The Incidence and Prevalence of Hypertension in the Province of Quebec

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Abstract

The objectives of this study were to estimate the prevalence, incidence and lifetime risk of developing hypertension after a given age in the Province of Quebec. An administrative database was used to form a cohort of 20,000 subjects selected in 1987 from a random sample of individuals aged 45 or older, living in the Province of Quebec. These individuals were followed from 1986 to 2003. Incident cases of essential hypertension were selected on the basis of an outpatient diagnosis of hypertension. The Framingham approach was used to calculate incidence rate. The incidence of hypertension in the Quebec cohort was 22 per 1,000 person-years for men and 31 per 1,000 person-years for women; it was higher for women for all the age groups under study. The lifetime risk of developing hypertension for subjects who attained the age of 46 free of hypertension in the Quebec cohort was 66%; this was 20% higher for women than for men (72% compared with 59%). In the Quebec cohort, the incidence of hypertension is very high particularly for women. The data provide evidence that, in Quebec, detection of hypertension is to be maximized, for both men and women.

Résumé

Les objectifs de cette étude étaient d'estimer la prévalence, l'incidence et le risque à vie de développer l'hypertension dans la Province de Québec. Une base de données administrative a été utilisée pour former une cohorte de 20 000 sujets choisis en 1987 à partir d'un échantillon aléatoire d'individus âgés de 45 ans et plus et habitant la Province de Québec. Ces individus ont été suivis de 1986 à 2003. Les cas incidents d'hypertension essentielle ont été choisis en se basant sur un diagnostic de suivi d'hypertension à l'externe. L'approche de Framingham a été utilisée pour calculer le taux d'incidence. L'incidence d'hypertension dans la cohorte de Québec était 22 par 1000 personnes-années pour les hommes et 31 par 1000 personnes-années pour les femmes; l'incidence était plus élevée pour les femmes pour toutes les tranches d'age. Le risque à vie de développer l'hypertension pour les sujets qui ont atteint l'âge de 46 ans sans hypertension dans la cohorte était 66%; ce risque était de 20% plus élevé pour les femmes que pour les hommes (72% comparé à 59%). Dans la cohorte de Québec, l'incidence d'hypertension est très haute notamment pour les femmes. Ces données fournissent des évidences en faveur du fait qu'il faut maximiser la détection de l'hypertension au Québec, à la fois chez les hommes et chez les femmes.

Contributions of Authors

This thesis is structured around a manuscript submitted for publication, which is logically joined and integrated through supplementary and connecting text. As the first author, I was actively involved in the study design, analysis and interpretation of data, and drafting and critical revision of the thesis and manuscript. Dr. Louise Pilote, as thesis supervisor, contributed all stages of the research: funding and data acquisition, study planning and execution, interpretation of results and critical revision of the thesis and the manuscript. She also lent her expertise in the area of cardiovascular epidemiology. Dr. Nancy Mayo, as thesis committee member, was involved in data acquisition, interpretation of results and critical revision of the thesis and the manuscript. She also provided her expertise in the area of clinical epidemiology. Dr. Hassan Behlouli was involved in data management.

Suggested Short Title

Prevalence and Incidence of Hypertension in Quebec.

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Finally I wish to thank all the staff members at the Division of Clinical Epidemiology at the McGill University Health Center who also contributed their time and knowledge to this project.

Dedication

To my family, whose support and encouragement throughout my life has been an inspiration to me.

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Introduction

Cardiovascular disease is the most prominent cause of death for both men and women in industrialized countries. Hypertension has been identified as a major risk factor for cardiovascular disease in epidemiological studies (1, 2). Unfortunately, women are under-represented in most cardiovascular and hypertension studies (3). Based on cross-sectional data, men demonstrate a steeper increase in blood pressure with age than women before menopause. After menopause, women demonstrate a steeper increase among individuals aged 60 years or older; mean systolic blood pressure of women is higher than that of men. The overall prevalence of hypertension seems to be higher for women (4-6). However, the incidence of hypertension is less studied than prevalence. A sex difference in the prevalence and incidence of hypertension is conceivable, but too few data exist in this field for definitive conclusions.

Literature Review

Burden of Hypertension

Hypertension is a major public health problem. According to the Global Burden of Disease Studies, hypertension is the leading risk factor for mortality (1, 2) and is ranked third in contributing to disability-adjusted years of life lost. Hypertension was the most common primary diagnosis in the United States (US) in 2000 with 35 million physician office visits (6, 7). At least 65 million people in the United States in 2000 were diagnosed with hypertension (8). Hypertension was a primary cause and a contributing cause of approximately 277,000 and 2,440,000 deaths respectively in the US in 2003 (9). At least one in five Canadians has high blood pressure (10-12).

In a recent study (13), 68.9% of hypertensive patients in the US were aware of their hypertension, 58.4% were treated and only 31% were controlled. In Canada, the results were even worse, with only 16% of patients with controlled hypertension in 1992 (10), but there has been improvement in the past decade, with more than 65% of patients with controlled hypertension in 2006 (11). The low level of well-treated hypertensive patients is peculiar since the benefits of treating hypertension have been well studied in the past 20 years. The reduction of stroke (35-40%) and major cardiovascular events (21-50%) are substantial (6, 14): this reduction in major cardiovascular events is even more pronounced for diabetic patients, reaching more than a 50% risk reduction (15). As well, hypertension leads to considerable losses in terms of years of life lost, years of work lost, and costs (16). The estimated overall cost of high blood pressure in the US in 2006 was 63.5 billion dollars (9). Moreover, poor control of hypertension is associated with higher drug costs and more physician visits (17). Hence, aggressive treatment of hypertension might help reduce health care costs and resource utilization.

Given these impressive data, hypertension is a major target for intervention programs all over the world (18). However, some sub-groups appear to be at higher risk for hypertension, or to respond differently to antihypertensive treatment; an important subgroup are women (6). Indeed, women seem to be an ignored group (3) given the fact that women tend to have a higher prevalence (9, 13, 19) and incidence (20) of hypertension, but tend to have lower level of blood pressure treatment and control (13). Moreover, as can be seen in the next section, it is possible that hypertension is a different condition in women compared with men, with different patterns of occurrence, response to treatment and outcomes (4, 21, 22). Thus, there is an important need for original data in the field of hypertension in women (3, 19).

Sex Differences in Hypertension

Few data exist on sex differences in hypertension, but some studies support the theory that hypertension is different between men and women. There are biological differences between men and women that could explain the putative differences in prevalence, incidence, response to treatment and outcome of hypertension. In this section, the evidence supporting these potential biological differences will be reviewed.

, Some studies have shown that there is a striking age-dependent sexual dimorphism in the occurrence of hypertension (4, 5, 20, 23-25). Appendix 1 illustrates the prevalence of high blood pressure in Americans age 20 and older by age and sex, with data derived from the National Health and Nutrition Examination Survey (NHANES): 1999–2002 (4). As shown in Appendix 1, before menopause women have a lower prevalence of hypertension than men, but after menopause women tend to have a higher prevalence of hypertension than men (4, 5, 23-27). However, a recent analysis of the 30-year longitudinal data from the Framingham study show that blood pressure is lower for women than men at all ages, but this difference declines with aging (5, 28). However, in an earlier analysis of the Framingham study, post-menopausal women had a higher incidence of hypertension than men (23). Another important difference between men and women is the occurrence of pregnancy-related hypertension and eclampsia (29), in addition to hypertension induced by oral contraceptive use (4-6). Hence, the overall pattern of occurrence of hypertension is clearly different between men and women (4, 5, 25-27).

There is evidence that the outcome of hypertension differs between men and women. Post-menopausal women possibly have an increased occurrence of left ventricular hypertrophy, diastolic dysfunction, aortic stenosis, and isolated systolic hypertension compared with younger women and men (22). There is also evidence that hypertension causes stroke more frequently in elderly women compared with men of the same age, and that hypertension is a more potent risk factor for chronic heart failure in women (3, 26). Although there is a lack of data concerning the sex differences in the outcome of hypertension, these data suggest that a sex difference is conceivable.

There is some evidence that women and men may respond differently to some antihypertensive treatments (3-5, 21, 22). However, the evidence is weak, because most of the hypertension trials do not include large numbers of women: women typically comprise only 20% of patients enrolled (3, 30). Hence, hypertension trials do not have the statistical power to study sex differences. Nevertheless, there is little doubt that women benefit from blood pressure reduction (30). Antihypertensive treatment tends to be more effective in preventing stroke in women than in men (31-33), but tends to be more effective in preventing coronary events in men than in women (32).. In addition, some antihypertensive drugs appear to have sex-specific adverse event profiles (34). Overall, women report twice as many adverse events as men. They are more likely to develop diuretic-induced hyponatremia and hypokalemia, angiotensin-converting enzyme inhibitors (ACEI)-induced cough and calcium channel blockers (CCB)-related peripheral edema (5, 34).

The choice of antihypertensive treatment seems to be different between men and women in clinical practice: women use diuretics more frequently than men, whereas men use beta-blockers, ACEI and CCB more often (35, 36). These differences are difficult to explain since, to date, it is not known whether the outcomes of specific drugs in women are different from those in men, and current guidelines do not recommend treating women differently than men (6, 32, 37, 38). These differences may be explained by the greater incidence of side effects in women when using ACEI and CCB, the lower rate of fracture when using thiazide-type diuretics and the

greater prevalence of coronary disease in men under 50 years of age, making the use of ACEI, CCB and beta-blockers more indicated for men in this age group (32). Moreover, ACEI and angiotensin receptor blockers (ARB) are contraindicated in women who are or intend to become pregnant, because of the risk of fetal developmental abnormalities (4).

Current guidelines do not suggest treating women and men differently (6, 32, 37, 38), but some specialists disagree with this approach (3, 4, 21, 30, 32). Animal studies have shown that estrogen deficit increases the number of angiotensin II receptor I (39), and, in humans, the ARB candesartan appears to be better at lowering blood pressure in women, compared with enalapril and hydrochlorothiazide in a large randomized controlled trial (40). However, CCBs appear to be less effective in women (41). The previous studies on ARB and CCB did not compare men with women directly since there were only women that were randomized in that study. As a result, it is not known whether these effects are sex-specific (40, 41). In conclusion, there are data suggesting that some antihypertensive treatments can have a sex-specific effect, but, due to the rarity of data, current guidelines do not propose treating women differently than men.

Why can hypertension plausibly be considered a different disease in women compared with men? Appendix 2 illustrates the sex-specific declines in steroid hormone secretion (22). Pre-menopausal women have a decreased prevalence of cardiovascular disease compared with men and post-menopausal women. Female cardioprotection occurs during reproductive years when estrogen levels are highest, and declines after menopause as estrogen levels decline, after approximately 45–50 years of age (22). As well, the higher incidence of hypertension in men and post-menopausal women compared with pre-menopausal women, as shown in Appendix 1, has been associated with sex-related differences and the possible protective effects of the female sex hormones, estrogen and progesterone, as shown in Appendix 2 (22). Appendix 3 exhibits the effect of estrogen and testosterone on the renin-angiotensin system (42), and Appendix 4 displays the estrogen-stimulated endothelium-dependent mechanisms of vascular smooth muscle relaxation through genomic and non-genomic pathways (43). The complex net effect of estrogens appears to result in suppression of the potent renin-angiotensin vasoconstrictor system, as shown in Appendix 3, which could explain at least in part the higher prevalence of hypertension in post-menopausal women (42). As seen in Appendix 4, vascular effects of female sex hormones include genomic effects (inhibition of vascular smooth muscle proliferation and activation of endothelial cell proliferation, vasodilatation) and non-genomic effects (vasodilatation), while male sex hormone testosterone exhibits a less potent vasodilatation effect (44). Furthermore, testosterone has been shown to stimulate the renin-angiotensin system (Appendix 3) (22). Sex differences in the regulation of vascular function, through genomic and non-genomic effects, may partially explain the greater incidence of hypertension in men and post-menopausal women (44). Hence, the sex differences found in the occurrence, outcome and treatment effect of hypertension are highly biologically plausible. As shown in Appendices 1 to 4, hypertension in women may be related to a decline in endogenous female sex hormone during menopause since these hormones have been shown to be related to vasodilatation and protection from hypertension in pre-menopausal women (4, 22, 42, 43). The apparent protective effect of endogenous estrogens was recently challenged by the report of the Women's Health Initiative study which showed some adverse effects of combined conjugated equine estrogen plus progestin therapy on stroke and coronary artery disease (45). However, these results could be related to the type of hormones used. A large body of researchers still postulated that endogenous female hormones have beneficial effects (44).

Measurements of Hypertension Occurrence: Prevalence and Incidence.

In the next sections, data are presented on hypertension occurrence, the advantages and disadvantages of different study design to measure prevalence and incidence of hypertension are discussed.

Prevalence of Hypertension

Data on the prevalence of hypertension abound (20). Based on these studies, hypertension was recently found to be the third major disease associated with the highest burden on health in the world and the leading risk factor for mortality (1, 2). Internationally, the prevalence of hypertension varies considerably, from 20% to 50% (Table A and Table B). In general, an average prevalence of hypertension of 35% is considered to be standard. . Some reports showed that the trends in the prevalence of hypertension are variable, but increase over time. It is expected that the prevalence of hypertension will increase by at least 25% between 2000 and 2025 (1), but a recent study demonstrated that the rise in hypertension prevalence will far likely exceed this predicted prevalence by 2025 (12). This increase over time in hypertension prevalence is due in part to an increase in obesity, diabetes and life expectancy (12), but also to the decrease in mortality associated with hypertension in the past decade (46). Varying ages, ethnic and sex distributions across studies may explain the differences in the rise in prevalence. First, it is well known that the prevalence of hypertension increases with age (20). Second, racial differences exist: hypertension is higher in African Americans, but lower in Hispanic and Asian individuals than in Caucasians. Third, sex differences exist: men demonstrate a steeper increase in blood pressure with age than women before menopause. After menopause, women demonstrate a steeper increase. Overall, the prevalence of hypertension appears to be higher for men before age 60, but higher for women after 60 years of age (20, 23, 24).

In North America, hypertension appears to increase over time and to be higher in the United States than in Canada (Table A). However due to the high degree of variation in survey response rates, study design, age range and definition of hypertension in prevalence studies, it is difficult to draw accurate comparisons of prevalence between Canada and United States. The same limitations apply to the results obtained internationally (Table B) (20). Data about hypertension prevalence in developing countries are scarce, but it is expected that the largest increase in hypertension prevalence will be reached in these countries, because of the greater increase in the prevalence of obesity diabetes and life expectancy in these countries compared with industrialized countries (1). In Quebec, data about hypertension prevalence are limited; only one study shows that the proportion of hypertensive patients age > 45 years was approximately 20% in 1987 and 23% in 1998 (47).

Several study designs have been use to measure prevalence of hypertension. Prior population estimates for the prevalence of hypertension have been based largely on cross-sectional studies of blood pressure measurements (Table A and B). These cross-sectional studies are limited by their inability to follow patients or assess trends over time, because they are conducted only at a single point in time and involve a relatively small sample of patients. Moreover, methods using direct blood pressure measurement are costly and time-consuming. The occurrence of white-coat hypertension may also over-estimate the true prevalence in these studies. Self-report surveys may under-estimate the true prevalence of hypertension, because participants tend to under-report hypertension (48). It is impossible to estimate the incidence of hypertension with these designs. Studies using administrative databases also have their own limitations. Firstly, they do not capture actual blood pressure. Secondly, they usually use a non-

validated algorithm to identify hypertensive patients. Thirdly, they are unable to capture undiagnosed hypertension, because they rely on physician screening of patients for hypertension. Therefore, these studies require that patients use the healthcare system, and that physicians code accurately for hypertension. Hence, in general, studies using blood pressure measurements tend to over-estimate the prevalence of hypertension whereas studies using databases or surveys tend to under-estimate the prevalence of hypertension (Table A).

Prompted by the substantial under-estimation of the projection for hypertension prevalence (12), there is a need for recent studies on the prevalence of hypertension that would be well-designed using a validated method to measure directly blood pressure, validated databases and a validated definition of hypertension. Using a uniform study design will permit to compare more accurately different studies made in different part of the world.

Incidence of Hypertension

There is by far less data on the incidence of hypertension compared with its prevalence (Table C). Most of the data on the incidence of hypertension comes from the Framingham prospective cohort study (23, 49). Using the Framingham prospective cohort, two studies on the incidence of hypertension were published, one in 1988 (23) and one in 2002 (49). In the more recent study, the lifetime risk of developing hypertension after a given age for middle-aged and elderly individuals was 90%, indicating a major public health problem (49). Women had a higher incidence of hypertension in the earlier report (23), but there was no significant difference between men and women in the more recent study (49). Studies on the incidence of hypertension (Table C) demonstrated that it increases with age, and is higher in African-Americans than in Caucasians, but failed to demonstrate a clear difference between sexes. Some studies showed higher results for women (12, 23), or equal results (49) or higher results for men (50, 51). However, results were more consistent with the fact that incidence of hypertension is probably higher among elderly women (23).

Incidence of hypertension appears to increase over time (Table C), but, due to the high degree of variation of survey response rates, study design, age range and definition of hypertension in incidence studies, it is difficult to draw accurate comparisons of incidence between studies (20). Furthermore, few studies exist outside United States. The same limitations discussed for the measurement of prevalence apply to the incidence studies. Moreover, these studies are based on a one-time measurement of blood pressure, which increases the occurrence of white-coat hypertension and may over-estimate the true incidence in these surveys. There is a need for recent and well-designed studies on the incidence of hypertension.

Study Rationale and Objectives

So far the burden associated with hypertension has been assessed on the basis of the prevalence of hypertension (20). However, the incidence of hypertension has been far less studied (20, 49). Incidence and prevalence convey different types of information, and are both important for describing the occurrence of a disease (Table D). Although prevalence can help measure the burden of hypertension in a population, only incidence can help measure the risk that an individual will develop hypertension (49). The long-term risk for developing hypertension in an individual is best described by the lifetime risk or the probability that an individual will develop hypertension over the course of his or her remaining lifetime. This former statistic needs measurement of incidence to be calculated. When studying the etiology of hypertension, which is a long lasting disease, it is better to analyze incidence rather than

prevalence, since prevalence mixes in the duration of hypertension, rather than providing a pure measure of risk. Despite these advantages, incidence is not measured as frequently as prevalence because it is more difficult to estimate. Cross-sectional studies allow measurement of prevalence only. Determination of incidence needs a more complex cohort design, including follow-up information over a relatively long period of time (Table D).

Recent reports show that, although the prevalence of hypertension is increasing over time, the incidence and lifetime risk of developing hypertension are increasing more probably because of an increase in life expectancy and obesity (49). Therefore, good data on both incidence and prevalence are needed to better appreciate the burden of this disease on a population, and to find differences among sub-groups to identified groups at higher risk for the disease.

Indeed, women tend to have a higher prevalence (9, 13, 19) and incidence (20) of hypertension, but they tend to have poorer blood pressure treatment (13). As well, the age at which hypertension takes place appears to be different between men and women (4, 5, 23, 25-27) (Appendix 1). However, given that some studies on the incidence of hypertension showed either higher results for women (12, 23), equal results (49) or higher results for men (50, 51), there is a need for population-based data to measure the incidence and prevalence of hypertension in women in order to clarify the sex difference in the occurrence of hypertension (3, 19).

In Canada, data on prevalence comes from two studies using blood pressure measurement, which were conducted between 1986 and 1992 all over Canada (10), and in 2006 in Ontario (11). Another study measured incidence and prevalence of hypertension between 1995 and 2005 using an administrative database in Ontario (12). Data on the prevalence of hypertension in the Quebec population is limited. Moreover, to the knowledge of the researchers, the incidence of hypertension has never been studied in the Quebec population. As well, the lifetime risk of developing hypertension after a given age has never been studied in Canada. (49). The objective of the current study was to estimate the prevalence, incidence and lifetime risk of developing hypertension after a given age in the Province of Quebec.

Methods

Study Design

A longitudinal incidence study was conducted on an historical cohort. An administrative database was used containing 20,000 subjects aged 45 or older, who were selected as a random sample from the RAMQ (Régie de l'Assurance Maladie du Québec) database. These subjects were followed from 1986 until 2003 (16 years of follow-up).

The RAMQ database is the physician and drugs claims database from the Province of Quebec. Since healthcare in the Province of Quebec is publicly funded for all, these databases cover all healthcare services provided to the whole population and contain information on all inpatient and outpatient diagnostic and therapeutic procedures. These databases also contain information on all outpatient prescriptions for patients 65 years of age or older, welfare recipients and self-employed. Survival status for more than 99% of patients is available (52). These databases have been validated for the accuracy of prescription claims (53, 54), and diagnostic codes (55). At each outpatient medical visit, the physician codes one diagnosis principally related to the visit. This diagnosis is assumed to be the acute condition for which the physician actually saw the patient or the principal chronic condition for which the physician follows the patient.

The current study received ethics approval from the Institutional Review Board of the Faculty of Medicine at McGill University, Montreal, Quebec, Canada.

Study Population

The study population is a random sample of 20,000 subjects selected in 1987, aged 45 or older, from the RAMQ database. These individuals were selected as follows: to be eligible for inclusion in the cohort, a subject had to be insured by the RAMQ insurance plan during 1987, and be aged 45 years or older. Among the eligible people, a random sample of 20,000 individuals was selected and data were obtained on this population for the period ranging from 1/01/1986 to 31/12/2003.

Essential Hypertension

Patients newly diagnosed as having essential hypertension were identified on the basis of an outpatient diagnosis of hypertension. The accuracy of the coding diagnoses for essential hypertension in administrative databases has been shown to be high, ranging from 74% to 96% (55-58). In the database, nearly 80% of individuals were found to have at least one diagnosis of hypertension, out of which 30% had only one diagnosis and 20% had only two diagnoses. Because hypertension is a chronic disease necessitating a specific long term follow-up, probably patients with only one or two diagnoses of hypertension in the whole database are misclassified as having hypertension. However, when a patient has more than three diagnoses of hypertension, more than 75% of these patients have a large number of hypertension diagnoses (ten or more) probably indicating a real follow-up for chronic essential hypertension. Moreover, it is recommended to measure blood pressure at least three times (at 3 different occasions) before making the final diagnosis of high blood pressure. Therefore, in the current study, at least three diagnoses of essential hypertension were used as the main inclusion criterion to ensure the selection of genuinely hypertensive patients. Other studies have used only two diagnoses with good accuracy (12, 59); nevertheless, based on our observations, the misclassification of the diagnosis of hypertension in administrative database appears to decrease with the use of three diagnoses.

A sensitivity analysis was conducted to determine the period during which these three diagnoses have to be made (Table E). As can be seen in Table E, most patients present at two years, are still present at four years. There is only mild improvement to require selection of patients over 3 years whereas a 6 month or a 1 year observation period probably results in a significant lost of true hypertensive patients. (Table E). We concluded that the optimal period during which the three diagnoses of hypertension have to be made is two years as other investigators have identified (12). Therefore, the following inclusion criteria were used for the diagnosis of essential hypertension: at least three outpatient visits with a diagnosis of essential hypertension (International Classification of Diseases, 9th Revision (ICD9) code 401 or ICD10 code i10) over a two-year period. Exclusion criteria were: 1) a diagnosis of essential hypertension in the first two years of the cohort (1986 and 1987), to exclude all prior prevalent cases (for the incidence calculations); 2) a diagnosis of any secondary form of hypertension (such as hypertension caused by endocrine causes); and 3) hypertension related to renal disease or pregnancy (ICD9 code 405 and 642 or ICD10 code i15 and o10). Using these criteria, incident cases of diagnosed hypertensive patients who were hypertension-free before cohort entry were identified in 1/01/1988 for the incidence calculation. For the prevalence calculation, the first two years were taken into account. The sensitivity and specificity to identify adults with hypertension with a similar algorithm were previously demonstrated to be high: the sensitivity ranged from 70% to 75%, and the specificity ranged from 76% to 95% (55-59).

Statistical Analysis

The prevalence is the number of individuals with a disease at a specified point in time (point prevalence) divided by the population at risk of having the disease at this point in time (Table D). The prevalence of hypertension was calculated one year after the beginning of the study (31/12/1988), at mid-point (31/12/1995), and at the end of the study (31/12/2003). The results were then stratified by age group and sex.

The incidence is the number of new cases of a disease in a defined population at risk of having the disease during a specified period of time (Table D). To calculate the incidence, the Practical Incidence Estimator (PIE) was used, which was developed to estimate the incidence of Alzheimer disease (60) and hypertension (49) in the Framingham Study. The population at risk in the dataset was defined as all individuals without hypertension at the specified time point.

PIE was used, because this method addresses important issues to calculate the incidence of hypertension. These issues include: 1) time of origin; 2) patients entered in the cohort at different ages; 3) length of follow-up: patients are followed for different periods of time; and 4) competing risk of death as both mortality rate and incidence of hypertension increase with age. Moreover, PIE enables the calculation of the remaining lifetime risk of hypertension at a given age, which has yet to be estimated in a Canadian cohort. Finally, using the same method as that used in the Framingham study allows better comparison of results. PIE, written in the SAS macro language, produces several estimates of disease incidence. These results were used to estimate the crude and age-specific incidence rates of hypertension, overall, stratified by sex and age-adjusted using direct standardization with the combined group as a standard. In choosing direct as opposed to indirect standardization, we considered the following points. First, indirect standardization is used to calculate the expected rate for the index population, given age-specific rates from a reference population. It is more stable than the direct method for uncommon events. Given that hypertension is a common event, indirect standardization was less appropriate. Second, using indirect standardization produces estimates that are not strictly comparable, because they are calculated using different weighting schemes that depend upon the age structures of the index/study populations. Direct standardization is an alternative to indirect standardization that does provide comparable measurements. Direct standardized estimate is simply a weighted mean event rate for a study population, using the group/stratum sizes of a reference population as the weighting scheme. In other words, directly standardized rates give an indication of the number of events that would occur in a standard population if the population had the same age-specific rates. For issues of comparability we chose direct standardization.

We also calculated the remaining lifetime risk of hypertension conditional on survival to age 46, 55 and 65 years of age free of hypertension. PIE produced the unadjusted cumulative incidence and the cumulative incidence adjusted for the competing risk of death. The development of hypertension increases with age and is therefore subject to the competing risk of death. In analyses where the models are adjusted for the competing risk of death, subjects without hypertension who died due to other competing causes do not contribute to the estimate for the measurement of the incidence of hypertension. This method prevents the erroneous inflation of the cumulative incidence. Subjects who die during the observation period are treated as censored observations in traditional survival analysis. Such censoring would be inappropriate for hypertension, since it assumes that failure from the event is still possible beyond the time at which the censoring occurred. For censored observations, the probability of failure from the event is distributed among those subjects remaining at risk. However, the potential contribution

of a subject who has died should be zero. Treating such subjects as censored inflates the estimate of the hypertension incidence. The analytic solution to the problem of competing risk of death in the calculation of incidence is that subjects without hypertension who died due to other competing causes should not contribute to the estimate of the development of hypertension.

Hypertension is known to increase with age. Hence, survival age was used as the time variable, because hypertension is more likely to change with age than with calendar time. For the same reason, date of birth was used as time origin, because hypertension is known to increase with age, and also because time origin has to be defined in a way that ensures individuals are comparable at the time origin.

The method of PIE uses age at entry into the study as the left truncation variable. A subject is left-truncated when it comes under observation after having been exposed to the risk of an event for some time. A subject is right-censored due to termination of the follow-up period. Follow-up time that occurs before the observation period was excluded by left-truncation, using age at entry into the study as the left truncation variable, because the risk set at any age must include only those individuals who were at risk at that age during the observation period.

In conclusion, using PIE to estimate the incidence of hypertension in a cohort of individuals who were hypertension-free in 1/01/1988 enables us to address important issues of incidence calculation:

1) Variable follow up: Individuals were followed for different periods of time. Time has to be taken into account in the denominator. Hence, each subject must contribute to the denominator the exact number of person-years found for this subject in the database.
2) Comparable time of origin: Time of origin was defined in a way that individuals were comparable at the time origin. Survival age was used as the time scale and date of birth as time origin, because hypertension is known to increase with age.
3) Different ages at study entry: By using age at entry into the study as the left truncation variable, we accounted for subjects entering the observation period at different ages.
4) Competing risk of death: Both mortality and hypertension increase with age. The cumulative incidence was adjusted for the competing risk of death with the assumption that subjects who have died contribute zero time because they cannot develop hypertension.

Limitations

The use of an administrative database to retrospectively estimate incidence has some limitations. This administrative database does not contain information on actual blood pressure measurements; therefore, the outpatient diagnosis of hypertension was used as a proxy for a hypertension diagnosis. These data were thus prone to misclassification likely principally leading to an under-estimation of hypertension for several reasons.. First, the estimation of hypertension can be under-estimated when physicians decide sometimes to code other diseases instead of hypertension when they see patients with a number of other chronic diseases. Second, this study is also limited to individuals who were actually followed by a physician. Therefore, the database does not capture individuals with hypertension who never see a physician or for whom blood pressure was not measured. This study is therefore limited to individuals who are followed by a physician thus leading to an under-estimation of hypertension particularly in men who are known to use the healthcare system less than women (4). Hence, the estimate of incidence can be under-estimated more for men than for women, which can magnify the sex differences observed in this study. This problem appears to be partly overcome by allowing a long period of time for

diagnosis (two years). Nevertheless, this estimate of the incidence of hypertension is likely under-estimated for both sexes, but particularly for men.

The data are also prone to misclassification because the diagnosis of hypertension is based on an outpatient diagnosis of hypertension done by a physician for administrative purpose. Blood pressure measurement was not standardized; moreover it is possible that blood pressure was not consistently measured at every visit. Indeed it is possible that some physicians' visits were misclassified as for hypertension by error (transcription error, blood pressure measurement error, white-coat hypertension). This measurement error can lead to an over estimation of the true incidence if a lot of normal individuals were misclassified as having hypertension. This problem is probably present in the database, but it seems to have a minimal impact on the results, because:

1) This problem is partly overcome by allowing three diagnosis of hypertension for patients to be classified as hypertensive.
2) The reliability of the coding diagnosis for essential hypertension in administrative databases has been shown to be high (55-58).

For the denominator, individuals at risk for hypertension were used. But given that the risk of hypertension increases with age, like the risk of death, the development of hypertension is subject to the competing risk of death. When adjusting for death, the risk is a bit lower, because the unadjusted results assume that all subjects lived for the entire lifespan. The adjusted result is then more realistic.

The generalizability of our findings is limited to individual aged 45 or older by design.

In conclusion, the estimates of hypertension in our study are a good approximation, with possibly moderate under-estimation.

Results

Preface to the Manuscript

There exist few data on the prevalence of hypertension in the Quebec population. Moreover, there are no data on the incidence of hypertension in the Province of Quebec. As well, the lifetime risk of developing hypertension after a given age has never been studied in Canada. Data on prevalence are essential for evaluating the burden of disease associated with hypertension and data on incidence are essential for measuring the risk of individuals for developing hypertension. The aim of this study was to estimate the prevalence, incidence and lifetime risk of developing hypertension after a given age in the Province of Quebec. To do so, an administrative database was used to capture prevalent and incident cases of hypertension.

INCIDENCE, PREVALENCE AND THE RISK OF DEVELOPING HYPERTENSION FROM 1988 TO 2003 IN QUEBEC: A POPULATION-BASED STUDY.

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ABSTRACT

The prevalence of hypertension has been well studied, but the incidence of hypertension has had by far less investigation since it is more difficult to ascertain incidence accurately. Moreover, the lifetime risk of developing hypertension after a given age has never been studied in Canada. The "gold standard" method for estimating incidence is to completely follow a cohort of hypertension-free individuals over time. Recently the availability of administrative health data has made the investigation of occurrence more feasible at a population level. The study objectives, therefore, were to estimate the prevalence, incidence and lifetime risk of developing hypertension after a given age in the Province of Quebec, and to compare Quebec's estimates with recent data on the incidence of hypertension from the Framingham cohort. A population-based longitudinal study was carried out using a health administrative database as the sampling frame. A random sample of 20,000 Quebec residents aged 45 or older in 1987 was selected. Members of the cohort who were hypertension-free in 1988 were followed to 2003. Incident cases of essential hypertension were identified based on three outpatient diagnoses of hypertension during two consecutive years. The incidence of hypertension in the Quebec cohort was 22 per 1,000 person-years for men and 31 per 1,000 person-years for women; rates were higher for women than men for all the age groups under study. The lifetime risk of developing hypertension for subjects who attained the age of 46 free of hypertension in the Quebec cohort was 66%, with 72% for women compared with 59% for men. The incidence of hypertension in Quebec was lower than that reported in the Framingham cohort where blood pressure was directly measured. Reasons for this discrepancy could be that the diagnosis of hypertension in Quebec is non-optimal, billing codes under-estimate the true incidence of hypertension; or there are true differences in hypertension incidence in the two populations. Notwithstanding these differences, in both Quebec and the Framingham cohort, the incidence of hypertension is very high, particularly for women. The data provide support for enhanced detection and treatment of hypertension in Quebec, particularly for women.

KEYWORDS: Hypertension, Women, Incidence, Prevalence, Databases, Public Health.

INTRODUCTION

Hypertension is a major public health problem. According to the Global Burden of Disease Studies, hypertension is the leading risk factor for mortality [1, 2] and is ranked third in contributing to disability-adjusted years of life lost.

Most information on hypertension comes from prevalence studies [3], but the incidence of hypertension has by far had less investigation since it is more difficult to ascertain incidence accurately [3, 4]. Estimates of prevalence are used to measure the burden and allocate healthcare resources. However only estimates of incidence can be used to identify effectiveness of public health interventions, and policies targeting this major cardiovascular risk factor. Moreover, only incidence estimates can be used to project an individual's risk of developing hypertension [4]. Thus, incidence conveys information about the risk of contracting hypertension, whereas prevalence indicates how widespread hypertension is. In addition, only incidence studies can be used for etiologic investigations of hypertension, a condition of long duration, given prevalence is the product of incidence and duration. Despite the advantages of incidence studies, incidence is not often measured, because it is the more difficult of the inherent difficulties in accurately ascertaining new occurrences of hypertension. The "gold standard" method for estimating incidence is to completely follow a population-based cohort of hypertension-free individuals over time.

Some sub-groups of the population are at greater risk for developing hypertension [5]. Among these, women appear to be a high risk group [6]. In fact, women tend to have a higher prevalence [7-9] and incidence [3] of hypertension, and yet they tend to have poorer blood pressure treatment [7]. As well, the age at which hypertension develops appears to be different between men and women [10-14]. Thus, there is a need for population-based data to measure the incidence of hypertension in women separately from men [6, 9]. In North America, recent data on the incidence of hypertension come principally from the Framingham prospective cohort study in the United States [4] and Ontario's administrative database study in Canada [15]. In the Framingham study, the lifetime risk of developing hypertension for both middle-aged and elderly individuals was 90%, indicating a wide-spread public health problem; however, there was not a significant difference between men and women. [4]. In Ontario, the incidence rose from 22.5 per 1,000 adults in 1997 to 32.1 per 1,000 adults in 2004; both prevalence and incidence were higher for women compared with men [15].

Data on the prevalence of hypertension in the Quebec population are limited. Moreover, to the knowledge of the researchers, the incidence of hypertension has never been studied in the Quebec population, which differs from Ontario and Framingham genetically and environmentally. As well, the lifetime risk of developing hypertension after a given age has never been studied in Canada. The objectives were to estimate the prevalence, incidence and lifetime risk of developing hypertension after a given age in the Province of Quebec, and to compare Quebec's estimates with recent data on the incidence of hypertension from the Framingham cohort.

METHODS

Study Design

A longitudinal incidence study was conducted on an historical cohort randomly selected from the insured population of Quebec. The "Régie de l'assurance maladie du Québec" (RAMQ) maintains databases for fee-for-service healthcare events and prescriptions filled, and was used to obtain a randomly selected sample of 20,000 people aged 45 or older insured during the year 1987. Through records of billing for services, people were followed for 15 years (from 1986 until 2003).

Healthcare in the Province of Quebec is publicly funded for all. This database contains information for inpatient and outpatient healthcare services (including diagnostic and therapeutic procedures). It also records information on prescriptions filled in the community for people 65 years of age or older, or people on income assistance or who are self-employed [16]. The RAMQ database has been validated for the accuracy of prescription claims [17, 18], and diagnostic codes [19]. Typically, at each outpatient medical visit, the physician codes one diagnosis principally related to the visit. This diagnosis is assumed to be the acute condition for which the physician actually saw the patient or the principal chronic condition for which the physician follows the patient.

Diagnosis of Hypertension

The main outcome for this study was a new diagnosis of essential hypertension based on at least three outpatient diagnoses of essential hypertension (International Classification of Diseases, 9th Revision (ICD9) code 401 or ICD10 code i10) during a two-year period. For the purpose of estimating incidence, people with hypertension in the year preceding selection (1986) or the first year of the cohort (1987), termed "prevalent cases", were excluded. Also excluded from the definition of an incident and prevalent case were people with any secondary form of hypertension and hypertension related to renal disease and pregnancy (ICD9 code 405 and 642 or ICD10 code i15 and o10). The accuracy of the coding diagnosis for essential hypertension in administrative databases has been shown to be high, ranging from 74% to 96% [19-22]. As well, the sensitivity and specificity for identifying adults with hypertension using a similar algorithm were previously demonstrated to be high: the sensitivity ranging from 70% to 75% and the specificity ranging from 76% to 95% [19-23].

Statistical Analysis

Point Prevalence

Point prevalence was estimated at the end of the study (December 31, 2003). Prevalence was estimated as the total number of people with hypertension divided by the number of people at risk of developing hypertension at the end of the study.

Incidence

To estimate incidence in Quebec, the same methodology, the Practical Incidence Estimators (PIE), was used as was used in the Framingham cohort to estimate the incidence rate of Alzheimer disease and hypertension. The PIE method has been described previously [4, 24]. Briefly, crude and age-specific cumulative incidence rates, and 95 confidence intervals (95% CI) were calculated, overall and stratified by sex. Survival age, instead of calendar time, was used as the time scale taking into account that subjects can enter the cohort at different ages and with varying duration of follow-up. Also estimated was the cumulative incidence adjusted for the competing event of death, where subjects without hypertension who died due to other competing causes were removed from the analysis to be sure not to inflate the cumulative incidence. Subjects who died during the observation period were not treated as censored observations as is usual in traditional survival analysis, because it assumes that failure from the event is still possible beyond the time at which the censoring occurred. This is inappropriate for hypertension, because the risk of developing hypertension for a subject who has died is zero. The future risk of hypertension for a defined time period and the remaining lifetime risk conditional on survival event-free to a specific age were also estimated. The life-time risk for developing hypertension for subjects who attained the age of 46, 55 and 65 years free of hypertension were estimated to calculate the overall risk in the study cohort.

This study received ethics approval from the Institutional Review Board of the Faculty of Medicine at McGill University, Montreal, Quebec, Canada.

RESULTS

The overall prevalence of hypertension was 38% at the end of the study (2003) (Table 1). The prevalence of hypertension increased progressively with age, with the exception of the oldest age group (86 years old and older). The highest prevalence was reached in the age group 81-85 years, with a prevalence of nearly 49% at the end of the study.

At the end of the study, the prevalence of hypertension was higher in women compared with men: 43% for women compared with 33% for men respectively (Table1). This represents a relative excess for women over men of almost 25%.

For the whole cohort, the incidence of hypertension was 27 per 1,000 person-years; it increased with age (with the exception of the oldest age group) and was higher for women of all age groups (Figure1). Overall the incidence of hypertension was 30% higher in women compared with men (31 compared with 22 per 1,000 person-years). The relative difference ranged from less than 5% to 40% depending on the age group. Interestingly, the differences between men and women increased with age, with the exception of the last age group (86 to 90 years old).

The unadjusted lifetime risk of developing hypertension in the overall Quebec cohort, conditional on survival free of hypertension to age 46, was 66%; this was 20% higher for women than for men (72% compared with 59%) (Figure 2). Fifty percent of men developed hypertension within 35 years, whereas 50% of women developed hypertension in less than 30 years. Women began to show a higher risk of hypertension from the start of follow-up, but this became significant only after 15 years of follow-up. When adjusting for the competing risk of death, the mortality-adjusted lifetime risk of hypertension decreased marginally for women (72% to 61%), but decreased more steeply for men (59% to 44%) (Figure 3). When using the mortality-adjusted lifetime risk of hypertension, the differences between men and women became wider (30% compared with 20%). By 25 years of follow-up for both sexes, the cumulative incidence adjusted for competing risk of death became to be significantly lower from the unadjusted cumulative incidence of hypertension.

The lifetime risk of developing hypertension conditional on survival free of hypertension to age 55 and 65, for both men and women, was also estimated and compared with the results obtained in the Framingham cohort [4]. Depending on the definition used for hypertension, the results were either similar or lower than those of the Framingham study. Actual blood pressure measurements in Framingham were associated with a higher incidence of hypertension compared with the Quebec results, whereas hypertension treatment in Framingham was associated with a similar incidence of hypertension compared with Quebec results.

In the Framingham cohort, there were only marginal differences between subjects aged 55 and 65 years, whereas, in the Quebec cohort, there was an 8% to 10% higher risk of hypertension in subjects aged 55 years old compared with subjects aged 65 years old for both sexes (data not shown).

DISCUSSION

This is the first study examining both the prevalence and incidence of hypertension in Quebec at the population level. As well, this is the first report on the lifetime risk of developing hypertension after a given age in Canada. This study demonstrated that the incidence and prevalence of hypertension is very high in the Quebec population, and therefore hypertension represents a high burden to its healthcare system, like everywhere else in the world [3]. The rates of prevalence and incidence are comparable with those from Ontario, despite the genetic and environmental differences between the two populations [15, 25].

The point prevalence of hypertension in the cohort is high: higher than the prevalence reported in Ontario in 1995, but lower than that reported in 2005 in Ontario [15]. The prevalence of hypertension in the Quebec cohort is high, because of aging of the cohort, the increase in obesity, and the reduced mortality of hypertensive patients in Canada [26]. It is also likely due to the increase in awareness of the Canadian medical community regarding the public health problem of hypertension [25, 27, 28]. Studies have shown that, during the past decade in Ontario, the prevalence of people treated for hypertension has increased [25, 27-30], possibly due to the introduction of the Canadian Hypertension Education Program in 1999, the strategic marketing from the pharmaceutical industry, and the profusion of major hypertension clinical trials published over the past two decades [28-31]. Therefore, there has been an increase in the detection and treatment of hypertension in Canada [25, 27-31], as shown in the recent Ontario hypertension survey [25]. However, the estimate in this study is lower than that reported in 2005 in Ontario [15], because an algorithm using three outpatient diagnoses of hypertension was used in the Quebec cohort compared with only two diagnoses in the Ontario study [15], both studies allowing a two-year period for diagnosis. The use of only two diagnoses of hypertension appears to increase the risk of misclassification leading to an over-estimation of hypertension. However, the use of three diagnoses of hypertension increase the risk of missing some hypertensive patients, leading to an under-estimation of hypertension, but this method leads to a more conservative estimation.

In the cohort, both the incidence and prevalence of hypertension were higher for women than for men. This observation has been made in other populations [1, 3], including a recent Canadian database study conducted in Ontario [15]. This is in agreement with other reports that demonstrated a striking age-dependent sexual dimorphism in the prevalence and incidence of hypertension [1, 3, 10-12, 15]. Before menopause, women have a lower prevalence of hypertension than men, but, after menopause, women tend to have a higher prevalence [10-14]. The higher prevalence of hypertension in men and post-menopausal women compared with pre-menopausal women has been associated with sex-related differences and the possible protective effects of the female sex hormones: estrogens and progesterone [32]. The complex net effect of estrogens appears to result in the suppression of the potent renin-angiotensin vasoconstrictor system, which could explain at least in part the higher prevalence of hypertension in post-menopausal

women [33]. Vascular effects of female sex hormones include genomic effects (inhibition of vascular smooth muscle proliferation and activation of endothelial cell proliferation and vasodilatation) and non-genomic effects (vasodilatation), while the male sex hormone testosterone exhibits a less potent vasodilatation effect [34].

Interestingly, studies using administrative data (like the current Quebec study and the database Ontario study [15]) show higher rates of both incidence and prevalence for women than men. In contrast, studies using direct blood pressure measurements (like the Framingham study [4] and the Ontario survey [25]) found higher results for men. It is plausible for women to have higher rates of physician-reported hypertension than men, because women tend to visit physicians more often than men, and, therefore, have more opportunities to receive a diagnosis of hypertension [35]. However, an increasing number of visits to the physician did not appear to increase the possibility of hypertension being diagnosed [15]. More studies are needed to address this difference.

The lifetime risk for developing hypertension in the Quebec cohort was very high, reaching 66%, but this was consistently lower than the risk (90%) estimated from the Framingham cohort [4]. The estimates from the Framingham cohort are likely to be an over-estimation of the true risk of hypertension, because it is based on a single occasion measurement of blood pressure, which is prone to the phenomenon of "white-coat" hypertension, which has been estimated at about 20% [36]. However, the Quebec estimates are likely an under-estimation of the true risk of hypertension, because of the need of a physician to actually code for hypertension as a reason for this visit. Among people with many co-morbidities, the reason for the visit may be inconsistently coded. Hence, the true value is probably somewhere between the Framingham and the Quebec estimates. Nevertheless, the incidence of hypertension in the Quebec cohort was nearly equal to the incidence of being treated for hypertension in the Framingham cohort. It has been previously demonstrated in 1992 that a large proportion of hypertensive patients in Canada were not diagnosed [37], a practice that has now markedly improved according to 2006 data [25]. Therefore, the lower incidence of hypertension in the Quebec administrative database, compared with the Framingham cohort, is likely to represent a sub-optimal diagnosis of hypertension in Quebec. The implication for Quebec is to increase the diagnosis of hypertension through efficient screening programs. This would be particularly important given the higher incidence of hypertension for women.

The use of administrative databases to estimate the incidence and prevalence of hypertension is subject to a number of limitations, even if the reliability of the coding diagnosis for essential hypertension in administrative databases has been shown to be high [19-22]. Administrative databases do not contain information on actual blood pressure; hence, outpatient diagnosis of hypertension was used as a proxy for hypertension. The misclassifications would lead most probably to an under-estimation of hypertension rather than an over-estimation. If it is recorded, it is likely present, but if not recorded, no inference can be made. This study is

also limited to individuals 45 years old and older and to individuals who have visited a physician during the 15-year study period. This latter group is likely to be small, but not zero. While not precise, the excess hypertension in women warrants public health attention.

PERSPECTIVES

In the Quebec cohort, the incidence of hypertension is very high, particularly for women. The prevalence and incidence of hypertension in the Quebec population was found to be at the same magnitude as everywhere in the world. Furthermore, it was seen that the incidence and prevalence of hypertension is consistently higher for women in the Quebec population. The incidence of hypertension appeared to be lower in the Quebec administrative database compared with the Framingham cohort. This difference is likely to represent, at least in part, the non-optimal detection of hypertension in the Quebec population. The public health implications of these results in Quebec are that the detection of hypertension is to be maximized through efficient diagnosis programs that target particularly women.

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CONFLICT OF INTEREST/DISCLOSURE

None.

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FIGURE LEGENDS

Figure 1: Sex-specific One-year Incidence of Hypertension per 1,000 person-years. Age-Specific (by age groups of five years), Crude and Age-Adjusted Rates.

Figure 2: Sex-specific Lifetime Risk of Hypertension. Conditional on Survival Free of Hypertension to Age 46 (Error bars: 95% confidence interval).

Figure 3: Sex-specific Lifetime Risk of Hypertension. Conditional on Survival Free of Hypertension to Age 46, Adjusted for the Competing Risk of Death (Error bars: 95% confidence interval).

TABLES

Table 1: Point Prevalence of Hypertension at the End of Study Period (2003), by Age and Sex.

Age Group (years)	Males	Females	Total
61-65	28*	33	30
66-70	33	41	37
71-75	34	46	41
76-80	36	51	44
81-85	41	54	49
≥86	28	39	35
Total	33	43	38

* = In percentage of all subjects at risk of developing hypertension at the end of the study.

Figures:

Figure 1: Sex-specific One-year Incidence of Hypertension per 1,000 Person-Years. Age-Specific (by age groups of five years), Crude and Age-Adjusted Rates.

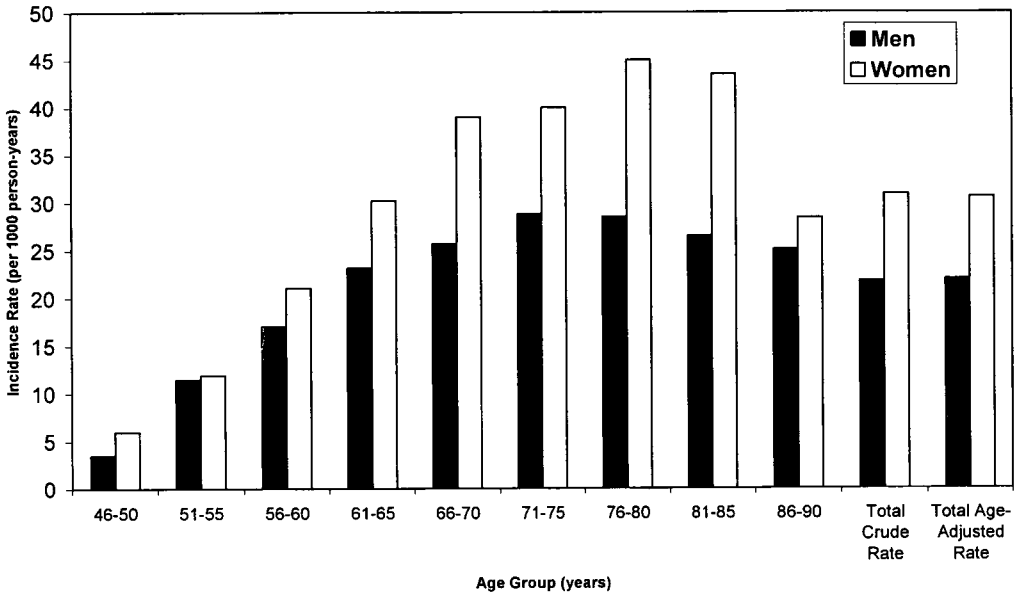


Figure 2: Sex-Specific esidual Lifetime Risk of Hypertension. Conditional on Survival Free of Hypertension to Age 46 (Error bars: 95% confidence interval).

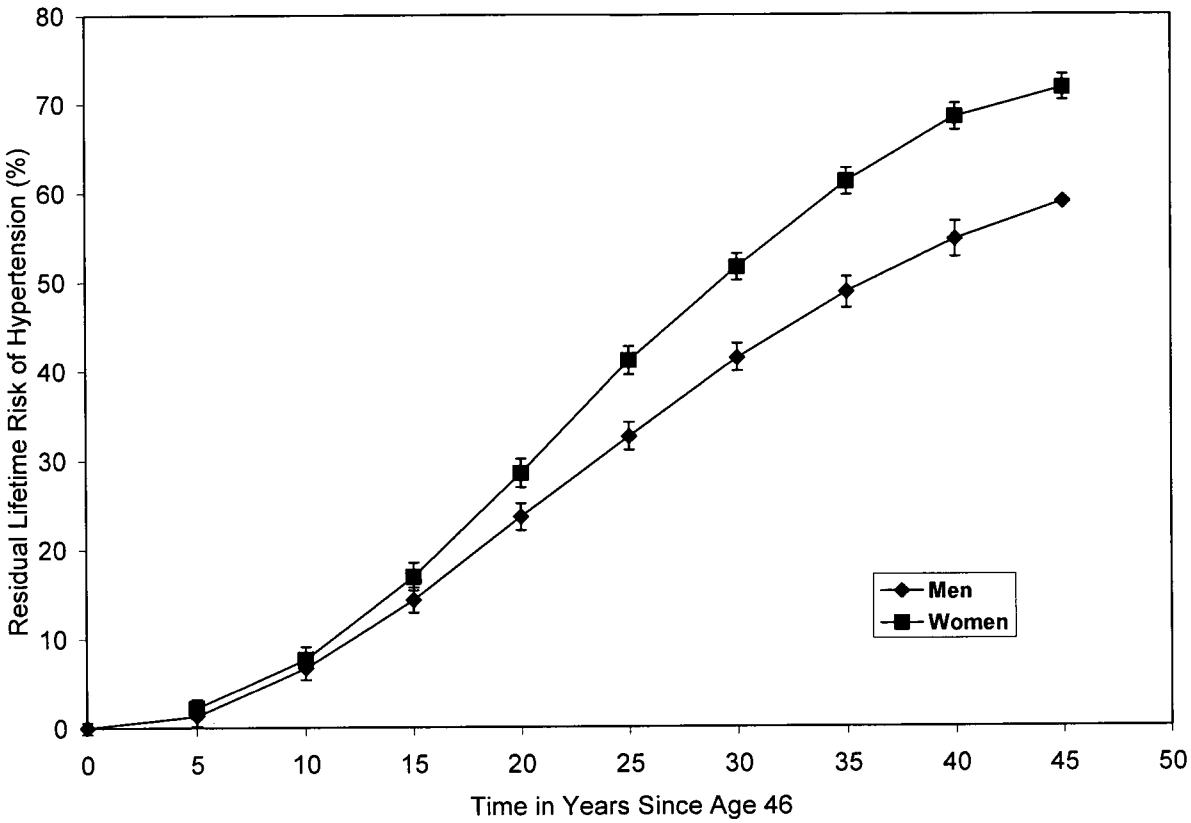
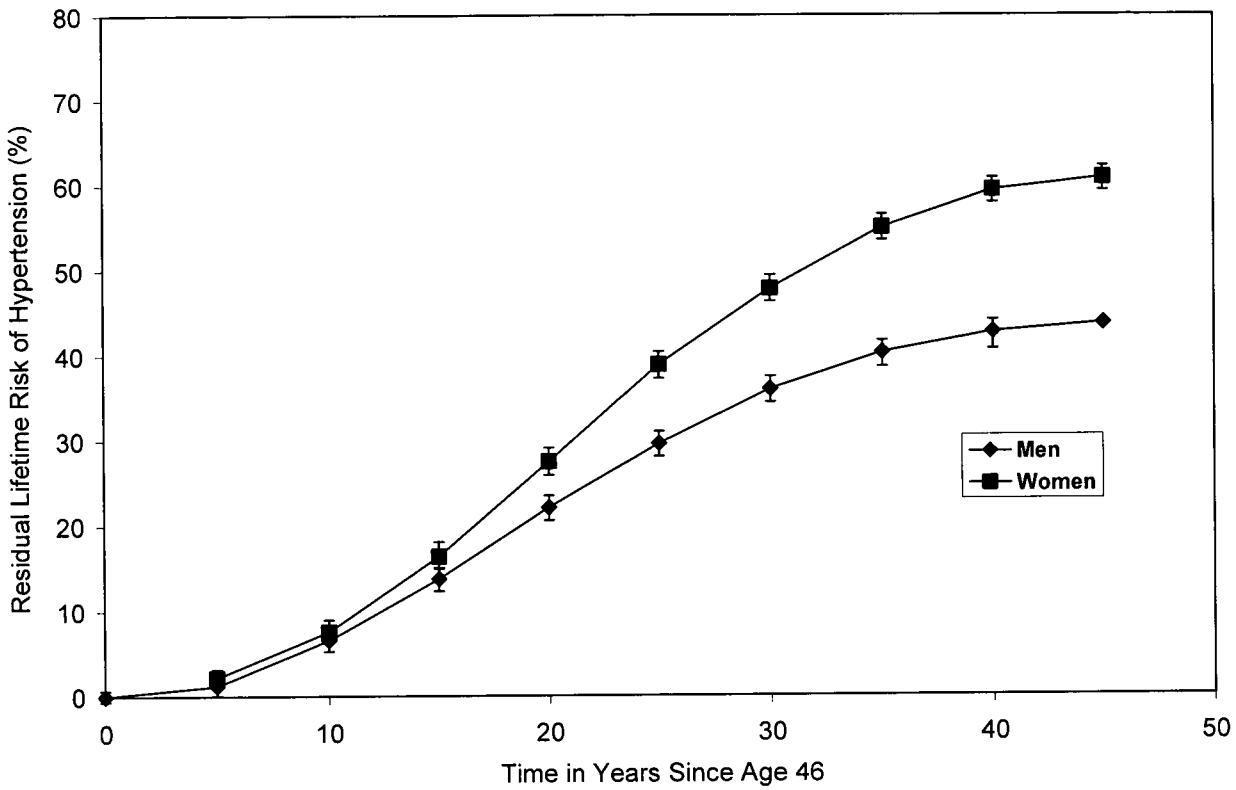


Figure 3: Sex-Specific Lifetime Risk of Hypertension. Conditional on Survival Free of Hypertension to Age 46, Adjusted for the Competing Risk of Death (Error bars: 95% confidence interval).



Discussion and Conclusion

Hypertension is a major public health problem. According to the Global Burden of Disease Studies, hypertension is the leading risk factor for mortality (1, 2). However, few data exist on hypertension in the Province of Quebec. The goal of this thesis was to measure the prevalence and incidence of hypertension at the population level in Quebec in order to measure the burden of this disease and to measure individual risk of developing hypertension.

The prevalence of hypertension has been well studied, but the incidence of hypertension has had by far less investigation, since it is more difficult to ascertain incidence accurately. Moreover, the lifetime risk of developing hypertension after a given age has never been studied in Canada. This study is the first to estimate both the prevalence and incidence of hypertension in Quebec. As well, this study is the first to estimate the lifetime risk of developing hypertension after a given age in Canada.

We found that the prevalence, incidence and lifetime risk of developing hypertension are high in the Province of Quebec. At the end of the study, the prevalence was almost 40%, and the lifetime risk of developing hypertension was about 60% after age 46 years. Prevalence and incidence were higher for women than for men; this was true for all the age groups, with the exception of the youngest. This observation has been made in other populations (1, 20), including a recent Canadian database study conducted in Ontario (12). This is in agreement with other reports that demonstrated a striking age-dependent sexual dimorphism in the prevalence and incidence of hypertension (1, 4, 5, 12, 20, 25). Before menopause, women have a lower prevalence of hypertension than men, but after menopause women tend to have higher prevalence (4, 5, 25-27). The higher prevalence of hypertension in men and post-menopausal women compared with pre-menopausal women has been associated with sex-related differences and the possible protective effects of the female sex hormones, estrogens and progesterone (22). The complex net effect of estrogens appears to result in suppression of the potent renin-angiotensin vasoconstrictor system, which could explain at least in part the higher prevalence of hypertension in post-menopausal women (42). The public health implication of the higher incidence and prevalence of hypertension in post-menopausal women compared with pre-menopausal and men is that the detection of hypertension is to be maximized through efficient diagnosis programs that target particularly post-menopausal women.

The point prevalence of hypertension in this cohort increased dramatically from baseline to the end of the study period (table F). Most of this increase is likely due to the increase in follow-up time from the beginning (1988) to the end of the study (2003). In fact, when allowing more observation time to capture individuals with three hypertension diagnoses over a consecutive two-year period, there is more chance of real hypertensive patients being uncovered. Other reasons for this increase include: aging of the cohort, the increase in obesity, and the reduced mortality of hypertensive patients in Canada (46). It is also likely due to the increase in awareness of the Canadian medical community regarding the public health problem of hypertension (11, 61, 62). Studies have shown that,

during the past decade in Ontario, the prevalence of people treated for hypertension has increased (11, 61-64), possibly due to the introduction of the Canadian Hypertension Education Program in 1999, the strategic marketing from the pharmaceutical industry, and the profusion of major hypertension clinical trials published over the past two decades (48, 62-64). Therefore, there has been an increase in the detection and treatment of hypertension in Canada (11, 48, 61-64), as shown in a recent Ontario hypertension survey (12). The point prevalence of hypertension in this cohort in 2003 is high: higher than the prevalence reported in Ontario in 1995, but lower than that reported in 2005 in Ontario (12), confirming the trend toward a higher prevalence of hypertension over time. However, this estimate is lower than that reported in 2005 in Ontario (12), because an algorithm using three outpatient diagnoses of hypertension was used in the Quebec cohort compared with only two diagnoses in the Ontario study (12), both studies allowing a two-year period for diagnosis. The use of only two diagnoses of hypertension seems to increase the risk of misclassification leading to an over-estimation of hypertension. However, the use of three diagnoses of hypertension increase the risk of missing some hypertensive patients, leading to an under-estimation of hypertension, but this method leads to a more conservative estimate.

The estimate of incidence in the Quebec cohort was lower than that found in the Framingham study, but at the same magnitude as most of other studies in this field (20). These differences aside, in both the Quebec and Framingham cohort, the incidence of hypertension is very high. Reasons for this difference could be that the diagnosis of hypertension in Quebec is non-optimal, billing codes under-estimate the true incidence of hypertension; or there are true differences in hypertension incidence in the two populations. The use of administrative databases to estimate the incidence and prevalence of hypertension is subject to a number of limitations. Administrative databases used in the Quebec cohort is likely to lead to an under-estimation of the estimates. But the diagnosis of hypertension in the Framingham study was likely over-estimated because of white-coat hypertension, which has been estimated at about 20% (65). Therefore, the true incidence is probably between the results found in these two studies, but this difference is likely to represent, at least in part, the non-optimal detection of hypertension in the Quebec population. The public health implications of these results in Quebec are that the detection of hypertension is to be maximized through more efficient programs particularly targeting men and post-menopausal women.

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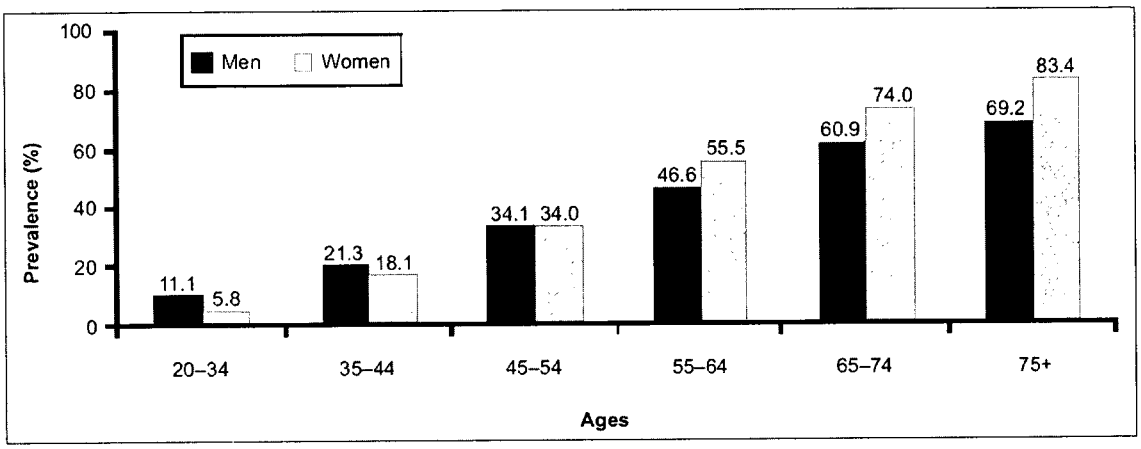
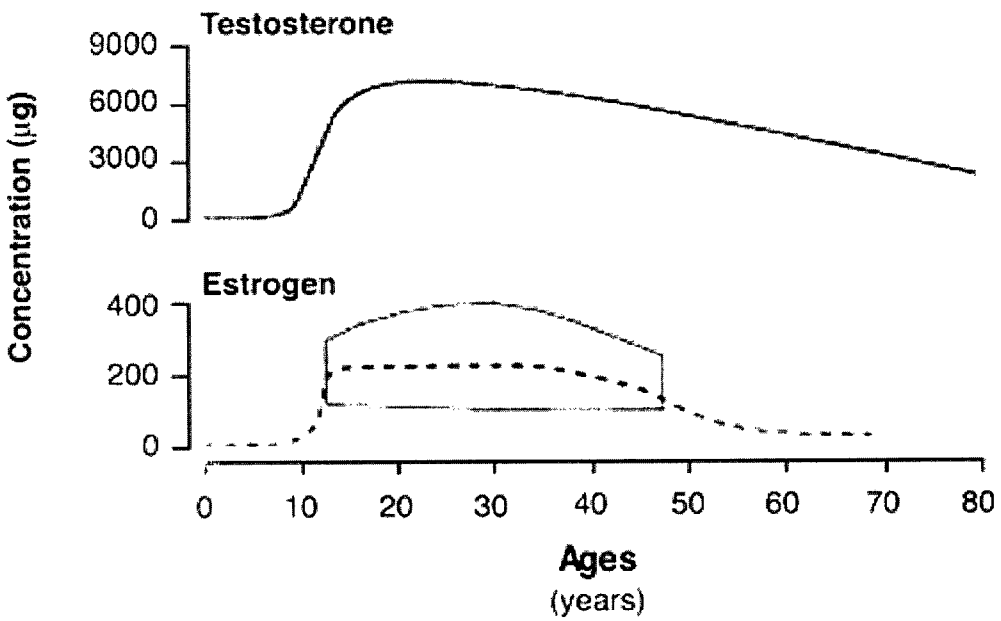
Appendix

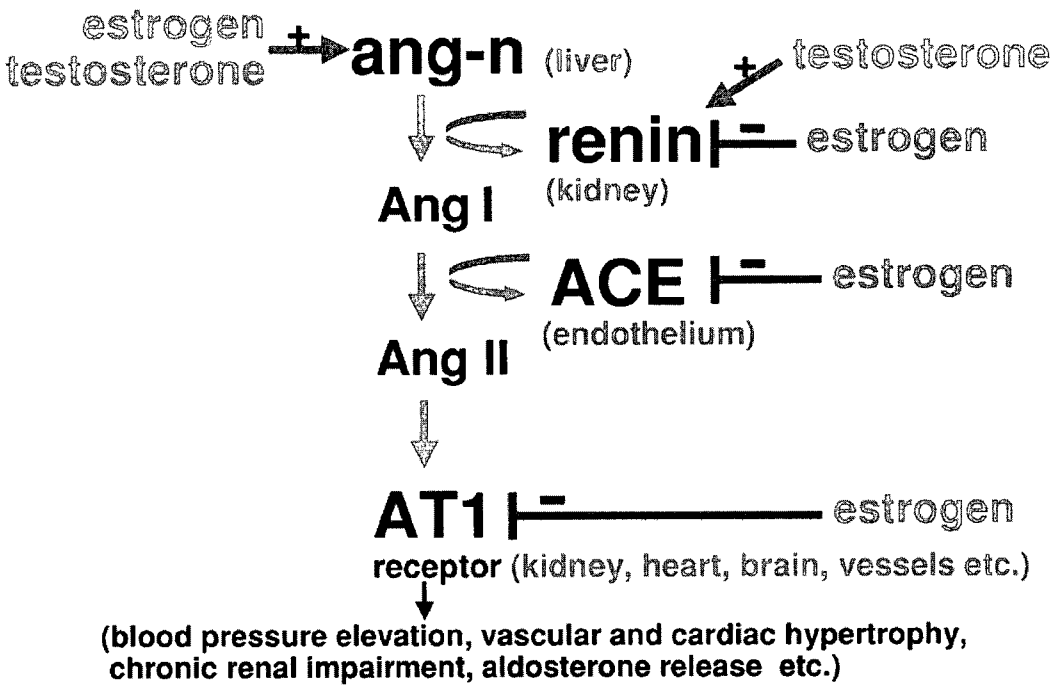
Appendix 1: Prevalence of High Blood Pressure in Americans Age 20 and Older by Age and Sex.
National Health and Nutrition Examination Survey (NHANES): 1999–2002.
Used with permission (4).



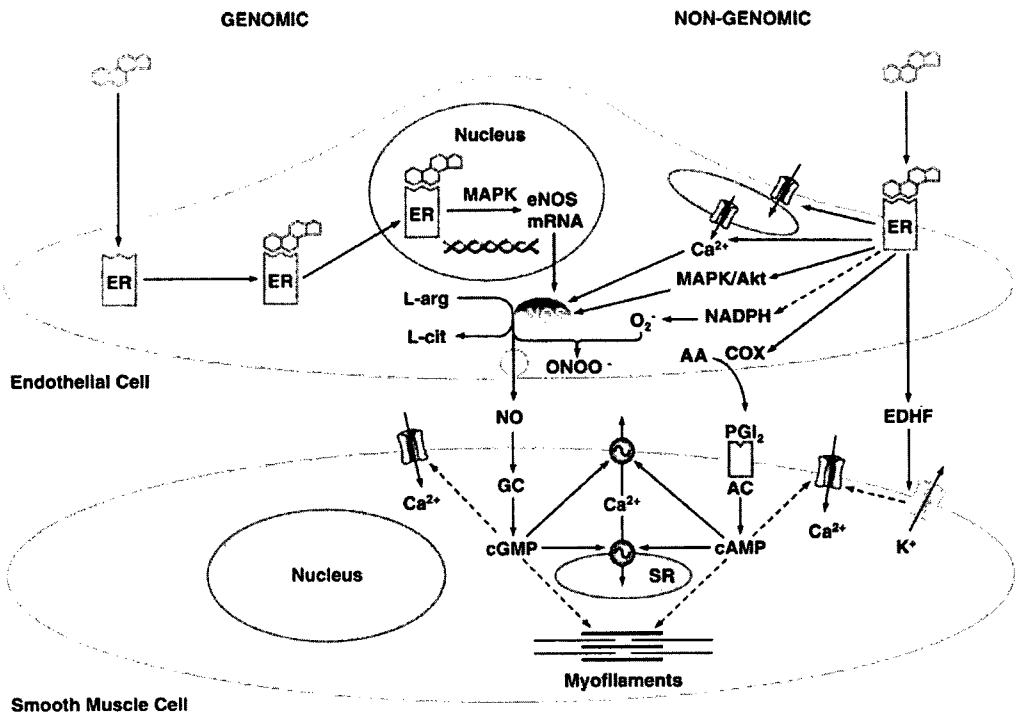
Appendix 2: Testosterone and Estrogen Amounts Secreted Daily by Age.
Female reproductive years are shaded. Pre-menopausal women have a decreased prevalence of cardiovascular disease compared with men and post-menopausal women. Female cardioprotection occurs during reproductive years when estrogen levels are highest, and declines after menopause as estrogen levels decline, after approximately 45–50 years of age.
Used with permission (22).



Appendix 3: The Cascade Leading to Angiotensin II Formation and Subsequent Receptor Activation and the Influence of Estrogen and Testosterone on Various Components.
(ang-n = angiotensinogen, ang I = angiotensin I, ang II = angiotenin II, AT1 receptor = Angiotensin II receptor type 1)
Used with permission (42).



Appendix 4: Estrogen-Stimulated Endothelium-Dependent Mechanisms of Vascular Smooth Muscle (VSM) Relaxation.



In the genomic pathway, estrogen binds to endothelial cytosolic/nuclear estrogen receptors (ER), leading to activation of mitogen-activated protein kinase (MAPK), increased gene transcription, endothelial cell proliferation, and increased endothelial nitric oxide synthase (eNOS) production. In the nongenomic pathway, estrogen binds to endothelial surface membrane ERs, which are coupled to increase $Ca2^+$ release from the endoplasmic reticulum and stimulation of MAPK/Akt pathway, leading to activation of eNOS and increased nitric oxide (NO) production. NO diffuses into the VSM cells, binds to guanylate cyclase (GC), and increases cGMP. cGMP causes VSM relaxation by decreasing $[Ca2^+]i$ and the myofilament sensitivity to $Ca2^+$. ER may also inhibit the production of NADPH, thereby preventing the inactivation of NO and the formation of peroxynitrites ($ONOO^-$). Endothelial ER may also activate cyclooxygenases (COX) and increase PGI2 production. PGI2 activates prostacyclin receptors in VSM, activates adenylate cyclase (AC), and increases the formation of cAMP. cAMP causes VSM relaxation by mechanisms similar to those activated by cGMP. ER may also increase the production of endothelium-derived hyperpolarizing factor (EDHF), which activates K^+ channels and causes hyperpolarization and inhibition of $Ca2^+$ influx via $Ca2^+$ channels leading to VSM relaxation. Interrupted arrows indicate inhibition. L-arg = L-arginine; L-cit = L-citrulline; AA = arachidonic acid.
Used with permission (43).

Table A: North-American Prevalence of Hypertension.

Country	Year	Age Range (years)	Design	Prevalence (%)	References
Canada	1986-1990	18-74	Survey*	20	(10)
Canada (Quebec)	1987	15 and older	Survey	28	(47)
Canada (Ontario)	1995	20 and older	Database cohort	15	(12)
Canada (Quebec)	1998	15 and older	Survey	37	(47)
Canada (Ontario)	2005	20 and older	Database cohort	25	(12)
Canada (Ontario)	2006	20-79	Survey*	21	(11)
United States	1960-1962	18-74	Survey*	30	(66)
United States	1971-1974	18-74	Survey*	36	(66)
United States	1976-1980	18-74	Survey*	32	(66)
United States (Minnesota)	1980-1982	25-74	Survey*	30	(67)
United States and Canada	1986-1999	16 and older	Variable*	28	(68)
United States	1987-1989	45-64	Survey*	35	(69)
United States	1988-1991	20 and older	Survey*	25	(66)
United States	1991	18 and older	Survey	21	(70)
United States	1991-1994	20 and older	Survey*	25	(13)
United States	1993-1997	50-79	Survey*+	38	(71)
United States (Minnesota)	1995-1997	25-74	Survey*	26	(67)
United States	1999-2002	20 and older	Survey*	29	(72)
United States	2001	18 and older	Survey	26	(70)

*Based on blood pressure measurement.

+Study in women only.

Table B: Worldwide Prevalence of Hypertension (except North America).

Country	Year	Age Range (years)	Design	Prevalence (%)	References
Japan	1980	30-74	Survey*	38	(73)
Czech Republic	1985	25-64	Survey*	47	(74)
Europe[a]	1986-1999	16 and older	Variable*	44	(68)
Australia	1989	25-64	Survey*	21-32	(75)
Egypt	1991	25 and older	Survey*	26	(76)
India	1999	18-60	Survey*	48	(77)
Korea	1999-2000	18-92	Survey*	34	(78)
Belgium	1999	16-67	Survey*	27	(79)
China	2000-2001	35-74	Survey*	27	(80)
Czech Republic	2000-2001	25-64	Survey*	39	(74)

[a]This includes United Kingdom, Finland, Germany, Italy, Spain and Sweden.
*Based on blood pressure measurement.

Table C: Worldwide Incidence of Hypertension.

Country	Years	Age Range (years) at baseline	Design	Incidence	References
United States	1971-83	20-49	Prospective cohort*	13% over 8 years	(50)
Netherlands	1977-1995	20-50	Prospective cohort*	15% over 18 years	(81)
United States	1985-1995	18-30	Prospective cohort*	10% over ten years	(51)
United States	1987-1995	30-54	Prospective cohort*	25% over seven years	(82)
Canada (Ontario)	1995	20 and older	Database cohort	2.6% (one year)	(12)
Canada (Ontario)	2005	20 and older	Database cohort	3.2% (one year)	(12)

*Based on blood pressure measurement.

Table D: Measurements of Disease Occurrence: Comparison Between Incidence and Prevalence.

	Prevalence	**Incidence**
Definition	The proportion of a population that are cases at a point in time	The rate at which new cases occur in a population during a specified period
Calculation	Total number of cases Population at risk at one point in time (point prevalence) Or Population at risk within a stated period (period prevalence)	Number of new cases Population at risk X time during which cases were ascertained Or Total person-years at risk
Usefulness	-Useful to describe disease of long duration -Useful to describe very rare disease -In study on the burden of a disease in a population -In planning health services	-Better to describe disease of short duration -To estimate the risk of developing a disease -In study of etiology of a disease
Weakness	-Weak for disease of short duration -What is done with the patients under remission but not cured?	-Weak to describe very rare disease -What is done do when pathological event happens more than once to the same individual?
Measurement	Data easier to collect and easy to calculate	Data hard to obtained (need a follow-up period) and complex to calculate
Link between prevalence and incidence	Prevalence = incidence X average duration of the disease	

Table E: Results of the Sensitivity Analysis for the Determination of the Period During Which Three Diagnoses of Essential Hypertension Have To Be Made.

Period	**% of hypertensive patients**
6 months	73%
1 year	86%
2 years	95%
3 years	98%
4 years	100%

Table F: Point Prevalence of Hypertension During Study Period, by Age and Sex.

	Baseline (1988)			Mid-point (1995)			End (2003)		
Age Group (years)	Males	Females	Total	Males	Females	Total	Males	Females	Total
46-50	2*	2	2	ne	ne	ne	ne	ne	ne
51-55	4	4	4	11	10	10	ne	ne	ne
56-60	3	6	5	11	14	12	ne	ne	ne
61-65	6	6	6	15	20	18	28	33	30
66-70	5	9	7	15	25	20	33	41	37
71-75	5	8	7	19	29	24	34	46	41
76-80	6	10	8	17	27	23	36	51	44
81-85	6	7	7	15	30	24	41	54	49
≥86	2	5	4	16	17	17	28	39	35
Total	4	6	5	14	21	18	33	43	38

ne = not estimable

* = In percentage of all subjects at risk of developing hypertension at the specified year.