-matched case-control study, we measured the association between prostate cancer risk and NSAIDs defined in terms of mean daily dose, cumulative duration, and timing of exposure. Eight year drug exposure history was obtained from the Quebec health insurance system database. Parallel analyses were performed for Aspirin and NSAIDs other than Aspirin. We controlled for detection bias and assessed the potential impact of protopathic bias. Analyses were performed with conditional logistic regression. Among the 2221 cases and 11,105 controls, there was a negative trend between cumulative duration of Aspirin use and prostate cancer risk (p-value = 0.0009). Also, exposure to a mean daily dose of Aspirin of at least 80 mg, maintained throughout the entire 8 years of follow-up, was associated with an 18 % reduction in prostate cancer risk (OR = 0.82, 95 % CI = 0.71-0.95). In more recent users of such a dose, the risk reduction was of seven percent. However, one year after the end of a seven-year regular Aspirin exposure, no residual protective effect persisted. No association was observed between prostate cancer risk and exposure to NSAIDs other than Aspirin. The results suggest that long-term and regular use of Aspirin, at a dosage beneath that usually recommended for an anti-inflammatory effect, may prevent prostate cancer.

2.1 Introduction

In North America and Western Europe, prostate cancer has become one of the most commonly diagnosed cancers and one of the leading causes of cancer death. Since the incidence of this disease increases strikingly with age[79], the number of new cases will continue to rise in the Western world as the population ages. So far the control of prostate cancer has focused on early detection and treatment but, in order to develop preventive strategies, researchers are investigating the protective effect of a wide range of agents[80]. Among them are non-steroidal anti-inflammatory drugs (NSAID)[80].

Many epidemiological studies have found that long-term use of NSAIDs is associated with a lower risk of colorectal cancer and adenomatous polyps[35]. NSAIDs may also help to lower incidence of, or death from, cancers at several other sites[35]. Despite continuing uncertainty, there is mounting evidence that NSAIDs antineoplastic effect is principally mediated through restoration of apoptosis and inhibition of angiogenesis[35]. The pathways through which NSAIDs exert their antineoplastic effects have not yet been totally elucidated but probably involves their shared ability to inhibit cyclooxygenase-2 (COX-2) isoenzyme[35]. COX-2 catalyze the transformation of arachidonic acid into prostaglandins, which are in turn involved in inflammation and carcinogenesis[35]. Moreover, some studies indicate that NSAIDs could also have antitumorigenic activity through COX-2 independent processes[35-38].

Several in vitro and in vivo laboratory studies have demonstrated that NSAIDs can decrease growth and increase apoptosis of prostate cancer cells[39-48]. The results of these studies suggest that NSAIDs may exert their prostatic antitumorigenic effect through both COX-2 dependent[39-41, 43, 44] and COX-2 independent[45-48] pathways. In epidemiological studies however, the protective effect of NSAIDs on prostate cancer development has not been conclusively demonstrated. In three studies, exposure to NSAIDs, or to a proxy of NSAID use, was associated with an increased risk of prostate cancer[49-51], which was statistically significant in one case[49]. In five other observational studies, NSAID exposure was associated with non statistically significant reductions of prostate cancer risk ranging from 5 to 18 %[52-56]. Conversely, in one case-control study[58] and in one cohort study[57] published recently, investigators reported statistically significant risk reductions of prostate cancer of at least 50 % in NSAIDs users. Discrepancies between these results could be

partly explained by misclassification of exposure, detection bias, different ages of study populations, and various lengths of follow-up.

Using the computerized database of the Quebec health insurance system, the Régie de l'assurance maladie du Québec (RAMQ), we conducted a population based matched case-control study. This database allows a more precise classification of exposure than has been possible in most previous studies. The aim of the study was to determine whether the use of NSAIDs, and Aspirin in particular, over an eight-year observation period, was associated with the risk of prostate cancer. We also assessed the effect of dosage, duration and timing of exposure, issues that have not yet been directly addressed.

2.2 Methods

2.2.1 Source population

We defined the source population as the population of male RAMQ enrolees who were aged 73 to 79, between January 1st, 1993 and December 31st, 1995. From 1975 to 1997, the RAMQ reimbursed all drugs prescribed on an outpatient basis to persons aged 65 and older, who became automatically eligible on the day of their sixty-fifth birthday. The insurance plan covered all Quebec's residents with the exception of first nations' members, military employees, and inmates of federal penitentiaries, who benefit from a federal program. From 1975 until May 1992, all eligible people presenting at a pharmacy with a medical prescription could receive their medication free of charge. Afterward, a co-payment of 2$ per prescription, up to a maximum fee of 100$ per year, was imposed. The RAMQ reimbursed pharmacists for all drugs dispensed under this insurance plan. Moreover, in Quebec, all residents benefit from a universal insurance plan for medical services.

We excluded all men who had a prostate cancer reported to the Quebec cancer registry between 1984 and the date of their inclusion in the source population. We also excluded all immigrants, refugees, and persons who had resided outside Quebec for 6 months or more after their sixty-fifth birthday in order to guarantee that the exposure period was free of any meaningful interruption.

2.2.2 Case and control definition

The cases were subjects from the source population who were diagnosed with prostate cancer (ICD-9 code 185, International Classification of Diseases, 9th revision), between January 1st, 1993 and December 31st, 1995, and were reported to the Quebec cancer registry. We considered the diagnosis date indicated in the first report to the cancer registry to be the date of diagnosis of the cases. The potential controls for each case were the subjects from the source population who were born on the same date as the case, and were alive on the date of diagnosis of the case. From every set of potential controls, 5 men were randomly selected. The date of diagnosis was assigned to each of the matched controls as their index date.

2.2.3 Information on the use of NSAID, aspirin and other drugs

Drug exposure data were obtained from the RAMQ pharmacists' computerized claims database, which keeps record of all drugs reimbursed since 1981. The database has been described in details elsewhere and a high level of reliability and validity of the prescription data has been demonstrated[72]. Dispensation of prescribed drugs could be reconstituted from the date of the sixty-fifth birthday, or January 1st, 1981, until the index date. Therefore, the information on the dispensation of prescribed drugs was available for a period of 8 to 14.9 years before the index date, depending on the subject's age. However, in order to include all subjects in the analyses and have an acceptable statistical precision, we only considered the exposure during the 8 years immediately preceding the index date.

Available information included the date of delivery, the class and identity of the drug (American Hospital Formulary System classification), the number of tablets, capsules or other vehicle dispensed, the drug dosage and the duration of the prescription period. All prescriptions of oral NSAIDs and Aspirin filled during the observation period were used in the creation of exposure variables, as described below. Since in most cases, Aspirin was prescribed at levels below that necessary for an anti-inflammatory effect, we constructed separate exposure variables for Aspirin and all other NSAIDs. For comparison of dosages of NSAIDs other than Aspirin, we used the « defined daily dose » (DDD), which is the average dosage of a drug taken by adults for the most frequent indication, according to the World Health Organization (WHO)[73].

2.2.4 Data analysis

For every subject, we measured the cumulative exposure to prescribed NSAIDs and Aspirin from eight years to three months before the index date. We calculated the odds ratios of prostate cancer (and 95 percent confidence intervals) in relation to the use of NSAIDs and Aspirin with conditional logistic regression. All categorical variables were introduced in the model using dummy variables with no use as the reference category.

We first compared the effect of no use to any use of drug. Second, we assessed the effect of duration of exposure by categorizing the cumulative duration of drug use into mutually exclusive classes up to six years or more. Third, we assessed the association between mean daily dose and the risk of prostate cancer separately for the subjects who had cumulated less than four years, and at least four years of drug use. Mean daily dose was computed over the period between the date of the first prescription of Aspirin or NSAIDs, found during the eight-years observation period, and three months before the index date. Mean daily dose was thereafter divided into three mutually exclusive categories. Finally, to measure the effect of timing of exposure, we compared nonusers to the subjects exposed exclusively four years to three months before the index date (the recent users), and the subjects exposed throughout the entire period of eight years to three months before the index date (the chronic users). The variables were constructed separately for Aspirin and NSAIDs and parallel analyses were performed. In order to sum dosages of different classes of NSAIDs, we computed, for each prescription, a standardized total dose by dividing the total number of mg of drug dispensed by the drug's DDD. Thereafter, to obtain a mean daily dose of NSAIDs for the follow-up period, we summed all standardized total doses dispensed during the follow-up period and divided by the number of days in that period. The standardized mean daily dose of NSAIDs can therefore be interpreted as a percentage of a usual daily dose to obtain an anti-inflammatory effect.

The potentially confounding variable considered was the dispensation of antihypertensive agents, which have recently been reported to be negatively associated with prostate cancer[65]. In the analysis of the relation between NSAIDs other than Aspirin and prostate cancer, we also considered the use of Aspirin as a potential confounder. Detection bias might occur if those taking NSAIDs or Aspirin are under increased medical surveillance compared to nonusers. To control such bias, we included in all analyses a dichotomized

variable indicative of medical contacts that occurred one to three months before the index date. We measured the existence of medical contacts by counting the number of different days where one or more prescriptions of any medication were dispensed. Since they are used in the treatment of benign prostatic hyperplasia, we also considered the dispensation of Finasteride or of Terazosine two years to one month before the index date as a potential source of detection bias. The criterion for confounding was a change of 10 % or more in the parameter estimate when the co-variable was introduced into the model.

In order to assess the presence of a protopathic bias, which might be caused by changes in drug use during the period preceding the diagnosis of prostate cancer[76], we examined the influence of three different lag times on the odds ratios. To do so, all the analyses described above were performed with exposure measures excluding either the last three months, the last year, or the last two years before the index date. We hypothesized that if men took NSAID or Aspirin to control symptoms of a yet undiagnosed prostate cancer, the odds ratios should tend toward positive values with shorter lag time periods.

2.3   Results

The study population comprised 2221 cases and 11,105 controls. At the index date the subjects were on average aged 75.7 years (73-79). Characteristics of the study population with regard to potential confounding and detection bias variables are given in table 1. In the following analyses, only the variable indicating a medical contact during the last months before the index date (*recent medical contacts*) had an influence on the parameter estimates and was kept in the models to control for detection bias.

There were 155,988 prescriptions of Aspirin and 108,332 prescriptions of NSAIDs other than Aspirin dispensed to the study population (table 2). Diclofenac, Naproxyn, Ibuprofen, and Indomethacin accounted for 65 % of the 108,332 NSAID prescriptions (table 2). Cumulative duration of Aspirin use reached 4,722,901 days whereas cumulative duration of NSAIDs reached 2,599,234 days (table 2). Fifty-eight percent (58 %) of the subjects were never exposed to prescribed Aspirin while 38 % were never exposed to prescribed NSAIDs. The prescribed duration of drug use for Aspirin was on average 30.28 days while it was 23.99 days for NSAIDs. The prescribed daily dose of Aspirin, as measured by dividing the total number of mg prescribed by the total number of days the drug was recommended, was

on average of 706 mg. It was below 325 mg in 51 % of the prescriptions and above 2600 mg in 1 % of them. WHO does not provide a DDD for the anti-inflammatory effect of Aspirin but, as an indication, the Canadian pharmacist association suggest a daily dose ranging from 2600 to 3900 mg for Aspirin to provide an anti-inflammatory effect[81]. For NSAID prescriptions, the average prescribed daily dose was 116 % of the drug's respective DDD. About 5 % of NSAID prescriptions recommended a daily dose below 50 % of the drug's DDD while 38 % recommended a daily dose above 100 % of the drug's DDD. Throughout the observation period, the prescribed duration and dosage of Aspirin and NSAIDs to the study population were fairly constant from one year to the other.

Use of Aspirin eight years to three months before the index date, defined as a binary variable and compared with no use during the same period, was associated with an adjusted odds ratio of prostate cancer of 0.94 (95 % CI, 0.85-1.03). The use of NSAIDs during the same period, was associated with an adjusted odds ratio of prostate cancer of 1.07 (95 % CI, 0.97-1.18).

To assess the duration-response gradient, we categorized Aspirin use into mutually exclusive classes up to six years or more of cumulative duration of use (table 3). Until four years of cumulative exposure, no clear trend in the risk of prostate cancer relative to nonusers was observed. However, relative to nonusers, the risk of prostate cancer was 0.92 (95 % CI, 0.71-1.19) in those who cumulated between 4 and 5 years of use, 0.70 (95 % CI, 0.52-0.95) in those who cumulated 5 to 6 years of use, and 0.66 (95 % CI, 0.51-.84) in those who cumulated at least 6 years of use. The Chi-square for trend was statistically significant (p-value, 0.0009). No trend was found in the association between the cumulative duration of exposure to NSAIDs other than Aspirin and prostate cancer (p for trend, 0.152) (table 3).

In the group with less than four years of Aspirin use, we found no association between mean daily dose and prostate cancer risk (table 4). Conversely, in the group with at least 4 years of cumulative duration of Aspirin use, the risk of prostate cancer was 0.81 (95 % CI, 0.62-1.05) in those with a mean daily dose below 325 mg, and 0.72 (95 % CI, 0.59-0.88) in those with a mean daily dose of at least 325 mg (table 4). For NSAIDs other than Aspirin, the analysis did not reveal any trend between the mean daily dose and the risk of prostate

cancer for either the subjects who cumulated less than four years of use or for those with four or more years of cumulative duration of use (table 4).

Moreover, to understand the effect of the timing of exposure, we compared nonusers to recent users and to chronic users. Recent users were defined as those with no exposure to Aspirin 8 to 4 years prior to the index date but a mean exposure of at least 80 mg per day from 4 years to 3 months prior to the index date, whereas chronic users were those with a mean daily dose of Aspirin of at least 80 mg throughout the entire period of 8 years to 3 months before the index date. Compared to nonusers, the risk of prostate cancer was 0.94 (95 % CI, 0.79-1.12) in recent users, and 0.82 (95 % CI, 0.71-0.95) in chronic users (table 5). Among chronic users of Aspirin, the mean daily dose received over the 8-years observation period was below 325 mg, between 325 and 650 mg, between 650 and 1300 mg, and above 1300 mg, in 44 %, 34 %, 19 %, and 3 % of subjects, respectively. Definition of recent and chronic use for NSAIDs was similar to that used for Aspirin use except that minimal exposure was considered to be 10 % of a usual daily dose to obtain an anti-inflammatory effect instead of 80 mg. No trend was noticed when comparing nonusers to recent and chronic NSAID users (table 5). Among chronic users of NSAIDs, the mean daily dose received over the 8-year observation period, was above 50 % of the usual daily dose to obtain an anti-inflammatory effect in 38 % of the subjects.

Interestingly, as shown in table 6, the risk of prostate cancer in those who were regular Aspirin users (on average at least 80 mg per day) throughout the period of 8 to 1 year before the index date but who had no exposure in the last year before index date was not different from the risk in nonusers (OR, 1.03; 95 % CI, 0.84-1.25).

All the above results were performed with a drug exposure measurement that excluded the last three months before the index date (three-months lag time). In order to estimate the impact of protopathic bias, we compared these odds ratios to those obtained with a drug exposure measurement that excluded either the last year, or the last two years before the index date. For Aspirin, as in the three-months lag time analyses, the odds ratios obtained with a one-year or two-year lag time revealed a negative association between prostate cancer risk and drug exposure (results not shown). Also, as we shortened the lag time the negative association became stronger, suggesting that the three-month lag time model was not affected by any significant protopathic bias. For NSAIDs, we did not observe any clear

trend in the association between drug exposure and prostate cancer risk for any of the three lag time periods, and shortening the lag time period did not seem to affect the odds ratios in any clear direction (result not shown).

2.4 Discussion

In these data we observed, with regard to the cumulative duration of Aspirin use, an absence of trend until 4 years of use but a statistically significant negative trend afterward with a 34 % reduction in prostate cancer risk in men who cumulated 6 or more years of drug use. We also found that the effect of dosage was only apparent in the subject with at least four years of use. In this group, compared to nonusers, we observed a 19 % and 28 % prostate cancer risk reduction when exposed to less than 325 mg daily and 325 mg or more daily, respectively. It is likely that the group with fewer than four years of cumulative use included a high proportion of irregular Aspirin users and this might explain why no association was observed. With regard to the timing of exposure we noted that, in comparison to nonusers, the subject exposed to a mean daily dose of Aspirin of at least 80 mg throughout the entire 8 years preceding index date had a 18 % reduction in prostate cancer risk. The more recent users (last four years before index date) of such a dose had a seven percent reduction in prostate cancer risk. However, subjects with a regular Aspirin use who stopped taking Aspirin one year before index date had a risk of prostate cancer comparable to nonusers. We did not observe any association between prostate cancer risk and exposure to NSAIDs other than Aspirin.

The population-based case-control design used in this study reduces the possibility of selection bias. Also, ascertaining exposure through a preregistered database precludes recall bias. Nonetheless other systematic errors could have affected our results. Even though we adjusted for medical contacts in the months preceding the index date, a difference could persist between comparison groups with regard to the probability of having a prostate cancer detected. If this is so, it would most likely underestimate the association measures. Alternatively, earlier mortality may have precluded a diagnosis of prostate cancer in NSAID or Aspirin users compared with nonusers. In the prospective study conducted by Roberts et al.[57] however, mortality rates during follow-up were similar among NSAID users – of which 87 % were using Aspirin - and nonusers. Likewise, in their study population there was no difference in preclinical signs of prostate cancer at the beginning of follow-up

between NSAID users and nonusers. Our association measures could also be blurred by misclassification of exposure. First, we did not account for drugs obtained without prescriptions. However, since RAMQ reimbursed all prescribed drugs to senior Quebec citizens, it is unlikely that any significant amounts of drugs were systematically bought over the counter. Second, our exposure measure relied on drug dispensation rather than actual drug consumption and they could be a significant gap between these two realities, particularly for NSAIDs, other than Aspirin, which are mainly prescribed for the management of temporary pain or inflammation. In the case of Aspirin, which is often prescribed for cardiovascular disease prophylaxis, it seems less plausible that drug consumption deviated from that recommended on prescription. This could be the reason why no protective effect was demonstrated for NSAIDs other than Aspirin. Third, misclassification of exposure could originate from errors in the RAMQ pharmacist claims database, but it should be of limited importance since the database has been shown to be very reliable[72]. These three possible sources of misclassification of exposure should equally affect cases and controls. Prostate cancer cases were identified through the Quebec cancer registry, which relies solely on hospitalization data. Since prostate cancer investigation and treatment, particularly in those over 70 years of age, do not necessarily involve hospitalization, this registry does not capture all incident prostate cancer cases. This under-declaration should not bias our results unless it differently affects the exposed and non-exposed cases. It is difficult to speculate on factors that could have induced more or less declaration to the QCR in the exposed or non-exposed, and in the exposed to Aspirin in comparison to the exposed to NSAIDs other than Aspirin. Nonetheless, this bias if present could not explain the dose-response relationship observed in the chronically exposed to Aspirin.

Apart from age and use of antihypertensive drugs, we did not control for any of the established or suspected prostate cancer risk factors. As suggested by Barry[82], men taking low-dose prophylactic Aspirin might have other health-related behaviors that attenuate their risk of prostate cancer. They could, for example, reduce their intake of animal fat or supplement their diet with vitamins or other micronutrients among which some are under investigation as potential prostate cancer chemopreventive agents. It has also recently been hypothesized that genetic polymorphisms might be a potential confounder of the association between NSAID exposure and prostate cancer risk[83]. On the other hand,

confounding by race is unlikely in this study because of the characteristics of the Quebec senior population in the middle of the 1990s and of the eligibility criteria that limit the inclusion of immigrants into the study population. With regard to confounding by family predisposition to prostate cancer, it also seems unlikely because most hereditary prostate cancer is diagnosed before the age of 70[84]. Finally, it could be that men took NSAID or Aspirin to control symptoms caused by a yet undiagnosed prostate cancer. However, in the presence of such a protopathic bias, the lag time analysis should have revealed weaker rate ratios with the shorter lag time periods.

In the interpretation of our findings certain limits must be recognized. We measured dosage and duration of exposure within a time span of eight years before index date. Therefore, we cannot assess the effect of lifetime cumulative dosage or duration of use. Neither can we evaluate the effect of age at onset of exposure. Also, since a fairly important proportion of the subjects in the higher categories of exposure in our study were already taking Aspirin at the beginning of the 8 years observation period (~ 50 %), it is plausible that the protective effect appears after a longer duration of exposure than what we observed. Moreover, we only assessed the effect of NSAID or Aspirin exposure on the risk of prostate cancer as a whole. Norrish et al.[55] observed a stronger protective effect of NSAIDs on advanced prostate cancer compared to total prostate cancer, suggesting that NSAIDs could act differently on aggressive tumors than on small tumors with slow-doubling time.

Other investigators have reported statistically significant inverse associations between NSAID use and prostate cancer. In a community-based cohort study, Roberts et al.[57] observed that men aged 50 to 79 who were exposed daily to NSAIDs had a 55 % reduction in the risk of prostate cancer. In men aged 70-79, they found a 83% prostate cancer risk reduction. In this study, 87 % of NSAID exposure was attributable to Aspirin use. In another study, Nelson et al.[58] found that men exposed to at least one pill per day of Aspirin or Ibuprofen had a 66 % reduction of prostate cancer in comparison to nonusers. The risk reduction was about the same for men exposed to at least one pill per day of prescribed NSAIDs. Prior to these two studies, others had observed less impressive negative associations that had not reached statistical significance. Paganini-Hill et al.[54], Schreinemacher and Everson[53], and Norrish et al.[55] reported protective effect of NSAID exposure on prostate cancer incidence, with rate ratios ranging from 0.84 to 0.95. Thun et

al.[52] found a 18 % reduction of prostate cancer mortality, when he compared a group of men exposed to 16 pills or more per month to the non exposed, and Bucher et al.[56] found that, at autopsy, analgesic abusers had a reduced risk of prostate cancer of 16 % in comparison to non abusers.

On the other hand, a recent case-control study observed a statistically significant positive association between NSAID use and prostate cancer[49]. This study reported an odds ratio of 1.33 in the group exposed to at least 7 prescriptions during the observation period, in comparison to nonusers. This is the only published study on the association of NSAIDs and prostate cancer which ascertained exposure through a preregistered computerized database, as we have done. Three major methodological differences could explain the discrepancy between the results of this study and ours. First, they measured exposure during the period of 36 to 12 months before the index date while we measured exposure over the period of 96 to 3 months before index date. Second, they analysed jointly Aspirin and other NSAIDs. In our data, no protective effect is demonstrated when Aspirin and NSAIDs are considered together. Third, Langman et al. did not apply any correction for detection bias. As suggested in Roberts et al. study[57], men taking NSAIDs on a regular basis are more likely to have frequent medical contacts, digital rectal examinations, and PSA measurements than men who do not take NSAIDs. Without any control of this enhanced probability of detection in the exposed, any protective association might be blurred[75]. In our data, an inverse association is only present when adjustment is made on a proxy of medical contacts in the months preceding the index date. It is also noteworthy that the two recent studies that demonstrated strong protective effects of NSAIDs on prostate cancer used designs that precluded detection bias. In one of them, controls were chosen within a population of men who consulted for prostate cancer screening[58] and in the other, both exposed and non exposed were questioned and examined at regular intervals for prostate cancer detection[58]. Finally, there are two other published epidemiologic studies with results that do not support the hypothesis of a protective effect of NSAIDs on prostate cancer risk. Looking at the association between rhumatoid arthritis and prostate cancer incidence, Gridley et al.[50] found a non significant positive association, just as Neuget et al.[51] who observed a rate ratio of 1.60 (95 % CI, 0.82-3.11) in Aspirin users when compared to nonusers.

With respect to duration and timing of exposure, our results are in accordance with published literature on the association between NSAIDs and colorectal cancer. First, drug use needs to be regular and maintained over many years before cancer incidence decreases and second, tumor growth resumes soon after termination of NSAID treatment[35]. Moreover, regular and long-term use of Aspirin at doses similar to those recommended for the prevention of cardiovascular disease, have been demonstrated to reduce the risk of colorectal cancer[85].

In this population-based case-control study, we observed that a regular exposure to Aspirin maintained over many years, at dosages beneath those usually recommended for an anti-inflammatory effect, was associated with a 20 to 30 % reduction in prostate cancer risk. We also found that one year after the end of a regular and long-term use of Aspirin, no residual protective effect on prostate cancer risk persisted. This might suggest that the drug delays rather than prevents cancer development. In our findings, the absence of protective effect of NSAIDs other than Aspirin on prostate cancer could result from misclassification bias. It could also suggest that Aspirin exerts a particular pharmacological effect not shared by the other NSAIDs. Prostate cancer detection can be strongly influenced by care seeking behaviors and this might have blurred results of many studies on the association of NSAIDs or Aspirin and prostate cancer. In future studies, emphasis should be placed on the control of such detection bias.

Table 1: Characteristics of the study population with regard to potential detection bias variables (recent medical contacts and, Finasteride or Terazosine dispensed two years to one month before index date) and potential confounding variable (antihypertensive agents dispensed).

Drug dispensed	Cases (n = 2221)	Controls (n = 11 105)	Age adjusted odds ratios (95 % CI)
Recent medical contacts*	1887	7710	2.48 (2.19-2.81)
Finasteride or Terazosine[†] (2 years to 1 month before the index date)	77	204	1.91 (1.47-2.49)
Antihypertensive agents[‡] (8 years to 3 months before the index date)	1319	5975	1.26 (1.15-1.38)

* The variable "Recent medical contacts" was positive if at least one prescription of any medication was dispensed during the period of one to three months before the index date.

[†] A 5-alpha reductase inhibitor and an alpha-adrenoreceptor antagonist used for the treatment of benign prostatic hyperplasia.

[‡] Includes all calcium channel inhibitors, angiotensine-converting enzyme inhibitors, vasodilatators, adrenergic antagonist and thiazidic diuretics dispensed.

Table 2: NSAIDs and Aspirin prescribed to the study population during the eight-year period prior to the index date.

Classes of drugs	Prescriptions no. (% of total)*	Cumulative Duration Days (% of total)*	Defined Daily Dose (Mg)
ASPIRIN	155 988	4 722 901	ND[†]
NSAIDs	108 332	2 599 234	------
DICLOFENAC	22 122 (20.42)	529 410 (20.37)	100
NAPROXYN	22 075 (20.38)	517 381 (19.91)	500
IBUPROFEN	13 309 (12.29)	298 651 (11.49)	1200
INDOMETHACIN	13 007 (12.01)	312 976 (12.04)	100
PIROXICAM	10 133 (9.35)	283 238 (10.90)	20
KETOPROFEN	9270 (8.56)	229 138 (8.82)	150
SULINDAC	5572 (5.14)	136 022 (5.23)	400
FLURBIPROFEN	4761 (4.39)	106 440 (4.10)	200
TIAPROFENIC ACID	4237 (3.91)	104 907 (4.04)	600
Others[‡]	3846 (3.55)	81 071 (3.12)	-------

* Percentage applies to NSAIDs class only.

[†] WHO does not provide a DDD for the anti-inflammatory effect of Aspirin.

[‡] Includes Diflunisal, Fenoprofen, Tenoxicam, Tolmetin, Phenylbutazone or Oxyphenbutazone, Nabumetone or Mefenamic acid. DDD are respectively 750, 1200, 20, 700, 300, and 1000 mg.

Table 3: Relative risk of prostate cancer associated with the cumulative duration of use of prescribed NSAIDs and Aspirin dispensed during the period of eight years to three months before the index date.

Cumulative Duration of use (years)	Cases (n = 2221)	Controls (n= 11 105)	Age adjusted odds ratios (95 % CI)	Multivariate model odds ratios (95 % CI)*
Aspirin				
No exposure	1218	6444	1.00	1.00
>0 to 1	444	1972	1.19 (1.06-1.35)	1.02 (0.91-1.16)
>=1 to 2	144	701	1.09 (0.90-1.32)	0.88 (0.73-1.07)
>=2 to 3	111	457	1.29 (1.04-1.60)	1.04 (0.83-1.29)
>= 3 to 4	97	393	1.31 (1.04-1.65)	1.04 (0.82-1.31)
>= 4 to 5	76	355	1.13 (0.88-1.46)	0.92 (0.71-1.19)
>= 5 to 6	53	306	0.92 (0.68-1.24)	0.70 (0.52-0.95)
>= 6	78	477	0.86 (0.68-1.11)	0.66 (0.51-0.84)
NSAIDs				
No exposure	751	4347	1.00	1.00
>0 to 1	1098	5215	1.22 (1.10-1.35)	1.06 (0.95-1.17)
>=1 to 2	163	644	1.46 (1.21-1.76)	1.21 (1.00-1.46)
>=2 to 3	61	348	1.02 (0.77-1.35)	0.80 (0.60-1.07)
>= 3 to 4	50	198	1.46 (1.06-2.01)	1.14 (0.83-1.57)
>= 4 to 5	38	122	1.80 (1.24-2.62)	1.40 (0.96-2.04)
>= 5	60	231	1.50 (1.12-2.01)	1.14 (0.85-1.54)

* The relative risks were adjusted for age and recent medical contacts. The variables exposure to antihypertensive agents and exposure to Finasteride or Terazosine did not change parameter estimates. For Aspirin, p-value for trend = 0.0009, for NSAIDs, p-value for trend = 0.152.

Table 4: Relative risk of prostate cancer associated with the mean daily dose of prescribed NSAIDs and Aspirin, dispensed eight years to three months before the index date, and stratified according to the cumulative duration of drug use.

Mean daily dose	Cases (n=2221)	Controls (n=11 105)	Age adjusted odds ratios (95 % CI)	Multivariate model odds ratios (95 % CI)*
Aspirin				
No exposure	1218	6444	1.00	1.00
Less than 4 years of use				
< 325 mg	645	2896	1.18 (1.06-1.31)	0.99 (0.89-1.10)
>= 325 mg	151	629	1.27 (1.05-1.54)	1.03 (0.85-1.25)
At least 4 years of use				
< 325 mg	73	375	1.03 (0.79-1.33)	0.81 (0.62-1.05)
>=325 mg	134	761	0.93 (0.77-1.13)	0.72 (0.59-0.88)
NSAIDs				
No exposure	751	4347	1.00	1.00
Less than 4 years of use				
< 50 % of DDD[†]	1304	6179	1.22 (1.11-1.35)	1.05 (0.95-1.16)
>=50 % of DDD	68	227	1.74 (1.31-2.31)	1.37 (1.03-1.82)
At least 4 years of use				
< 50 % of DDD	9	31	1.70 (0.81-3.57)	1.30 (0.62-2.76)
>= 50 % of DDD	89	321	1.60 (1.25-2.04)	1.23 (0.96-1.58)

* The relative risks were adjusted for age and recent medical contacts. The variables exposure to antihypertensive agents and exposure to Finasteride or Terazosine did not change parameter estimates.

[†] Mean daily dose of NSAIDs can be read as the percentage of a usual daily dose taken to obtain an anti-inflammatory effect, as suggested by WHO Defined Daily Dose (DDD).

Table 5: Relative risk of prostate cancer associated with the timing of use of prescribed NSAIDs and Aspirin dispensed in the period of eight years to three months before the index date.

Timing of exposure*	Cases (n=2221)	Controls (n=11 105)	Age adjusted odds ratios (95 % CI)	Multivariate model odds ratios (95 % CI) [†]
Aspirin				
No exposure	1218	6444	1.00	1.00
Recent exposure[‡]	179	785	1.21 (1.02-1.44)	0.94 (0.79-1.12)
Chronic exposure[§]	292	1496	1.03 (0.90-1.19)	0.82 (0.71-0.95)
Other exposure	532	2380	1.18 (1.06-1.33)	1.01 (0.90-1.13)
NSAIDs				
No exposure	751	4347	1.00	1.00
Recent exposure	52	281	1.07 (0.79-1.46)	0.88 (0.64-1.20)
Chronic exposure	274	1050	1.51 (1.30-1.76)	1.20 (1.02-1.40)
Other exposure	1144	5427	1.22 (1.10-1.35)	1.06 (0.95-1.17)

* For Aspirin, were considered as exposed those whose mean daily dose was at least of 80 mg and for NSAIDs, at least of 10 % of the usual daily dose taken for a systemic anti-inflammatory effect.

[†] The relative risks were adjusted for age and recent medical contacts. The variables exposure to antihypertensive agents and exposure to Finasteride or Terazosine did not change parameter estimates.

[‡] Recent use is defined as an exposure four years to three months before the index date with no exposure eight to four years before the index date.

[§] Chronic use is defined as an exposure throughout the entire period of eight years to three months before the index date.

Table 6: Relative risk of prostate cancer associated with a pattern of use of prescribed NSAIDs or Aspirin characterized by regular use from eight to one year before the index date with no use in the year prior to the index date.

Timing of exposure*	Cases (N=2221)	Controls (N=11 105)	Age adjusted odds ratios (95 % CI)	Multivariate model odds ratios (95 % CI)[†]
Aspirin				
No exposure	1218	6444	1.00	1.00
Former regular exposure[‡]	134	626	1.13 (0.93-1.38)	1.03 (0.84-1.25)
Other exposure	869	4035	1.14 (1.03-1.25)	0.92 (0.83-1.02)
NSAIDs				
No exposure	751	4347	1.00	1.00
Former regular exposure[‡]	162	785	1.20 (0.99-1.44)	1.02 (0.84-1.23)
Other exposure	1308	5973	1.27 (1.15-1.40)	1.08 (0.97-1.19)

* For Aspirin, were considered as exposed those whose mean daily dose was at least of 80 mg and for NSAIDs, at least of 10 % of the usual daily dose taken for a systemic anti-inflammatory effect.

[†] The relative risks were adjusted for age and recent medical contacts. The variables exposure to antihypertensive agents and exposure to Finasteride or Terazosine did not change parameter estimates.

[‡] Former regular exposure is defined as an exposure eight to one year before the index date with no exposure in the years previous to the index date.

Chapitre III : Antihypertensive drug use and the risk of prostate cancer

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Résumé

Nous avons mesuré l'association entre le risque de cancer de la prostate et l'exposition aux antihypertenseurs dans une étude cas-témoins appariés. L'exposition était définie en terme binaire et en terme de durée cumulative d'exposition et de profil d'utilisation. Les renseignements sur la maladie et l'exposition médicamenteuse provenaient de deux registres nationaux informatisés. Nous avons contrôlé pour le biais de détection et l'usage d'AAS. Parmi les 2221 cas et 11 105 témoins, le risque de cancer de la prostate chez les exposés aux antihypertenseurs était de 0.98 (IC, 0.88-1.08) par rapport à celui chez les non-exposés. Lorsque analysée par classe, seule l'exposition aux bêta-bloquants s'est avérée associée au risque de néoplasie prostatique (RC=0.86, IC=0.77-0.96). Par rapport aux non-exposés, le risque était de 0.89 (0.75-1.05), 0.91 (0.75-1.09), et 0.82 (0.69-0.96) chez ceux ayant cumulé moins d'un an, un à quatre ans et plus de quatre ans d'exposition aux bêta-bloquants, respectivement. Aussi, les sujets ayant cumulé plus de quatre ans d'exposition aux alpha-bloquants affichaient une réduction statistiquement non-significative de 25 % du risque de cancer de la prostate.

Abstract

To verify if exposure to antihypertensive drugs was associated with prostate cancer (PCa) risk, we conducted a matched case-control study using record linkage between two population-based databases. We defined exposure as a binary variable, and in terms of timing and cumulative duration of use. We controlled for detection bias and Aspirin use. Among the 2221 cases and 11 105 controls, use of any antihypertensive agent was associated with an adjusted relative risk of PCa of 0.98 (95 % CI, 0.88-1.08). Of the different classes of antihypertensives, only beta-blockers were associated with a reduction in PCa risk (OR = 0.86, CI = 0.77-0.96). In those who cumulated < 1, 1-4, and >= 4 years of beta-blocker use, the risk was 0.89 (0.75-1.05), 0.91 (0.75-1.09), and 0.82 (0.69-0.96), respectively. Also, subjects with >= 4 years of alpha-blocker use had a non-significant 25 % reduction in PCa risk. Our results suggest that beta-blockers and long-term use of alpha-blockers may prevent PCa whereas calcium channel blockers or angiotensin-converting enzyme inhibitors do not influence PCa risk.

3.1 Introduction

Prostate cancer is the most frequent cancer diagnosed in men of Western countries and the second leading cause of cancer death[7]. In spite of numerous researches, knowledge of prostate cancer physiopathology and risk factors is currently insufficient to permit the development of primary prevention strategies[86]. There is, however, converging evidences that certain drugs and nutrients affect the occurrence and evolution of prostate cancer[14]. The chemopreventive efficacy of some of these agents is, at present, assessed through randomized controlled trials[14].

Cardiovascular drugs, particularly those used for the treatment of hypertension, have long been suspected to cause cancer. Recent reviews on the subject refute this hypothesis and even suggest that some classes of antihypertensives could reduce cancer risk[64]. Even though the population at greatest risk of prostate cancer is frequently exposed to these medications because of its age [1], few studies have investigated the relation between prostate cancer risk and antihypertensive drug use. Assessing this relation is relevant with regard to the identification of prostate cancer risk factors, a better understanding of prostate cancer physiopathology and the eventual development of new chemopreventive agents.

To investigate the association between antihypertensive drug use and the risk of prostate cancer, we conducted a matched case-control study using record linkage between the Quebec health insurance system database and the Quebec cancer registry. We aimed to verify whether exposure to antihypertensive agents as a whole and exposure to specific classes of antihypertensive drugs, over an eight-year observation period, was associated to prostate cancer risk.

3.2 Methods

3.2.1 Source population

The source population was composed of males enrolled in the Quebec health insurance system who were aged 73 to 79, between January 1st, 1993 and December 31st, 1995. This insurance system, administered by the Régie de l'assurance-maladie du Québec (RAMQ), covers all Quebec's residents with very few exceptions. Men who had a prostate cancer reported to the Quebec cancer registry between 1984 and the anticipated date of their

inclusion in the source population where excluded. We also excluded all immigrants, refugees, and persons who had resided outside Quebec for six months or more after their sixty-fifth birthday in order to guarantee that follow-up was free of any meaningful interruption.

3.2.2 Case and control definition

The cases were subjects from the source population who were diagnosed with prostate cancer (ICD-9 code 185, International Classification of Diseases, 9th revision), between January 1st, 1993 and December 31st, 1995, and were reported to the Quebec cancer registry. We considered the diagnosis date indicated in the first report to the cancer registry to be the date of diagnosis for the cases. The potential controls for each case were the subjects from the source population who were born on the same date as the case, and were alive on the date of diagnosis of the case. From every set of potential controls, five men were randomly selected. The date of diagnosis was assigned to each of the matched controls as their index date.

3.3.3 Information on the use of drugs

Drug exposure data were obtained from the RAMQ pharmacists' computerized claims database, which keeps record of all drugs reimbursed since 1981. The database has been described in details elsewhere and a high level of reliability of the prescription data has been demonstrated[72]. From 1975 to 1997, the RAMQ reimbursed all drugs prescribed on an outpatient basis to persons aged 65 and older. Dispensation of prescribed drugs could therefore be reconstituted from the date of the sixty-fifth birthday, or January 1st,1981, until the index date. Even if we had data for more years for the older subjects, in order to include all men in the analyses and have acceptable statistical precision, we only considered the exposure during the immediate 8 years preceding the index date.

Available information included the date of delivery, the class and identity of the drug (American Hospital Formulary System classification), the number of tablets, capsules or other vehicle dispensed, the drug dosage and the duration of the prescription period. All prescriptions of antihypertensives filled during follow-up were used to create exposure variables, as described below. We divided antihypertensives into calcium channel blockers (CCBs), angiotensin-converting enzyme (ACE) inhibitors, beta-blockers (BBs), thiazidic

diuretics and similars, and a class that we named "Others" that includes vasodilatators and centrally acting adrenoceptor antagonists. We also performed analyses for alpha-blockers (ABs), a subgroup of vasodilatators. For comparison of dosages we used the "defined daily dose" (DDD), which is the average daily dosage of a drug taken by adults for the main indication, according to the World Health Organization (WHO)[73].

3.3.4 Data analysis

For every subject, we measured the cumulative exposure to any antihypertensive and to each class of antihypertensives from eight years to three months before the index date. We calculated the relative risks of prostate cancer (and 95 percent confidence intervals) in relation to the use of antihypertensives or to specific classes of antiypertensives with conditional logistic regression. All categorical variables were introduced in the model using dummy variables with no use as the reference category.

We first compared the effect of no use to any use of antihypertensive drugs. Second, we compared the effect of no use to the use of specific classes of antihypertensive drugs. Third, we assessed the effect of duration of use by dividing the cumulative duration of use, to each class of antihypertensive drugs, into four mutually exclusive categories. Finally, to measure the effect of timing of exposure, we compared nonusers to subjects exposed mainly four years to three months before the index date (recent users), and to subjects exposed throughout the entire period of eight years to three months before the index date (chronic users). The effect of duration and of timing of exposure were both assessed in multivariate models that allowed mutual adjustment for concomitant exposure to different classes of antihypertensive drugs. For each class of antihypertensives, "recent users" were those with a negligible exposure (less than 20 % of the usual daily dose) 8 to 4 years prior to the index date but a mean daily exposure of at least 50 % of the usual daily dose 4 years to 3 months before the index date. "Chronic users" were those with a mean daily dose of at least 50 % of the usual daily dose throughout the entire period of 8 years to 3 months before the index date. The measurement of average daily dose of a specific class of antihypertensive agents was done as follows. We computed, for each prescription, a standardized total dose by dividing the total amount of mg of drug dispensed by the drug's DDD. Thereafter, to obtain the mean daily exposure to a class of drug, we added up all class specific standardized total doses dispensed during the period, and divided the total by the number of days in that

period. The standardized mean daily dose can therefore be interpreted as a percentage of the average daily dosage taken by adults for the treatment of hypertension, as suggested by WHO's DDD.

Detection bias might occur if those taking antihypertensive drugs are under increased medical surveillance compared to nonusers. To minimize such bias, we included in all analyses a dichotomized variable indicative of medical contacts that occurred one to three months before the index date. We measured the existence of medical contacts by counting the number of different days where one or more prescriptions of any medication were dispensed. Because Aspirin use has been reported to be associated with prostate cancer [57], [58], we considered the cumulative duration of use of prescribed Aspirin eight years to three months before the index date as a potential confounder.

3.3   Results

The study population comprised 2221 cases and 11 105 controls. At the index date, the subjects were on average 75.7 years old. During the 8-year observation period, the study population received 495 889 prescriptions of antihypertensive drugs, which represents 15 035 467 days of study-drug exposure (table 7). Thiazidic and similar diuretics accounted for 28.97 % of the prescriptions while CCBs, ACE inhibitors and BBs accounted for 25.73 %, 12.69 %, and 24.61 %, respectively (table 7). Forty-five percent (45.26 %) of the study population had no exposure to any antihypertensive drug. Like previous studies on the association between cardiovascular drugs and cancer risk, we performed all analyses regardless of diuretic use. Moreover, use of diuretics never confounded the association measures in any of the following analyses. Table 8 shows the characteristics of the study population with regard to potential confounding and detection bias variables.

Use of any antihypertensive agent 8 years to 3 months before the index date, defined as a binary variable and compared with no use during the same period, was associated with an adjusted relative risk of prostate cancer of 0.98 (95 % CI, 0.88-1.08) (table 9). Results of testing monotherapy to individual classes of antihypertensive agents during the same period are shown in table 9. Relative to nonusers, the risk of prostate cancer was 0.79 (95 % CI, 0.66-0.96) in those exclusively exposed to BBs. Risk in those exposed to monotherapy in any of the other classes of antihypertensive drugs was not significantly different from that

in nonusers. Introducing dichotomized variables of exposure to each class of antihypertensive drug in a multivariate model, showed similar results (Table 10). After entering the co-variables, Aspirin use and recent medical contacts, only exposure to BBs contributed significantly to the model. The adjusted odds ratio for BBs was 0.86 (95 % CI, 0.77-0.96). Odds ratios were close to unity and statistically non-significant for CCBs, ACE inhibitors, and the class composed of the other antihypertensives agents.

We assessed the relation between prostate cancer risk and class specific cumulative duration of antihypertensive drug use in a multivariate model. Relative to nonusers, the risk of prostate cancer in those who cumulated less than 1 year, 1 to 4 years, and at least 4 years of BB use was, respectively, 0.89 (95 % CI, 0.75-1.05), 0.91 (95 % CI, 0.75-1.09), and 0.82 (95 % CI, 0.69-0.96) (table 11). We observed no clear trend between cumulative duration of drug use and prostate cancer risk for the other classes of antihypertensive agents (table 11).

To understand the effect of the timing of exposure, we compared nonusers to recent and chronic users of antihypertensive drugs in a multivariate model. For BBs, the risk of prostate cancer was 0.89 (95 % CI, 0.56-1.39) in recently exposed, and 0.80 (95 % CI, 0.62-1.04) in chronically exposed, when compared to nonusers (table 12). No clear trend was observed for any other class of antihypertensive drugs (table 12).

During the observation period, only 471 (3.5 %) of the participating men were exposed to ABs. Relative to nonusers, the risk of prostate cancer in those who cumulated less than 1 year, 1 to 4 years, and at least 4 years of AB use was 1.32 (95 % CI, 1.00-1.74), 0.97 (95 % CI, 0.60-1.56), and 0.74 (95 % CI, 0.35-1.58), respectively.

Antihypertensive drugs and Aspirin are likely to be prescribed concomitantly for the primary and secondary prevention of cardiovascular diseases. Therefore, we also assessed the modifying effect of Aspirin use on the BB-prostate cancer association. We did so by including in a conditional logistic regression model a continuous variable for both cumulative duration of BB use and of Aspirin use, and an interaction term between these two variables. After adjustment for recent medical contacts, we found a reduction in prostate cancer risk of 3 % (OR = 0.97, 95 % CI = 0.94-1.00) for each additional year of BB use, and of 5 % (OR = 0.95, 95 % CI = 0.92-0.98) for each year increment in Aspirin

use. The relative risk associated with the interaction term was 1.00 (95 % CI, 0.99-1.01), suggesting no effect modification under the multiplicative model hypothesis. According to this model, a 8-year cumulative exposure to both BBs and Aspirin would reduced prostate cancer risk by close to 50 % (predicted OR, 0.54). Men from the study population who cumulated at least 4 years of use of BB and Aspirin had a risk of prostate cancer of 0.69 (95 % CI,0.50-0.97), compared to nonusers.

3.4 **Discussion**

In this population-based case-control analysis of 2221 incident prostate cancer cases and 11 105 controls, globally, the risk of developing prostate cancer was independent of the use of antihypertensive drugs. It was also independent of the specific use of CCBs and ACE inhibitors. However, we observed a statistically significant reduced risk of prostate cancer in BB users; an effect that demonstrated a consistent dose-response gradient. With regard to ABs, which have been shown to suppress prostate cancer cell growth in laboratory studies[67-70], we observed a statistically non-significant 25 % reduction in prostate cancer risk in the subjects who had cumulated at least 4 years of use.

The relatively large size of our study ensures considerable statistical precision for effect assessment within the main classes of antihypertensive drugs. Also, relying on computerized linkage of databases precludes recall bias. Nonetheless, other systematic errors could have affected our results. By introducing in all the statistical models the covariable *recent medical contacts*, we diluted the effect of the detection bias – which is a selection bias - but we could not expect to control it totally. Therefore, protective effects could remain underestimated in our results. Also, prostate cancer cases were identified through the Quebec cancer registry, which relies solely on hospitalization data. Since in a small fraction of prostate cancer cases, investigation and treatment are done on an outpatient basis, this registry does not capture all the incident cases. This under-declaration should not bias our results unless it differently affects the exposed and non-exposed cases, and it is difficult to speculate on factors that could have done so.

Of the three established prostate cancer risk factors that are age, race, and family history of the disease, we only controlled for age. Confounding by race is unlikely, however, because the Quebec senior population in the middle of the 1990s was mainly composed of white

persons, and also because the eligibility criteria limited the inclusion of immigrants into the study population. With regard to confounding by family predisposition to prostate cancer, it also seems unlikely since most hereditary prostate cancers are diagnosed before the age of 70[84]. Moreover, we were not able to control for any of the factors that, without being firmly proven, are suspected to influence prostate cancer risk. Unless confounding by any of these suspected risk factors had differently affected BB users, this limitation should not explain why the findings for BBs differ from those obtained for the other classes of antihypertensives. Finally, we controlled for Aspirin use which is, with the other NSAIDs, considered as a potential prostate cancer chemopreventive agent[87]. In our study population, NSAIDs other than Aspirin did not confound results whereas Aspirin use changed the odds ratios by a factor of 2 to 5 %.

The idea that hypertension is in some way linked to malignancy remains the subject of discussions[88, 89] and the few studies that measured the association between hypertension status and incident prostate cancer do not support this hypothesis[65, 90]. Findings are more controversial with regard to the relation between heart pulse and incident prostate cancer, as two published studies found positive associations[65, 91] while two others did not[90, 92]. Under the hypothesis where high blood pressure or resting heart beat, as surrogate markers of sympathetic activity or some other underlying factor, would be positively associated to prostate cancer risk, not controlling for pre-treatment blood pressure or resting heart rate would have most likely underestimate any protective effect in our study.

In the interpretation of our results, certain limits must be recognized. Since 80 % of the subjects with at least 4 years of cumulative BB use in our study were already taking this class of drug at the beginning of the 8-year observation period, it is plausible that the protective effect becomes apparent after a longer duration of exposure than that observed. The proportion already exposed at the beginning of the observation period was 46 % and 20 %, respectively, among subjects that had cumulated at least 4 years of CCB and of ACE inhibitors use.

The relative risk of prostate cancer in antihypertensive users was estimated in many studies focusing on the association between cardiovascular drugs and cancer as a whole[59, 93-100]. Unfortunately, their statistical precision for specific cancer sites was weak and their results were inconsistent. More specific ascertainment of this relation comes from one case-control

and one cohort study. In the former, which comprised 1217 cases and 1400 controls under 70 years of age, Vézina *et al.*[66] observed a negative odds ratio of borderline statistical significance, for BB use (OR = 0.8, 95 % CI = 0.7-1.0). For thiazidic diuretics, ACE inhibitors, and CCBs, they found odds ratios above 1.00. In the cohort study, Fitzpatrick *et al.*[65] followed 2442 men, aged 65 or older, for an average of 5.6 years during which 209 incident prostate cancers occurred. In this study, use of any antihypertensive drug, compared with no use, was associated with an adjusted hazard ratio of prostate cancer of 0.7 (95 % CI, 0.5-0.9). Hazard ratios below 1.00 were found for use of each class of antihypertensives but reached statistical significance only for CCBs. Inspired by a model proposing that high blood pressure and high heart rate could be markers of an increased central sympathetic nervous activity that would induce an androgen-mediated stimulation of prostate cancer growth[101], the authors hypothesized that antihypertensive drugs could reduce prostate cancer development through the suppression of androgen production. Finally, laboratory studies suggest that ABs, a class of drugs used for the treatment of hypertension and benign prostatic hyperplasia, increase apoptosis and inhibit angiogenesis in human prostate cancer cells[67-70]. This anti-tumor effect would be independent of the drugs' capacity to antagonize α1-adrenoceptor[67]. To our knowledge this effect had not yet been investigated in observational or clinical studies.

In accordance with the two previous observational studies, our results suggest that exposure to BBs reduces prostate cancer development. They also suggest a protective effect with long term use of ABs but, in this case, the number of exposed subjects was too small to allow any precise assessment. If real, the anticarcinogenic effect of beta-adrenoceptor antagonists, and possibly of alpha-adrenoceptor antagonists, could be related to a sympathetic nervous system mediated suppression of androgen production, as suggested by Fitzpatrick *et al.*[65]. It could also be mediated by another mechanism yet to be identified. Confirmation of these findings may help understanding prostate cancer physiopathology and foster the development of new preventive and management strategies.

Table 7: Antihypertensive agents prescribed to the study population during the eight-year period prior to the index date.

Classes of drugs	Prescriptions no. (% of total)	Cumulative Duration Days (% of total)
Any Antihypertensive drug	495 889	15,035 467
Calcium channel blockers	127 599 (25.73)	3 743 144 (24.90)
Angiotensin-converting enzyme inhibitors	62 907 (12.69)	1 826 796 (12.15)
Beta-blockers	122 053 (24.61)	3 753 560 (24.97)
Thiazidic diuretics and similars	143 663 (28.97)	4 522 964 (30.08)
Others[*]	39 667 (8.00)	1 189 003 (7.91)

[*] Includes Alpha-blockers (AB) (Doxazosin, Prazosine, Terazosine), arteriolar smooth muscle agents (Hydralazine, Minoxidil), and centrally acting adrenoceptor antagonists (Clonidine, Methyldopa, Reserpine).

Table 8: Characteristics of the study population with regard to potential detection bias variable (Recent medical contacts) and confounding variable (Aspirin use).

Subject Characteristics	Cases (n = 2221)	Controls (n= 11 105)	Age adjusted odds ratios (95 % CI)	Fully adjusted odds ratios (95 % CI) [*]
Recent medical contacts [†]				
NO	334	3395	1.00	-------
yes	1887	7710	2.48 (2.19-2.81)	-------
Aspirin use [‡]				
none	1218	6444	1.00	1.00
>0 to 4 years	796	3525	1.20 (1.08-1.32)	1.00 (0.90-1.11)
>= 4 years	207	1136	0.96 (0.82-1.13)	0.75 (0.64-0.88)

[*] The relative risks were adjusted for age and recent medical contacts.

[†] The variable "Recent medical contacts" was positive if at least one prescription of any medication was dispensed during the period of one to three months before the index date.

[‡] Cumulative duration of Aspirin use during the period of eight years to three months before the index date.

Table 9: Relative risk of prostate cancer by type of antihypertensive drug used in monotherapy during the period of eight years to three months before the index date.

Antihypertensive use*	Cases	Controls	Aged adjusted Odds Ratios (95 % CI)	Fully adjusted Odds Ratios[†] (95 % CI)
None[‡]	1075	5946	----	----
Calcium channel blockers	234	972	1.33 (1.14-1.56)	1.07(0.91-1.26)
Angiotensin-converting enzyme inhibitors	126	507	1.37 (1.12-1.68)	1.09 (0.88-1.34)
Beta-blockers	154	865	0.98 (0.82-1.18)	0.79 (0.66-0.96)
Others[§]	61	264	1.28 (0.96-1.71)	1.10 (0.82-1.48)

* Only the cases and controls with monotherapy in a specific class of antihypertensive agents, during the eight-year observation period, were used to measure the effect of a specific class of antihypertensive drug.

[†] The relative risks were adjusted for age, recent medical contacts, and Aspirin use.

[‡] Reference category.

[§] Refers to the subjects who only received drugs that we included in the category "Others".

Table 10: Relative risk of prostate cancer by type of antihypertensive drug used during the period of eight years to three months before the index date, assessed in a multivariate model.

Variable	Adjusted odds ratios *	95 % Confidence interval
Calcium channel blockers	1.05	0.94-1.17
Angiotensin-converting enzyme inhibitors	1.05	0.93-1.19
Beta-blockers	0.86	0.77-0.96
Others	1.03	0.89-1.20

* Apart from mutual adjustment for concomitant use of different classes of antihypertensives, the relative risks were adjusted for age, recent medical contacts, and Aspirin use.

Table 11: Relative risk of prostate cancer in relation to the cumulative duration of use of each class of antihypertensive drug dispensed eight years to three months before the index date, assessed in a multivariate model.

Variable	Adjusted odds ratios *	95 % Confidence interval
Calcium channel blockers		
>0-1 year	1.21	1.04-1.41
>= 1 - 4 years	0.95	0.81-1.12
>= 4 years	0.96	0.81-1.15
Angiotensin-converting enzyme inhibitors		
>0-1 year	1.11	0.94-1.32
>= 1 – 4 years	1.01	0.85-1.19
>= 4 years	1.00	0.76-1.31
Beta-blockers		
>0-1 year	0.89	0.75-1.05
>=1 – 4 years	0.91	0.75-1.09
>= 4 years	0.82	0.69-0.96
Others		
>0-1 year	1.06	0.85-1.31
>=1 – 4 years	0.93	0.71-1.22
>= 4 years	1.16	0.89-1.53

* The relative risks were adjusted for age, recent medical contacts, and Aspirin use.

Table 12: Relative risk of prostate cancer associated with the timing of use of each class of antihypertensive drug, dispensed eight years to three months before the index date, assessed in a multivariate model.

Variable	Adjusted Odds ratios *	95 % Confidence interval
Calcium channel blockers		
Recent users[†]	1.01	0.81-1.26
Chronic users[‡]	0.97	0.76-1.23
Other users[§]	1.07	0.94-1.21
Angiotensin-converting enzyme inhibitors		
Recent users	0.96	0.73-1.26
Chronic users	1.07	0.72-1.59
Other users	1.06	0.93-1.22
Beta-blockers		
Recent users	0.89	0.56-1.39
Chronic users	0.80	0.62-1.04
OTHER USERS	0.87	0.77-0.99
Others		
Recent users	0.26	0.06-1.11
CHRONIC USERS	1.17	0.85-1.63
Other users	1.04	0.88-1.23

* The relative risks were adjusted for age, recent medical contacts, and Aspirin use.

[†] Recent users were those with a negligible exposure 8 to 4 years prior to the index date but a mean daily dose of at least 50 % of the usual daily, as proposed by World Health Organisation's defined daily dose, from 4 years to 3 months prior to the index date.

[‡] Chronic users were those with a mean daily dose of at least 50 % of a usual daily dose throughout the entire period of 8 years to 3 months before the index date.

[§] Other users were those that were exposed but whose pattern of exposure did not meet the criteria for recent or chronic use.

Chapitre IV : Discussion

4.1   Synthèse des résultats

Dans cette recherche, nous avons observé que l'exposition régulière et prolongée à l'AAS était associée à une réduction du risque de cancer de la prostate. Ceux recevant 80 mg ou plus d'AAS quotidiennement, depuis 8 ans, avaient 18 % moins de risque de développer un cancer de la prostate que les non-exposés. Nous avons également noté un gradient dose-réponse parmi ceux utilisant de l'AAS depuis au moins quatre ans. Par contre, nos résultats suggèrent que l'effet protecteur de l'AAS s'estompe rapidement lorsque cesse l'exposition. Ceci laisse croire que l'AAS pourrait retarder plutôt que prévenir le développement du cancer de la prostate. Nous n'avons observé aucune association entre l'usage des AINS, autres que l'AAS, et le risque de cancer de la prostate. Un biais de classification explique peut-être cette dernière constatation.

Par ailleurs, nos travaux montrent que la prise d'antihypertenseurs, en soi, ne conférerait aucune protection contre le cancer de la prostate. De même, l'usage des inhibiteurs des canaux calciques ou des inhibiteurs de l'enzyme de conversion de l'angiotensine, deux importantes classes d'antihypertenseurs, serait indépendant du risque de survenue d'un cancer de la prostate. Par contre, nous avons noté une association négative entre l'exposition aux bêta-bloquants et le cancer de la prostate. Parmi ceux régulièrement exposés à cette classe d'antihypertenseurs au cours des 8 années d'observation, il y avait 20 % moins de néoplasie prostatique que parmi les non-exposés.

Nous avons donc observé que l'AAS et les bêta-bloquants démontraient tous deux un effet protecteur contre le cancer de la prostate. Puisqu'ils sont souvent utilisés simultanément en chimioprévention des maladies cardiovasculaires, nous avons voulu vérifier l'existence d'un effet synergique entre eux. Pour ce faire, nous avons mesuré leur interaction dans le modèle multiplicatif. Selon ce modèle, présenté au chapitre III, le terme d'interaction unissant les deux variables avoisine la valeur de 1,00. C'est donc dire que les effets de ces deux substances sur la carcinogenèse prostatique se multiplient, comme le prévoit le modèle multiplicatif, sans plus. Ceci soutient l'idée qu'elles opéreraient sur la carcinogenèse par des modes d'action indépendants l'un de l'autre. L'AAS agirait vraisemblablement en inhibant la synthèse des prostaglandines au niveau de l'épithélium prostatique et les bêta-bloquants, en atténuant la stimulation androgénique via le système nerveux autonome sympathique. (Le mode d'action des bêta-bloquants est cependant tout à

fait hypothétique à ce stade-ci.) Ainsi, d'après le modèle prédictif que nous avons construit, les hommes exposés à ces deux médicaments pendant huit ans réduiraient leur risque de cancer de la prostate d'environ 50 %, par rapport aux sujets soumis à ni l'une ni l'autre de ces substances. Nous devons interpréter ce modèle avec prudence toutefois, car nous y traitons en variable quantitative continue des variables qui ne respectent pas entièrement le postulat de la linéarité. Dans notre population participante, les hommes exposés pendant au moins 4 ans à l'AAS et à un bêta-bloquant présentaient 31 % moins de cancer de la prostate que les non-exposés.

Dans le domaine de la chimioprévention des cancers, on émet comme priorité de recherche l'identification de combinaisons d'agents aux pouvoirs chimiopréventifs complémentaires[16]. On espère ainsi identifier des régimes thérapeutiques plus efficaces et moins toxiques[16]. Dans l'étude SELECT, par exemple, on administre à un groupe du Sélénium, à un autre l'alpha-tocophérol et à un troisième une combinaison des deux substances[16]. Si l'effet que nous avons observé chez les utilisateurs de bêta-bloquants et d'AASs se confirme, il pourrait s'agir là d'une combinaison thérapeutique intéressante pour la chimioprévention du cancer de la prostate, d'autant plus que ces deux agents sont bien connus et déjà couramment employés.

4.2   Validité de l'étude

Tel que mentionné aux chapitres II et III, le recours à une banque de données informatisées et préenregistrées pour mesurer l'exposition médicamenteuse élimine la possibilité d'un biais de rappel. Cette banque de données nous a également permis d'estimer l'effet du dosage, de la durée et du profil d'exposition dans le temps. Ceci constitue une qualité et une originalité importante de la recherche, car dans presque toutes les études préalablement publiées sur les mêmes sujets on n'analysait que l'exposition ponctuelle. Par ailleurs, divers biais peuvent avoir affecté les résultats de notre recherche.

Nous avons identifié les cas de la population de l'étude par l'intermédiaire du Fichier des tumeurs du Québec (FTQ). Ce dernier ne recense que les cas de cancer survenus chez des individus ayant séjourné en centre hospitalier de soins de courte durée ou ayant été admis pour une chirurgie d'un jour. La principale raison d'hospitalisation des nouveaux cas de cancer de la prostate est la prostatectomie. On la recommande dans le traitement des stades

T_{1b}, T_{1c}, T_{2a}, T_{2b}, T_{2c} et parfois T_3, chez les hommes dont on juge l'espérance de vie supérieure à 10 ans[19]. D'autres modalités thérapeutiques comme la surveillance, la radiothérapie ou la cryothérapie peuvent toujours remplacer la prostatectomie. Ces interventions ne nécessitent pas d'hospitalisation. Par ailleurs, les consensus cliniques ne préconisent jamais la prostatectomie pour traiter les stades T_{1a} et T_4. Les cas de cancer de stade 4 reçoivent généralement une hormonothérapie administrée en externe tandis que les stades T_{1a} sont surveillés. À noter que le FTQ devrait malgré tout recenser les stades T_{1a} puisque, par définition, ceux-ci sont découverts fortuitement lors d'une résection transurétrale de la prostate, intervention qui nécessite une hospitalisation. Par conséquent, le FTQ ne capte pas tous les nouveaux cas de cancer de la prostate. Comme nous l'avons mentionné à la section 1.5, jusqu'à 30 % des cas n'y seraient pas recensés (Jacques Brisson, Université Laval, communication personnelle). Ce problème d'exhaustivité n'induira de biais que s'il affecte différemment les exposés et les non-exposés. Une déclaration moindre chez les exposés, par rapport aux non-exposés, engendrerait un biais de sélection qui amplifierait un effet protecteur tandis qu'une déclaration accrue provoquerait l'inverse. Les exposés à des médicaments comme l'AAS, les AINS ou les antihypertenseurs traînent possiblement des antécédents médicaux plus lourds que les non-exposés à ces mêmes médicaments. Le cas échéant, leur urologue pourrait les considérer moins aptes à subir une chirurgie. Par contre, les exposés bénéficient vraisemblablement d'une surveillance médicale plus étroite que les non-exposés. Leur cancer a donc davantage de chance d'être diagnostiqué à un stade clinique où la prostatectomie constitue le traitement de choix. De plus, vu leurs antécédents médicaux plus sévères, ils ont apparemment davantage de chance d'être récupérés au FTQ suite à des hospitalisations sans lien avec la prostatectomie. Il est difficile de prévoir l'impact réel de chacun de ces facteurs. Cependant, divers éléments laissent penser que ce biais ne saurait expliquer entièrement les résultats observés. Premièrement, dans l'étude prospective de Roberts *et al.*[57], la mortalité au cours du suivi était identique chez les non-exposés et les exposés aux AINS, à 87 % composés d'AAS. Ceci suggère que l'utilisation d'AINS ou d'AAS n'est pas forcément un bon indicateur du degré de comorbidité chez les hommes âgés. Deuxièmement, nous avons mesuré des rapports de cotes passablement différents pour des classes de médicaments qui, en principe, devraient être des indicateurs de comorbidité à peu près équivalents. Dans l'étude sur les antihypertenseurs, tout particulièrement, les différentes classes des substances étudiées ont toutes des indications thérapeutiques assez semblables, pourtant nous ne constatons d'effet

que chez les utilisateurs de bêta-bloquants et d'alpha-bloquants. Troisièmement, nous avons noté un gradient dose-réponse chez les utilisateurs chroniques d'AAS. Si les associations négatives de la première étude s'expliquaient entièrement par une sous-déclaration au FTQ chez les exposés à l'AAS, nous ne devrions pas voir de relation dose-réponse.

Alors que tous les cas inclus dans l'étude ont forcément eu au moins un contact avec un médecin, il existe parmi les témoins des individus qui n'ont jamais consulté de médecin. Les cas et les témoins diffèrent donc systématiquement quant à leur opportunité respective de détection d'un cancer asymptomatique. Ce biais de sélection, dit biais de détection, pourrait atténuer un effet protecteur. Cependant, son impact est probablement minime dans la présente recherche puisque rares sont les individus de 73 à 79 ans sans contact avec le réseau de la santé.

Au chapitre II, nous avons évoqué la possibilité d'un biais de « mortalité par cause compétitive ». Pour qu'il advienne, deux conditions doivent être remplies. D'une part, le taux de mortalité des sujets exposés de la population source doit avoir excédé celui des non-exposés, de cette même population, dans les années précédant celles où nous avons constitué la population participante. D'autre part, cet excès de décès doit avoir affecté préférentiellement ceux susceptibles de développer un cancer de la prostate. Bien que dans leur étude prospective Roberts *et al.*[57] n'observent pas d'excès de mortalité chez ceux exposés aux AINS - dont 87 % étaient exposés à l'AAS, un tel excès semble plausible. En effet, la prise régulière de l'un ou l'autre des médicaments auxquels nous nous sommes intéressés peut fort bien indiquer une morbidité accrue. Par contre, nous entrevoyons plus difficilement les raisons pour lesquelles cet excès de mortalité toucherait préférentiellement ceux susceptibles de développer un cancer de la prostate. Ainsi, bien que théoriquement possible, nous ne croyons pas qu'un biais par mortalité pour cause compétitive affecte les mesures d'association d'une façon significative.

Toujours au deuxième chapitre, nous émettons la possibilité d'un biais non-différentiel d'information sur l'exposition. Ce biais peut avoir trois sources, toutes tributaires des caractéristiques du registre des réclamations pharmaceutiques de la RAMQ. Premièrement, ce registre néglige complètement la consommation des médicaments achetés sans ordonnance. Cependant, pour les substances pharmaceutiques que nous avons étudiées, les résultats de deux enquêtes nationales montrent qu'au Québec, dans les années 1980 et

1990, les personnes âgées consommaient très peu de médicaments non prescrits. Pour les AINS (incluant l'AAS) par exemple, l'enquête sociale et de santé de 1992-1993 indique que 96,6 % de ce que les hommes de 65 ans et plus avaient consommé dans les deux jours précédant l'entrevue leur avaient été prescrit par un médecin (Nathalie Audet, Institut de la statistique du Québec, communication personnelle). En 1987, selon l'enquête santé Québec, c'est 96,1 % des AINS consommés qui étaient prescrits (Nathalie Audet, Institut de la statistique du Québec, communication personnelle). Donc, bien qu'il ignore la dispensation des médicaments en vente libre, le registre informatisé des réclamations pharmaceutiques de la RAMQ n'en constitue pas moins un reflet assez juste de l'entièreté des substances pharmaceutiques dispensées, du moins pour la population, la période de temps et les médicaments qui nous concernent. Deuxièmement, ce registre peut comporter des erreurs. Toutefois, si l'on s'en remet à l'étude de Tamblyn *et al.* publiée en 1995[72], la validité et l'exhaustivité des informations qu'il renferme seraient tout à fait satisfaisantes. Le lecteur désireux d'approfondir ce point peut consulter l'article précité à l'annexe 2. Troisièmement, le registre reflète l'achat et non la consommation réelle de médicaments. Ce problème de discordance entre l'achat et la consommation se pose surtout pour les AINS autres que l'AAS. En effet, vu leurs indications thérapeutiques, il est possible que les patients respectent moins bien une ordonnance médicale d'AINS qu'ils ne respecteraient une ordonnance l'AAS ou d'antihypertenseurs. Cette dernière source d'imprécision sur la mesure de l'exposition pourrait expliquer pourquoi nous n'observons aucune association entre le cancer de la prostate et l'usage d'AINS autres que l'AAS.

Nous avons pris soin d'ajuster les mesures d'association pour le degré de surveillance médicale - ou degré d'accès aux tests de détection précoce du cancer de la prostate - auquel les sujets étaient soumis, et ce, par l'intermédiaire de la variable *recent medical contacts*. Or, cette variable est une mesure bien imparfaite des opportunités de détection du cancer de la prostate. Il apparaît donc vraisemblable qu'un certain degré de confusion résiduelle persiste à cet égard. Le cas échéant, l'erreur systématique ferait tendre une mesure d'association négative vers la valeur nulle et pourrait même en inverser le sens. Aussi, comme nous avons utilisé les données sur la dispensation des médicaments prescrits pour constituer cette mesure de la surveillance médicale, l'introduction de cette covariable dans les modèles multivariés soulève la possibilité d'un problème de surajustement. Celui-ci se manifestera, entre autres, si la covariable est une variable intermédiaire entre l'exposition et

la maladie. Plusieurs facteurs militent contre cette éventualité. Premièrement, les ordonnances d'AAS, d'AINS ou d'antihypertenseurs représentent une faible proportion de toutes les ordonnances ayant servi à construire la covariable *recent medical contacts*. Seulement six pour cent était des ordonnances d'AAS et cinq pour cent, des ordonnances d'AINS. Deuxièmement, nous n'avons aucune raison de croire que l'arrêt ou la poursuite de la consommation d'AAS, d'AINS ou de l'une ou l'autre des classes d'antihypertenseurs soit déterminé par le risque de cancer de la prostate. Donc, même si les ordonnances à ces médicaments-là représentaient une proportion beaucoup plus grande - voir la totalité - des ordonnances utilisées pour constituer la covariable, nous pourrions raisonnablement défendre que les variables d'exposition et la covariable se situent sur des chaînes causales différentes. Troisièmement, bien que la covariable *recent medical contacts* soit partiellement correlée aux variables d'exposition, ce qui était prévisible et attendu, jamais n'avons nous rencontré de problème de colinéarité dans l'élaboration des modèles multivariés. Donc à notre avis, bien qu'à prime abord plausible, le surajustement n'atténue pas artificiellement les rapports de cote ajustés.

Outre la médication concomitante, la seule autre variable potentiellement confondante pour laquelle nous avons ajusté est l'âge. Compte tenu des critères d'éligibilité à l'étude et des caractéristiques démographiques du Québec de l'époque, la variable race ne devrait pas être une source de confusion significative. Au Québec, en 1996, parmi les hommes âgés de 70 ans et plus, seulement 0,7 % étaient de race noire et 1,1 % d'origine asiatique (Hélène Paquet, Institut de la statistique du Québec, communication personnelle). De même, considérant l'âge de la population participante, la variable prédisposition familiale au cancer de la prostate ne devrait pas non plus générer de confusion. Cependant, plusieurs autres facteurs sont possiblement liés au risque de cancer de la prostate comme nous l'avons vu au premier chapitre. Nous ne pouvons donc exclure la possibilité de confusion par l'un ou l'autre de ces facteurs de risque suspectés. À noter que rares sont les études citées dans nos revues de littérature qui les aient pris en compte.

La confusion par indication (*confounding by indication*) est un autre biais classique des études de pharmacoépidémiologie. Il survient lorsque l'indication ou l'une des indications du médicament d'intérêt cause la maladie étudiée[77]. Par exemple, dans l'analyse de la relation entre les antidépresseurs et l'infertilité, la variable dépression peut causer ce type

d'erreur systématique. Dans notre recherche, ce biais n'est pas à craindre car aucune des indications des classes de médicament étudiées ne constitue un facteur de risque du cancer de la prostate.

Dans notre recherche, un biais de causalité inversée (biais protopathique) se produirait si la consommation des médicaments d'intérêt, pendant la période d'observation, était motivée par des symptômes ou signes cliniques d'un cancer de la prostate non encore diagnostiqué. Il pourrait aussi advenir si les sujets consommaient les médicaments d'intérêt après la date réelle du diagnostic du cancer, mais avant la date inscrite au FTQ. Ceci risque d'arriver si un laps de temps significatif sépare le moment du diagnostic et de l'hospitalisation permettant la notification du cas. Pour évaluer la présence de ce biais, nous avons fait des analyses qui sont décrites au chapitre deux. Les résultats de ces analyses suggèrent que les mesures d'association ne sont pas faussées par ce type de biais.

Comparativement à la plupart des études publiées sur la relation entre les AINS et le cancer de la prostate ainsi que sur la relation entre les antihypertenseurs et ce même cancer, nos deux études jouissent d'une très bonne précision au plan statistique. Au regard de la seconde étude, nous pouvons nous interroger sur la nécessité d'effectuer un ajustement du seuil de décision statistique pour contrecarrer l'effet de comparaisons multiples. Nous avons décidé de ne pas appliquer ce type de correction, car nous présentons séparément les rapports de risque de chaque classe d'antihypertenseurs et ne formulons aucune inférence globale, sur l'effet des antihypertenseurs, à partir des mesures d'association individuelles.

4.3   Limites de l'étude

Nous avons discuté les limites de la recherche aux chapitres II et III. Sommairement, elles concernent le fait que la période d'observation se borne aux huit années avant la date de référence et que l'effet des médicaments sur le risque de cancer ne soit pas stratifié selon le stade au diagnostic.

4.4   Conclusion

Bien que les deux études présentées dans cette thèse possèdent des qualités indéniables au regard de la précision statistique et de la mesure de l'exposition, elles s'avèrent sujettes à l'effet de plusieurs biais potentiels. Malgré cela, compte tenu de l'absence vraisemblable de

biais de causalité inversée, de la force de certaines des associations, de la présence de gradients dose-réponse et durée-réponse, de la consistance interne des résultats et de la concordance des résultats avec ceux d'autres études, elles peuvent être considérées comme crédibles. Toutefois, les résultats devront être confirmés par d'autres avant que nous puissions statuer sur l'existence de liens de causalité.

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Annexe 1 : Étude sur le dépistage du cancer de la prostate réalisée en parallèle aux deux études présentées dans la thèse

Linda Perron, Lynne Moore, Isabelle Bairati, Paul-Marie Bernard, François Meyer, PSA screening and prostate cancer mortality, CMAJ 2002, 166 (5): 586-591.

PSA screening and prostate cancer mortality

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Abstract

Background: Physicians have speculated that prostate-specific antigen (PSA) screening may be responsible for the reduction in prostate cancer mortality observed in the late 1990s. In order to test this hypothesis, we assessed the relation between the change in prostate cancer incidence in the early 1990s, attributed largely to PSA screening, and the subsequent change in prostate cancer mortality.

Methods: We divided the adult male population of Quebec aged 50 years and more into 15 birth cohorts. For each birth cohort, we computed the change in prostate cancer incidence between 1989 and 1993 and the change in prostate cancer mortality between 1995 and 1999. We then assessed the correlation between the changes in prostate cancer incidence and the subsequent changes in prostate cancer mortality by weighted linear regression. We also split up the study population into 15 regional populations and repeated the analysis described above.

Results: We found that even though most birth cohorts showed an increase in prostate cancer incidence and a subsequent decrease in mortality, the sizes of these changes were not inversely correlated (Pearson's $r = 0.33$, 1-sided $p = 0.89$). Similarly, in the regional population study, we found that a greater increase in prostate cancer incidence did not indicate a greater decline in mortality (Pearson's $r = 0.13$, 1-sided $p = 0.68$).

Interpretation: These results suggest that for our study population PSA screening was not associated with, and therefore cannot explain, the decline in prostate cancer mortality.

From the 1970s to the early 1990s, age-standardized mortality rates for prostate cancer increased steadily in Canada, making prostate cancer the second most common cause of death from cancer in men. In 1995, however, the prostate cancer mortality rate started to decline.[1-7] It has been speculated that prostate-specific antigen (PSA) screening, introduced into North American medical practice by the end of the 1980s, may be responsible for this decline in mortality.[4,8-10] However, many physicians and scientists consider that even if PSA screening was effective in preventing or postponing death from prostate cancer, it is too early to observe such an effect.

The effectiveness of screening with the PSA test to reduce prostate cancer mortality has not yet been established by randomized controlled trials. Moreover, the 2 studies that have attempted to establish whether the recent decline in prostate cancer mortality seen at the population level could be attributed to PSA screening did not support this hypothesis.[11,12]

Our aim was to test whether the declining trend in the prostate cancer mortality rate seen between 1995 and 1999 in the Quebec population could be attributed to PSA screening. We hypothesized that the changes in prostate cancer incidence between 1989 and 1993 were to a large extent attributable to PSA screening and that, if PSA screening had reduced prostate cancer mortality, an inverse association should be observed between the changes in incidence and mortality. Therefore, we expected to find a negative correlation showing the greater the increase in incidence due to PSA screening, the greater the decrease in prostate cancer mortality.

Methods

Study population

We conducted 2 separate analyses to assess whether the changes in prostate cancer incidence between 1989 and 1993 were related to the changes in prostate cancer mortality that occurred between 1995 and 1999. The year 1993 was chosen as the cutoff point for incidence because it corresponds to the peak of the epidemic period of prostate cancer incidence caused by improved detection using PSA screening. The year 1999 was selected as the cutoff point for the assessment of the mortality rate, because the latest data are available for that year.

For the first analysis, the study population was composed of 15 birth cohorts. Each birth cohort included all adult male residents of Quebec born in 2 successive years. The men in these cohorts were aged between 50 and 79 years in 1993 and between 56 and 85 years in 1999.

For the second analysis, the study population consisted of 15 geographically defined populations of Quebec. There are 16 administrative regions in Quebec, but we grouped together the regions of Côte-Nord and Nord-du-Québec because each has a small population. In this case, we used data from the male population aged 50–79 years to compute the changes in prostate cancer incidence rates and from the male population aged 55–84 years to compute the changes in prostate cancer mortality rates.

Data sources

The provincial Institut de la Statistique du Québec provided information about all deaths from prostate cancer for the years 1986 through 1999. The initial disease or condition that ultimately led to death (the underlying cause) was considered to be the cause of death. Data about all newly diagnosed cases of prostate cancer were obtained from the Quebec provincial cancer registry for the years 1986 through 1996. Information about the adult male population of Quebec by age and calendar year was extracted from Statistics Canada census publications. Age-standardized rates of prostate cancer incidence and mortality were computed using the 1991 Canadian population as the reference population.

Variables

The 2 variables computed were the magnitude of change in the prostate cancer incidence rate during the period 1989–1993 (the incidence difference) and the magnitude of change in the prostate cancer mortality rate during the period 1995–1999 (the mortality difference).

The difference in the prostate cancer incidence rates of the birth cohorts between 1989 and 1993 results from changes in prostate cancer detection (mainly by PSA screening) and the effect of 4 years of aging of the cohorts. Because we aimed to capture the degree of exposure of each cohort to PSA screening, we needed to exclude the effect of aging from the measure of incidence difference. To do so, we computed the difference between the 1993 observed prostate cancer incidence rate and an expected 1993 prostate cancer incidence rate. The expected rate was the rate that would have appeared in a given birth cohort, in 1993, if aging had explained most of the increase in incidence between 1989 and 1993. Therefore, the difference between the observed and the expected 1993 incidence rates captures the increase in prostate cancer incidence of each birth cohort, between 1989 and 1993, above that which could be explained by aging.

In order to obtain the expected 1993 prostate cancer incidence rate for each birth cohort, we built a predictive model. Using a Poisson distribution, we carried out a regression analysis of the number of incident prostate cancer cases by age and calendar year, in a generalized linear model.[18] The data used to derive the predictive model were provided by all birth cohorts of men living in Quebec who were aged 50–79 years during 1986–1989. This period was not affected by changes in medical practice with regard to prostate cancer screening, and aging explained most of the increase in incidence in the cohorts from one calendar year to the next. Thereafter, the expected incidence rate of each birth cohort for 1993 was computed using the parameter estimates of the predictive model. The difference between the 1993 observed and expected prostate cancer incidence rates was divided by the 1993 expected rate in order to obtain a relative difference in incidence rate. Therefore, if the observed rate is twice the expected rate, the relative difference in incidence rate equals 1.0 or 100%.

Similarly, for each birth cohort, we computed a relative mortality rate difference. It was the difference between the 1999 observed and expected mortality rates, divided by the 1999 expected rate. The expected 1999 mortality rate was calculated using the same method as described for incidence. The observations used to derive this predictive model were provided by all birth cohorts of men living in Quebec who were aged 56–85 years during 1992–1995.

For the geographically defined study population, the measure of the incidence difference was more straightforward. It was the difference between the 1993 age-standardized prostate cancer incidence rate and the mean age-standardized prostate cancer incidence rate for the years 1986–1989. We divided this rate difference by the mean 1986–1989 rate to obtain a relative incidence rate difference. Similarly, for each Quebec region, we computed the relative difference between the age-standardized 1999 prostate cancer mortality rate and the mean age-standardized prostate cancer mortality rate for the years 1992–1995. Because the age-standardized prostate cancer incidence and mortality rates were very stable during the years 1986–1989 and 1992–1995 respectively, we used the 4-year mean rates instead of a 1-year rate for greater precision.

Analysis

In both study populations, we assessed the association between the relative incidence difference and the relative mortality difference by weighted linear regression. To test the hypothesis that there might be an inverse relation between the 2 variables, 1-sided p values were calculated for Pearson's product-moment correlation coefficient (r).

Results

Quebec experienced a 47% increase in its age-standardized prostate cancer incidence rate between 1989 and 1993, as it rose from 336 cases per 100 000 man-years to a peak of 493 cases per 100 000 man-years (Fig. 1). The age-standardized rate of prostate cancer mortality in Quebec decreased by 15% between 1995 and 1999, that is, from 124 deaths per 100 000 man-years to 105 deaths per 100 000 man-years (Fig. 1).

Fig. 2A shows that the 15 birth cohorts had increases of 22%–178% in prostate cancer incidence rates in 1993, compared with 1989. It also shows that 11 of the 15 birth cohorts experienced a decline in the prostate cancer mortality rate in 1999, compared with 1995. These declines ranged from –3% to –50%. The scatter plot of the relative incidence and mortality differences in the 15 birth cohorts is presented in Fig. 2B. Weighted linear regression analysis of these 2 variables resulted in a Pearson's product-moment correlation coefficient of 0.33 (1-sided $p = 0.89$, determination coefficient $[r^2] = 10.9\%$). Therefore, even though most cohorts had a positive incidence difference and a negative mortality difference, the sizes of the differences are not negatively correlated. This means that, within the 15 birth cohorts, a greater increase in prostate cancer incidence is not associated with a greater decline in mortality. For example, the cohort born in 1942/43, which had a larger increase in incidence than the one born in 1914/15 (177% v. 31%), did not experience a larger decrease in mortality (–26% in both cohorts) (Fig. 2B).

Fig. 3A shows that the 15 Quebec regions experienced a 44%–155% elevation in the age-standardized prostate cancer incidence rate between 1989 and 1993. In addition, all but 2 regions had an age-standardized prostate cancer mortality rate in 1999 that was lower than their 1995 corresponding rate. The rates ranged from –12% to –57%. Although we anticipated that large centres would have a greater increase in incidence, because PSA screening was more likely to have been adopted earlier, the 2 largest urban areas, Montreal (region 6) and Quebec City (region 3), did not show a greater increase in incidence from 1989 to 1993 than the other Quebec regions. Fig. 3B shows the scatter plot of relative incidence and mortality differences in the 15 Quebec regions. Weighted linear regression analysis of these

2 variables resulted in a Pearson's product-moment correlation coefficient of 0.13 (1-sided $p = 0.68$, $r^2 = 1.7\%$). Therefore, as in the birth cohorts, a greater increase in prostate cancer incidence within the 15 Quebec regions did not indicate a greater decline in mortality. For example, the Quebec City area showed a greater increase in incidence than the Montreal area (67% v. 44%) but experienced a smaller decline in mortality (–12% v. –16%).

Interpretation

The age-standardized incidence rate of prostate cancer in the male population of Quebec, aged 50 years and more, rose sharply from 1989 to 1993, whereas the age-standardized mortality rate slowly decreased from 1995 to 1999. This increase in incidence was presumably caused by the detection of preclinical cases following the introduction of PSA screening. By dividing the study population into 15 birth cohorts and into 15 regional populations, we aimed to assess whether the rise in incidence was correlated with the fall in mortality.

Our results do not show the anticipated inverse correlation between the differences in incidence rate and the differences in mortality rate. In fact, in both study populations, even if the rate differences were in the expected direction (increase in incidence and decrease in mortality), the sizes of the changes were not negatively correlated. In other words, we did not observe that a larger increase in incidence, due to PSA screening, was associated with a larger fall in mortality 6 years later.

These results need to be considered with caution. First, we relied on a single year for the increase in incidence (1993) and a single year for mortality reduction (1999). In fact, the change in incidence of any single year should be
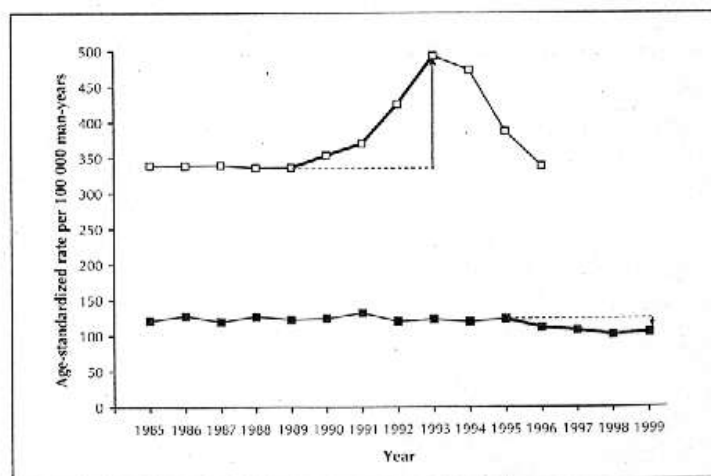

Fig. 1: Age-standardized incidence rates (white squares) and mortality rates (black squares) for prostate cancer among men in Quebec, aged 50–85 years.

reflected downstream over several years. Moreover, we did not measure directly the degree of exposure to PSA screening. There is, however, a clear consensus among health researchers that the changes in prostate cancer incidence rates in the early 1990s are good indicators of the extent to which PSA testing was used for screening purposes.[14,15] Second, because prostate cancer incidence and mortality rates are strong functions of age, the correlation performed with the birth cohorts might be distorted by age, even though we took aging into account while computing the rate differences. Nevertheless, the correlation test performed with the rate differences of the 15 regions is not limited by this, because in this case all the rates were age-standardized. Finally, it is probable that the completeness of the Quebec cancer registry with regard to this cancer decreased over the study period, because individuals with prostate cancer were being managed increasingly as outpatients and the Quebec cancer registry relies exclusively on hospital discharge sources. This underestimate of prostate cancer cases should affect all age groups and all regions equally.

Other researchers have studied the possible relation between PSA screening and the decline in the rate of prostate cancer mortality and have suggested that there is no link between the intensity of screening activities and the recent decrease in prostate cancer death rates. Etzioni and colleagues addressed the question of whether the PSA tests conducted in the late 1980s and early 1990s could provide a reason for the decline in prostate cancer mortality observed from 1992 through 1994 in the United States.[11] Using simulation models, they showed that if PSA screening reduced prostate cancer mortality by 20% over 10 years (as postulated in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial[16]) and if the mean lead time (time by which diagnosis is advanced by screening) was close to 3 years, PSA screening could explain most or all of the decline in prostate cancer mortality since 1991 in the United States. However, using the hypothesis of a 5-year lead time, which better corresponds to

our current knowledge about the mean lead time associated with initial PSA screening[17] (the lead time for repeat screens is much longer), PSA screening could not explain the recent decline in prostate cancer mortality rate.[11]

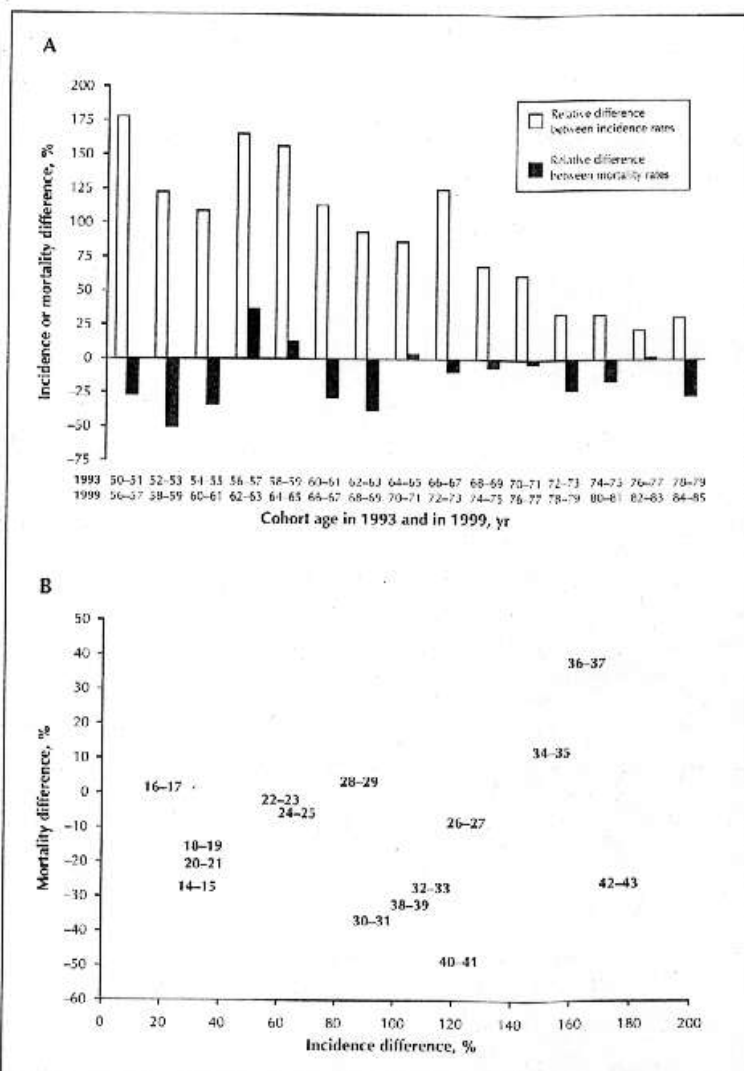In another study, Oliver and colleagues compared data

Fig. 2: (A) Relative differences between observed and expected prostate cancer 1993 incidence rates (incidence difference) (white bars) and relative differences between observed and expected prostate cancer 1999 mortality rates (mortality difference) (black bars) for each birth cohort (born from 1914/15 to 1942/43). (B) Scatter plot of the incidence differences and the mortality differences in the 15 birth cohorts. The numbers in the figure correspond to the last 2 digits of the years of birth of the men in each cohort (e.g., 22–23 refers to the cohort of men born in 1922/23 and therefore aged 70–71 years in 1993 and 76–77 years in 1999). Weighted Pearson's product-moment correlation coefficient = 0.33 (1-sided p = 0.89)

from the United States with those from England and Wales with regard to age-standardized prostate cancer incidence and mortality rates.[12] The authors noted that in spite of very divergent trends in inc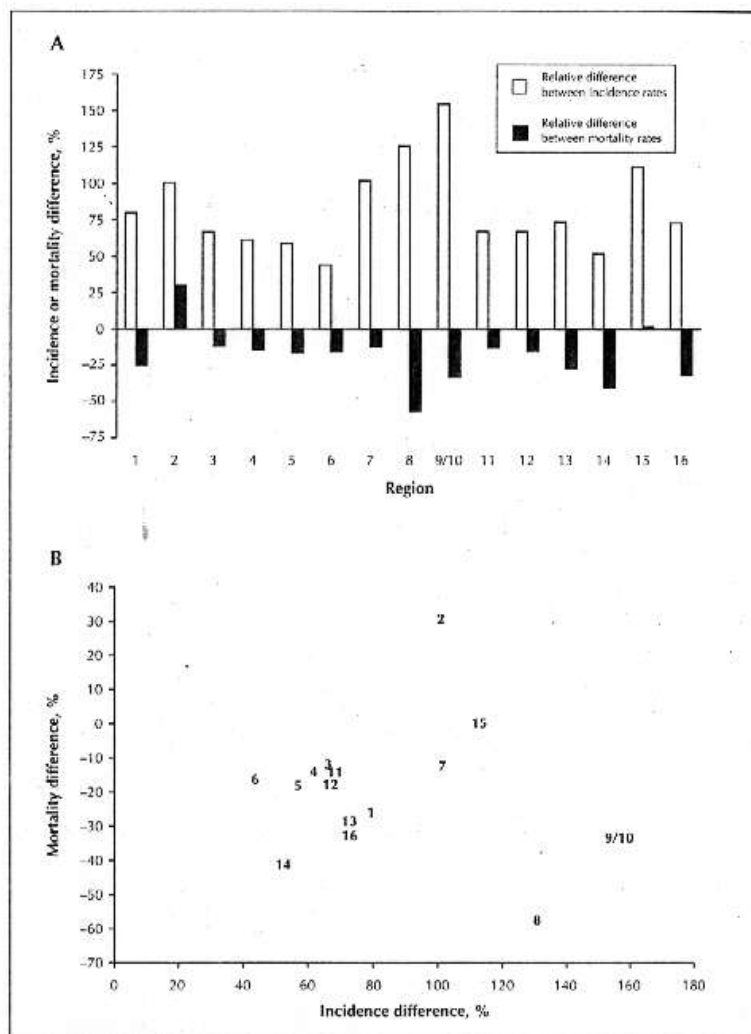idence reflecting a different use of PSA testing, a similar reversal in secular mortality trends was observed in the United States, England and Wales between 1991 and 1997. They, thus, concluded that falling death rates in the United States did not, for the moment, support claims for the effectiveness of prostate cancer screening.

Randomized trials that address the issue of the efficacy of screening for prostate cancer are underway in Europe and in North America.[18] Only one group has published preliminary results, and these suggest that PSA screening markedly reduced prostate cancer mortality up to 5 years after screening.[19] However, in this report, most of the results did not come from the comparison of screened and unscreened groups as randomized, and they may reflect more bias than real efficacy.[20,21] Moreover, when the groups formed by randomization were compared, prostate cancer mortality rates were identical in the 2 groups.[21]

Therefore, in accordance with the observational studies described here, our results do not support the hypothesis that the present decline in prostate cancer mortality is attributable to PSA screening. If PSA screening is effective in preventing or postponing death from prostate cancer, its impact at a population level has yet to be felt. Moreover, there may be other explanations for the recent decline in prostate cancer mortality, consisting primarily of changes in disease management and in hormonal treatment of advanced disease.[22,23]

Fig. 3: (A) Relative differences between 1993 and mean 1986/89 age-standardized prostate cancer incidence rates (incidence difference) (white bars) and relative differences between 1999 and mean 1992/95 age-standardized prostate cancer mortality rates (mortality difference) (black bars) for each region. Codes for regions: 1 Bas St-Laurent; 2 Saguenay; 3: Quebec City; 4 Mauricie et Centre-du-Québec; 5 Estrie; 6 Montreal; 7 Outaouais; 8 Abitibi; 9/10 Côte-Nord and Nord-du-Québec; 11 Gaspésie; 12 Chaudière-Appalaches; 13 Laval; 14 Lanaudière; 15 Laurentides; 16 Montérégie. Weighted Pearson's product-moment correlation coefficient = 0.13 (1-sided $p = 0.68$). (B) Scatter plot of the incidence differences and the mortality differences in the 15 regions. The numbers in the figure correspond to the Quebec regions as outlined above.

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Annexe 2 : Article scientifique analysant la validité de la banque de données des réclamations pharmaceutiques de la RAMQ

Tamblyn R,Lavoie G, Petrella L, Monette J. The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Quebec, J Clin Epidemiol 1995, 48 (8):999-1009.

THE USE OF PRESCRIPTION CLAIMS DATABASES IN PHARMACOEPIDEMIOLOGICAL RESEARCH: THE ACCURACY AND COMPREHENSIVENESS OF THE PRESCRIPTION CLAIMS DATABASE IN QUÉBEC

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Abstract—Despite the potential benefits of using prescription claims databases for pharmacoepidemiological research, little work has been reported on the nature of available information or its accuracy. The purpose of this study was to describe information contained within the prescription claims database in Québec, and to assess the accuracy of drug information that might be used to monitor drug exposure and physician prescribing. The comprehensiveness of the prescriptions claims database was assessed by examining 1,917,214 records of dispensed prescriptions for a regionally stratified random sample of 65,349 Québec elderly in 1990. We found that values in key fields (individual identifiers, drug, quantity, date dispensed and duration) were missing or out of range in 0–0.4% of records. The accuracy of data were examined in 723 prescriptions filled by 306 elderly patients attending one internal medicine clinic. Of these prescriptions, 83% were filled by the patient and correctly identified the patient and drug and in 89% of these 599 records, the prescribing physician was correctly identified. The quantity and duration of the prescriptions were accurate in 69.1% and 72.1% of records, respectively. We conclude that the prescription claims database in Québec may represent one of the most accurate means of determining drugs dispensed to individuals. There may be limitations in using this database for dosing information.

INTRODUCTION

Over the past 50 years there has been an exponential growth in the number of drugs available for the treatment and prevention of disability and disease. Over 20,600 drugs have been approved for marketing in Canada and, in 1991, 9.9 billion of the total 66.8 billion dollars in Canadian health care costs was spent on prescription medication [1]. Rising drugs costs and fiscal constraints in health care budgets have inspired a growing interest in post-market assessment of drug utilization and effectiveness.

The most accurate and efficient methods of evaluating this aspect of medical care in the population have not been clearly defined. In particular, there has been some debate over the potential utility of using existing administrative prescription claims databases rather than primary data collection for drug monitoring [2].

The data collected in the administration of the universal government health insurance plan in Canada has provided unprecedented opportunities to conduct population-based studies of health care utilization [3–7] and health outcomes [8–10]. As part of this insurance plan all Canadian provinces cover the cost of

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prescription drugs for individuals 65 years of age or older and for individuals receiving social assistance [1]. Provinces vary in their lists of insured drugs (provincial formularies), as well as in the type of data that is administratively retained in relationship to the reimbursement of drug claims. Information in the prescription claims databases is only available for drugs dispensed from community pharmacies. Drugs dispensed to patients during hospital or nursing home stays are covered by institutional global budgets and thus are not included in records of reimbursed prescriptions in claims data.

Only Saskatchewan has information about drugs dispensed to the entire population [1, 12], but most other provinces retain sufficient data to allow drug utilization to be assessed in the elderly. The potential to study utilization among the elderly is important because 40% of all prescriptions are dispensed to seniors [13] and there is a relative absence of empirical information on the effectiveness of drugs in this age group [2]. In addition, increasing use of drugs with age and age-related changes in drug metabolism and excretion makes the elderly particularly vulnerable to adverse drug-related events [14, 15].

Records of dispensed prescriptions do not provide as accurate an assessment of drug exposure as biologic indicators. However, Inui *et al.* [16] demonstrated that auditing prescription refills among veterans provided a reasonably precise estimate of drug serum levels. Thus records of dispensed prescriptions may potentially be used in post-market assessment of drug exposure. In fact, since medication histories are often incomplete [17], and over half of elderly patients may have difficulty recalling their medication [18–22], database records of dispensed prescriptions may represent one of the most accurate methods of assessing drug utilization in this population.

As illustrated in a number of studies [20, 21, 23–25], prescription database information can be linked to other health care databases allowing the adverse effects of potential exposure to different drugs to be assessed.

The prescribing patterns of physicians have been recognized as an important determinant of drug utilization and drug costs in a population [26–29]. Physicians vary in their propensity to prescribe [30, 31], and only part of this variation appears to be explained by their practice population [32–34]. Furthermore, there is consistent evidence that suboptimal prescribing is respon-

sible for an important proportion of admissions for drug-related illness [35–39], and that a disproportionately small number of physicians are responsible for the majority of inappropriate prescriptions [40, 41]. Methods of conducting utilization and quality control reviews of prescribing practice are considered desirable [42]. As medical charts have notoriously incomplete information on prescribed medication [17–43], prescription claims databases may represent a more accurate means of documenting an individual physician's prescribing patterns.

Despite the potential benefits of using provincial prescription databases for research, little work has been reported on the nature of available information or its accuracy. The purpose of this study was to describe information contained within the provincial prescription claims database in Québec, and to assess the accuracy of drug information that might be used to monitor drug exposure and physician prescribing.

METHODS

Description of the Québec prescription claims data

To assess the comprehensiveness and quality of information provided in the Québec prescription database, we took a regionally stratified random sample of 65,349 elderly from the registry of insured individuals in the province in 1990 [44]. All prescription records for these individuals from 1 January, 1990 to 31 December, 1990 were retrieved for the prescription claims files of the Régie de l'assurance maladie du Québec (RAMQ), the government body responsible for medicare registration and the payment of prescription claims and physician services. The description and reporting requirements for each field in the prescription record was determined by reviewing relevant government documents [45, 46], and by information provided by administrative personnel within the Conseil consultif de pharmacologie, and the RAMQ. Frequency distributions were used to estimate the percent of missing and out of range data in each field as well as the characteristics of prescriptions dispensed for persons in this age group.

Accuracy of RAMQ data regarding drug, duration, quantity and prescribing physician

We used a second study sample to assess the accuracy of information retained in the

prescriptions claims database. Prescriptions written for the 311 elderly patients who attended the internal medicine clinic of the Royal Victoria Hospital over a 3 month period were compared with prescription claims for these same patients in the files at the RAMQ. The hospital provided consent to access patient files, and the clinic physicians provided consent to access their prescription files for these patients from the RAMQ. Prescriptions for these 311 patients were retrieved from clinic files and coded by medicare number, date, drug identification code, quantity, and duration. When a prescription included multiple refills, only the quantity and duration of the first prescription was coded.

Since the date the prescription was filled by the patient was not known, two time intervals were used to query the RAMQ file for these prescription records: a dispensing date that allowed 1 week for the prescription to be filled (time interval 1), and a dispensing date that allowed 1 month for the prescription to be filled (time interval 2). A two step linkage process was used. First, we linked abstracted clinic prescriptions with RAMQ prescription records by patient medicare number and drug identification code number. This provided us with an estimate of the proportion of prescriptions which were (a) filled by the patient, and (b) where patient medicare number and drug identification number were correctly coded. In the second step, we attempted to link records successfully matched in the first step by prescribing physician identification number. This step provided additional information on the proportion of records that accurately identified the prescribing physician. Records that were not linked in this second step were reviewed, and inaccuracies in prescribing physician identification were categorized into one of three groups: (1) transposition errors (all numbers in the 7 digit physician identification were correct except for one number), (2) misattribution of the prescribing physician by the pharmacist (two or more digits of the prescribing physician number were incorrect), and (3) researcher coding errors (the number for the prescribing physician in the RAMQ files was the number of another prescribing physician in the clinic from which the data were abstracted). The accuracy of the quantity and duration of prescribed medication, fields which would be used in daily dose estimation, was assessed using records successfully linked by medication code, prescribing physician and patient. Differences in the recorded quantity and duration in the RAMQ files and prescription data were estimated. Frequency distributions were used to summarize the data on linked and unlinked records. Chi-square tests were used to determine if differences in the proportion of records linked for individual physicians could be attributed to chance.

RESULTS

Description of the RAMQ database

In 1990, 753,446 of the estimated 770,925 elderly in Québec were registered with RAMQ and thus were eligible for the provincial drug plan [44]. In the same year, 1453 community pharmacies invoiced the RAMQ for drugs dispensed to Québec residents. Most prescription claims were submitted in electronic form [2] where billing software packages are used to screen for missing and out of range data. A description of the data retained by the RAMQ for each prescription record is summarized in Table 1. We found that the percent of missing or out of range data for prescription information was very small. In 7520 (0.4%) of the 1,917,214 prescription records retrieved, the patient's medicare number was incorrect and no payment was provided for these prescriptions. For the remaining information, missing or out of range data varied from 0 to 0.7%. In approx. 5000 records in which information was declared as missing, the relevant data would have been found in the first record of a multiple record pharmacy preparation. As we have no way of grouping these records, we are likely overestimating the amount of missing data.

In Table 2, the characteristics of all prescriptions dispensed to the sample of 65,349 elderly are summarized. Two-thirds of all prescriptions were for diuretic, cardiovascular, psychotropic or non-steroidal anti-inflammatory drugs, the five most common drugs being from these respective categories. The vast majority of prescriptions (94.5%) were for 30 days or less. Most dispensed prescriptions were based on a written order by a physician practicing within the province (98.9%). Two-thirds of prescriptions were for refills of a previous order and in 12.4% of instances the prescribed drug was substituted by the pharmacist with a generic product.

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Table 1. Description of the prescription claims database of the Régie de l'assurance maladie du Québec and the frequency of missing and out of range values for each variable in a random sample of 1,917,214 claims

Variable	Required for payment	Description	Missing/out of range values
Patient identification	Yes (must be the medicare number of eligible cardholder)	Each medicare registrant is given a unique 12 digit medicare number which is comprised of the first three letters of the last name, the first digit of their first name, the birth year, month, and day (for birth month, 50 is added to distinguish females from males), and two additional numbers which ensure that the individual's identification is unique. In Québec, females are legally required to retain their maiden name for all civilian records. The patient's medicare number is recorded by the pharmacist for each prescription claim.	7520 (0.4%)*
Special consideration	Yes (in specific) circumstances)	In a few exceptional circumstances, a medicare number will not be known and therefore will not be recorded on the prescription claim. In these instances, the pharmacist will record the individual's name and address and record a specific code for the reason in the special consideration column: "D" for dispensing in an emergency situation, and "C" for dispensing to an individual under 1 year of age. In addition, this field is used to designate a "rebilling" for a claim (designated "B") when a previous claim was denied because of missing data in one or more fields.	no entries in this field
Prescribing physician identifier	Yes (must be the license number of licensed MD, dentist or optometrist)	Each prescription claim contains an identification number for the prescribing physician, dentist or resident. For prescribers who are licensed in Québec, the identification number is the individual's professional license number, a seven digit code comprised of the individual's year of medical school graduation along with a unique identifier. For physicians who ar not licensed in Québec, the pharmacist enters the name and address of the prescribing physician, and a code of 1111111 is assigned by the RAMQ (i.e. the physician number is not unique). The only exception to this rule is for physicians who are licensed in another province but have registered with the RAMQ because they frequently provide services to Québec residents who live close to the provincial borders. The identification number for these physicians is unique and reflects the same information as those licensed in Québec.	0% (no codes = 1111111)
Dispensing pharmacy identifier	Yes (must be the number for a registered pharmacy in Québec or within 36 km of Québec, and a licensed pharmacist in Québec or registered with registered with the RAMQ)	Each prescription claim contains a unique 6 digit identification number for the dispensing pharmacy. The first two digits identify the location of the pharmacy (inside or outside of Québec), and the remaining 4 numbers provide unique identification. Pharmacies outside of Québec, but within 36 km of the Québec border, are registered if they accept the Québec fee schedule for dispensing claims. A unique 7 digit identification number is recorded on each claim for the dispensing pharmacist which represents the pharmacist location (inside or outside of Québec), and the pharmacist's license number provided by the Ordre des Pharmaciens.	0%
Date dispensed	Yes (date must be entered and within the eligible time window for payment)	On each record of a dispensed prescription, the pharmacist records the date (year, month, day) that the drug was dispensed, and the RAMQ standardizes this in the Julian date format (e.g. 93/02/25 is converted to 93056). The pharmacist must invoice the RAMQ for dispensed prescriptions within 3 months of the dispensing date to be eligible for payment. If a claim is incomplete or incorrect, the pharmacist has 3 months from the non-payment notification date to resubmit the corrected claim to the RAMQ.	0%
Drug class	No	With the exception of "non-drugs", restricted medication, pharmacy preparations, and pharmacists' services, all drugs in the Québec formulary are categorized by the American Hospital Formulary System. The drug class is automatically assigned to a prescription claim on the basis of the drug identification number by a computer program at the RAMQ. For the special category of pharmacy services and preparations, medication supplies, and restricted medication, a drug class code of 99 is used.	0%

Table 1—*continued*

Variable	Required for payment	Description	Missing/out of range values
Drug code†	Yes (must be a valid DIN number listed in the provincial formulary or other accepted service code listed in the pharmacist's manual)	For each dispensed prescription (or service), the pharmacist records an 8 digit drug identification number (DIN) for the product (or service) dispensed. This code identifies the name of the product, the unit dose, the manufacturer, the form, and the unit cost (e.g. DIN # 00012718: Dalmane, 30 mg, Roche, capsules, $0.1436). One record is created for each product (or service) dispensed. The only exception is for pharmacy preparations (médicaments magistraux) where one record is submitted for each component of the prepared drug (e.g. for Ventolin: Record # 1 = médicament magistral, DIN # 999830, quantity-60, duration-15; Record # 2 = ventolin sol. inh., DIN # 334227, Record # 3 = saline solution, DIN #906816). There is no certain method which could be used to identify and group all of the records belonging to a pharmacy preparation.	0%
Quantity	Yes (few exceptions)	For each dispensed prescription the pharmacist records the quantity dispensed using a 5 digit field with two decimal places which are used to record the exact quantity of liquid preparations and suspensions. The only time that the quantity is not required for payment is for pharmaceutical services (e.g. refusal to fill a prescription, pharmaceutical opinion).	7504 (0.4%)
Duration	Yes (few exceptions)	For each dispensed prescription, th pharmacist records the duration of the prescription. For PRN prescriptions, the pharmacist records the minimum number of days required to complete the prescription assuming that the patient took the medication on every occasion in which it was prescribed (e.g. Ativan 5 mg hs prn, 30 tabs would be given a value of 30 days for duration). The only time that prescription duration does not have to be recorded for payment is for pharaceutical services, and for multiple records submitted for a pharmaceutical preparation. With the latter, only one of the possible 3–5 records for component substances in a pharmaceutical preparation must contain a recorded duration.	0 (0.0%)
Type of order (verbal, written)	Yes (few exceptions)	For each prescription dispensed, the pharmacist indicates whether the order was provided verbally or in writing. Similar to duration and quantity, type of order does not have to be recorded for pharmaceutical services, or for more than one record submitted for a multi-record pharmaceutical preparation.	12,973 (0.7%)
New Rx or refill	Yes (few exceptions)	For each prescription, the pharmacist indicates whether the prescription was a new prescription or a refill (renewal) of a previous prescription. New prescription does not mean a "new drug" for the patient, only a new order (as opposed to a refill from a previous order). The exceptions are the same as those for type of order and duration.	12,934 (0.7%)
Substitution	Yes (few exceptions)	Unless the physician writes "no substitution" on a prescription, the Québec drug plan will pay for the median cost of a drug in a specific group. The only exceptions to this rule are for restricted medications. Thus, the pharmacist may substitute a generic equivalent for a drug prescription which is above the median cost category, or ask the patient to pay for the difference in cost. For each dispensed prescription, the pharmacist records whether the original prescription was dispensed (code = 00), the original prescription was substituted with a generic drug (code = 03), the original prescription was dispensed which was above the median cost category because the physician wrote "no substitution" (code = 04). Exceptions are the same as for type of order and duration.	0 (0.0%)

*For 7520 prescription records, the RAMQ found that the patient's medicare number was incorrect (could not be found in the file or medicare registrants). Both incorrect and corrected records are retained in the prescription database. For these incorrect records, the RAMQ substituted zeros for all fields as these patients and information about these patients could not be adequately identified before sending the files to the investigators.

†The provincial formulary of insured drugs is published every 6 months. A diskette copy of the formulary and the pharmacy manual may be purchased from: Communications Services, Règie de l'assurance-maladie du Québec, P.O. Box 6600, Québec city, Québec, Canada G1K 7T3.

Payment made for each claim is retained by the RAMQ. It was not included in the data provided to the authors but is available.

Table 2 Description of 1,917,214 prescription records from the RAMQ database for 65,349 elderly in the province of Québec in 1990

	Frequency (%)
Drug class	
8:00 Anti-infectives	2.6
10:00 Antineoplastics	0.3
12:00 Autonomic nervous system medication	3.3
20:00 Coagulants/anticoagulants/iron	0.4
24:00 Cardiovascular medication	23.4
28:00 Central nervous syste medications	31.0
36:00 Diagnostic agents	0.5
40:00 Diuretics & electrolytes	13.5
48:00 Cough medication	0.0
52:00 Eye, ear, nose, throat medication	4.6
56:00 Gastrointestinal system medication.	4.1
60:00 Gold salts	0.0
64:00 Heavy metal antidotes	0.0
68:00 Hormones & their substitutes	7.7
76:00 Ocytocics	0.0
84:00 Skin, mucous membrane medication	3.4
86:00 Spasmolytics	2.5
88:00 Vitamins	0.7
92:00 Unclassified medications	1.1
99:00 Special classes	0.0
Diet supplements	1.0
Restricted medication	0.0
Pharmacy preparations & Adjunct agents	0.2
Medication supplies (e.g. syringes)	0.1
Pharmacist services & consults	0.7
Five most common medications	
Acetysalycylic acid	5.4
Lorazepam	5.0
Digoxin	3.4
Diltiazem	2.7
Triameterene	2.5
Prescriptions with generic substitution (%)	12.4
Prescription duration	
< 30 days	30.2
30 days	64.3
31–60 days	3.9
61–120 days	0.7
> 120 days	0.1
Type of order	
Verbal	13.9
Written	85.0
Type of prescription	
New	29.0
Refill	69.9
Prescriber	
Physician in Québec	98.9
Physician outside of Québec	0.5
Dentist	0.1
Resident/intern	0.2

Accuracy of the RAMQ data

In the 12-week period of data collection, 731 prescriptions were written for the 311 elderly patients who visited the internal medicine clinic. To assess the representativeness of these prescriptions, we compared the profile of drugs prescribed to elderly in the clinic with the prescription profile of our population-based sample of 65,349 elderly. The distribution of drugs prescribed in the internal medicine clinic was similar to the distribution seen in the Québec elderly population (Table 3). Slightly more than two-thirds of prescriptions (78%) were for cardiovascular medication, diuretics, or central nervous system drugs (Psychotropic medication, non-steroidal anti-inflammatory medication). Four of the five most common drugs prescribed in the database sample were also included in the top 6 drugs prescribed in the clinic. The only systematic difference seen between the two study samples was in the duration of prescriptions. Although the median prescription length was virtually identical for the major drug classes, almost three times as many clinic prescriptions were written for over 30 days in comparison to prescriptions in the database sample.

The medicare numbers for 5 of these 311 patients could not be found in the RAMQ files at the time of data retrieval and linkage. In subsequent re-verification of these patient's medicare numbers, two medicare numbers were miscoded by the research assistant, and for the remaining 3 patients, the medicare card had expired.* These 5 individuals and their 8 prescriptions were removed from subsequent analysis. Among the remaining 723 prescriptions records for 306 patients, 77% were recorded as being dispensed in 1 week and 83% of these prescriptions were dispensed within 1 month of the prescription date (linked successfully by patient medicare number and drug identification number) (Fig. 1). The remaining 124 prescriptions could not be found either because the patient did not fill the prescription or because the patient's medicare number or drug identification number was miscoded.

We evaluated the proportion of prescriptions found for patients of each prescribing physician

Table 3. A description of the 723 internal medicine clinic prescriptions included in the assessment of RAMQ database accuracy

	Frequency (%)	Rx duration for Medical clinic prescriptions		Typical Rx duration in sample of 1,917,214 Rx	
		Median	† > 30 days	Median	% > 30 days
Drug classes represented					
Cardiovascular medication	34.9	30	11.0	30	4.8
CNS medication	26.4	30	21.7	30	3.9
Diuretics & electrolytes	16.6	30	10.7	30	4.4
Hormones & substitutes	8.3	30	13.3	30	8.7
Gastrointestinal meds	5.5	30	12.5	30	3.8
Anti-infectives	2.5	10	0	10	1.7
Vitamins	1.4	30	33.3	30	12.7
Anti-coagulants/iron	1.1	30	12.5	30	9.5
Unclassified medication	1.1	30	0	30	6.3
Auto. nervous system meds	0.7	30	20.0	20	2.5
Spasmolytics	0.7	30	20.0	30	3
Skin preparations	0.4	7	0	10	1.9
Antineoplastic	0.1	30	0	30	6.7
Ten most common drugs					
Acetysalacylic acid	8.9				
Enalapril	6.5				
Hydrochlorathiazide	5.8				
Lorazepam	5.4				
Diltiazem	4.4				
Digoxin	4.1				
Potassium chloride	4.1				
Furosemide	3.9				
Levothyroxin	3.7				
Nifedepine	3.3				
Glyburide	2.5				
Lovastatin	2.2				
Isosorbide dinitrate	2.2				

Note: the denominator used to calculate the frequency of specific drugs was 727 because 5 drugs prescribed by physicians in the internal medicine clinic were combination products (e.g. coryphen: ASA + codeine). These drugs were assigned two drug codes, one to represent each of the active components in the medication.

(Table 4). If coding errors in patient identification or drug identification number were responsible for the 124 unlinked prescriptions, the percent of prescriptions that could not be linked should be similar for all physicians (i.e. randomly distributed). This was not the case. There were significant differences in the proportion of prescriptions found for the patients of each physician ($p = 0.0001$), varying from a low of 47.8% for physician 'D' to 96.9% for physician 'I'. These findings suggest that a failure to fill the prescription, rather than coding errors, was a more likely explanation for the majority of prescriptions which were not found in the RMAQ database.

The identification of the prescribing physician was accurately recorded in 89% of the 599 prescriptions that were successfully linked by patient medicare and drug identification number in time interval 2 (Fig. 1). As 19% of the recording errors in physician identification were made by researchers, the pharmacist accurately recorded the prescribing physician identification in 91% of records. In the 55 prescription records where pharmacy errors were made in physician identification, 43.6% were transposition errors and, in the remainder, a different prescribing physician was identified.

Among the 531 prescription records that accurately identified the patient, drug and prescribing physician, the quantity prescribed was accurate in 69.1% of instances, and the prescription duration in 72.1% of instances. Misclassification errors were not randomly distributed. It was five times more likely that the quantity and duration of a prescription was for less than the prescribed amount than for more.

DISCUSSION

In this study, we evaluated the comprehensiveness, completeness and accuracy of the prescriptions claims database in one Canadian province. We found that information contained
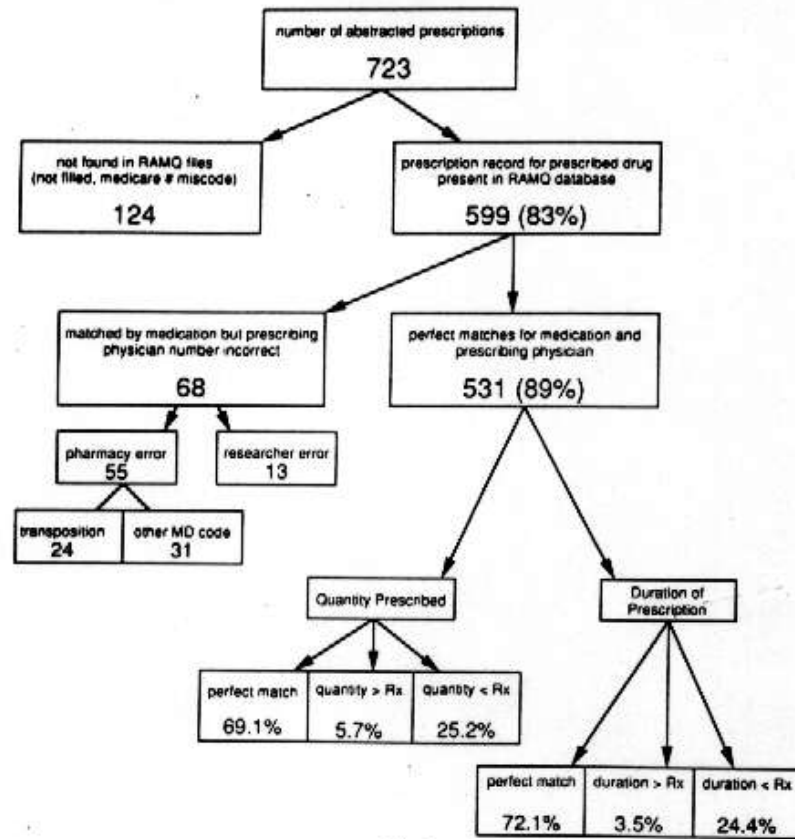
Fig. 1

in a random sample of 1,917,214 records for 65,349 elderly patients in Québec was remarkably complete, with less than 1% of information being out of range or missing. The integrity of this database is likely related to the policy to refuse payment for a dispensed drug unless all mandatory fields are completed and within range. In turn, most pharmacies use billing agencies and software to minimize errors in recording information about drugs dispensed. Perhaps for this reason, the accuracy of information recorded in the database is equivalent or

Table 4. The distribution of records successfully matched between clinic prescriptions and the RAMQ database by prescribing physician and time interval

Prescribing physician	Abstracted clinic prescriptions		Matched in time interval 2 (allowing 1 month to fill the prescription)	
	Number of patients	Number prescriptions	Number of patients	Percent of prescriptions found
A	7	18	5	77.8
B	37	67	22	61.2
C	32	79	25	82.3
D	12	23	7	47.8
E	36	73	30	69.9
F	64	144	45	82.6
G	24	53	19	77.4
H	43	136	30	70.6
I	16	32	13	96.9
J	5	12	4	83.3
K	30	86	22	60.5
Total	306	723	222	73.4

Records were matched by patient medicare number, prescribing physician number and drug identification code number.

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better than that reported for many registries that use primary data collection methods [8, 47, 48]. In this study, for at least 83% of the prescriptions written, the RAMQ files correctly recorded the drug and patient, and in 89% (or 73% of the total), the prescribing physician was also correctly identified. As an estimated 10% of patients do not fill prescriptions given to them during office visits [49], the actual accuracy of the data recorded by the RAMQ is probably substantially higher than 83%. Thus prescription claims data may provide a reasonably accurate measure of potential drug exposure for patients. In regular and long term drug therapy (such as for hypertension), refill rates could be used as a measure of 'compliance' or drug exposure over time.

In many studies of drug exposure and outcome, it is of interest to evaluate dose–response. In the RAMQ prescription database, average daily dose prescribed can be estimated by using three variables: the unit dose of the drug provided by the drug identification number, the quantity dispensed and the duration. We found that quantity and duration were accurate in 69% and 72% of prescription records, respectively, and that 88% of all misclassification errors were for less than the prescribed quantity and duration. The most likely explanation of this finding is that the pharmacist split a 60 or 90 day prescription into 2–3, 30 day supplies. Pharmacists cannot dispense more than is prescribed, but a pharmacist can restrict the amount dispensed in any one prescription. By splitting longer duration prescriptions, a pharmacist can: (1) carry out more regular monitoring of patient compliance, (2) reduce available supplies of drugs that may be misused or abused, and (3) minimize financial penalties inherent in dispensing more than a 30 day supply of a medication. With respect to the latter, a pharmacist would receive a dispensing fee of $8.60 for filling a 90 day prescription. If the 90 day prescription were split into three, 30 day supplies, the pharmacist would receive three dispensing fees for a total of $25.80. If it is assumed that the pharmacist split the prescription in all instances where dose and duration was less than the prescribed amount, then dose may be accurately estimated in 94.3% of prescriptions. Unfortunately, we were unable to confirm our hypothesis that misclassification errors in quantity and duration of a prescription were due to prescription splitting by the dispensing pharmacy. The validity of the dosing information in the prescription files should be examined in future research.

In this study we were interested in estimating whether prescription claims data could be used to profile the prescribing patterns of individual physicians. We found that in 89% of the records the prescribing physician was accurately identified, 91% if we delete researcher errors. Inaccuracies in recording the prescribing physician likely occur in instances where the physician number cannot be adequately deciphered, or when another physician who has prescribed previously for the patient is recorded by the dispensing pharmacist. In future, the advent of electronic prescriptions may result in more accurate information on the prescribing physician.

There are limitations in the RAMQ database that are important to note. Although medications prepared by the pharmacist represent a small proportion of all prescription records, data on the quantity and duration of these prescriptions cannot be retrieved because there is no method of grouping the 3–5 records which may be submitted for a pharmaceutical preparation. Drugs prescribed during periods of institutionalization would not be recorded in the database, and approximately one third of elderly individuals are admitted to a health care institution for some period of time during each year [44]. Also, no information is available on the use of over the counter medication, the clinical indication for a drug prescription, drug compliance, and other relevant patient information.

Finally, since we only studied the accuracy of 723 prescriptions written by 11 physicians for 306 patients at one center, our findings about the accuracy of drug, prescriber and dosing information must be interpreted cautiously. Our small sample may not be reflective of the entire prescribing and dispensing population.

CONCLUSIONS

The prescription claims database in Québec provides reasonably accurate information on drugs dispensed to seniors in the Québec population and the prescribing physician however there may be limitations in using this database for dosing information. Prescription claims data represent a rich potential resource for researchers and policy-makers in studying drug utilization and prescribing patterns. If these databases are coupled with primary data collection, and data from other health care databases,

they could provide the opportunity for population based studies of drug effectiveness.

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