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SERUM VITAMIN A AND PROSTATE CANCER

by

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A thesis submitted to the
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ABSTRACT

Background

Prostate cancer is a leading cancer in terms of both incidence and mortality in Canada and promises to become an increasing concern in the future. Despite its relative importance, few risk factors for prostate cancer have been identified. While a large number of dietary studies have examined the relationship between vitamin A and prostate cancer, studies using serum vitamin A levels are rare.

Objective

To assess the relationship between serum vitamin A level and the subsequent development of prostate cancer.

Methods

A population-based retrospective cohort study was conducted. Serum vitamin A levels were measured as part of the Nutrition Canada Survey (1970-1972). Study participants (3,014) were men 35 years of age or older at time of interview for whom a serum vitamin A level was recorded. Prostate cancer cases were identified through record linkage of the survey cohort to the Canadian Cancer Registry (1971-1986). An age-adjusted Poisson regression analysis was then conducted.

Results

One hundred cases of prostate cancer were identified. Men with serum vitamin A levels in the highest quartile were found to be at twice the risk of developing prostate cancer as those whose levels were in the lowest quartile (relative risk = 1.98; 95% confidence interval, 1.13-3.46). For men 80 years or older, the observed relative risk exceeded three (relative risk = 3.23; 95% confidence interval, 1.10-9.70).

Conclusion

This study suggests that serum vitamin A levels in men are positively associated with their risk of developing prostate cancer. This effect appears to be greatest among men 80 or more years of age. These findings should be interpreted with caution as this is the first study of appreciable size to report such an association and it remains possible that the results reflect, at least partially, the confounding effect of some unknown risk factor(s). Further research is needed to clarify the role of serum vitamin A in prostate cancer etiology.

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1. INTRODUCTION

1.1 Background

At the beginning of this decade, prostate cancer surpassed lung cancer to become the most frequently diagnosed cancer* among Canadian males[1]. Only lung cancer is currently responsible for more cancer deaths among males each year[1]. An estimated one in every eight Canadian males will be diagnosed with, and approximately one in twenty-six will die from, prostate cancer in their lifetime[1]. The 19,800 new cases and 4,100 deaths projected for prostate cancer in 1997 represent 28% of the new cancer cases and 13% of the cancer deaths projected among males for the year[1].

Though the number of small latent tumours seen in autopsy series seems to be rather consistent across countries and ethnic groups[2,3], there exists considerable international variation in the incidence of larger latent or clinically apparent prostate cancer tumours[4]. The Canadian incidence rate of prostate cancer has been reported to be among the three highest in the world[5]. From 1985 to 1992, the average annual rate of increase of the incidence rate of prostate cancer in Canada (5.3%) was unsurpassed by any other cancer site among males[1]. The corresponding figure for mortality (0.7%) was exceeded, among males, by only melanoma and non-Hodgkin's lymphoma[1].

A proportion of the increased incidence of prostate cancer may be attributed to incidental early detection at prostatectomy for benign disease[6], or to the use of new

*Excluding non-melanoma skin cancer.

diagnostic tools such as prostate specific antigen and transrectal ultrasound[7]. Because of the high proportion of latent prostate cancers in elderly men[2,3] the widespread use of techniques which lead to the detection of these cancers could result in significant changes in the observed number of cases.

An additional explanation for the increased incidence of prostate cancer may be that there have been increases in the prevalence of risk factors for prostate cancer. Unfortunately, little is known about the etiology of prostate cancer. Although numerous factors including hormones, sexual activity, smoking, education, occupation, and diet have been postulated, few are well-established risk factors. In the early 1980s, researchers began to study the possibility of an association between vitamin A and prostate cancer. This was prompted by studies that had associated vitamin A with somewhat reduced risk of cancer of the oral cavity[8], larynx[9], lung[10], and bladder[11].

Vitamin A is a generic term for all substances that possess the biologic properties of retinol[12]. It may be ingested either as a preformed vitamin or as a provitamin[13]. Preformed vitamin A is naturally found only in food from animal sources[13], mostly in the form of retinyl ester[14] though small amounts of retinol are present as well[15]. Common dietary sources of preformed vitamin A are liver; various dairy products such as milk, cheese, butter, and ice cream; and fish, such as herring, sardines, and tuna[14]. Provitamin A are carotenoids. Of the approximately 600 carotenoids found in nature, only 50 are converted into vitamin A[14]. Common dietary sources of provitamin A carotenoids are

carrots, yellow squash, dark-green leafy vegetables, corn, tomatoes, papaya, and oranges[14], although a small amount is contained in dairy products[12].

Ninety percent of the vitamin A in the body is stored in the liver, mostly in the form of retinyl ester. Other tissues contain about 9% while approximately 1% is found in the serum[15]. The release of vitamin A from the liver is mediated by binding to retinol-binding protein[16]. Transportation of retinol bound to retinol-binding protein involves a complex system which is affected by malnutrition, such as protein and zinc deficiencies; by hormonal changes affecting protein synthesis and metabolism; and by diseases of the intestine, liver, and kidney[17]. Serum vitamin A exists mainly in the form of retinol[14]. Under normal physiological conditions, retinol and retinyl ester account for approximately 90% and 8% of serum vitamin A respectively[15]. Serum vitamin A is homeostatically controlled over the physiologic range of liver vitamin A concentrations (eg. 20-300 μg/g). When liver vitamin A concentrations are below 20 μg/g, serum vitamin A values tend to fall. Above 300 μg/g, serum values tend to increase. At very high intakes of dietary vitamin A, serum vitamin A values can be greater than 300 μg/dl[15].

The relationship between serum vitamin A and prostate cancer is unclear. While there have been a number of published reports examining serum vitamin A or serum retinol[18-25], only four of these studies[22-25] accrued a sufficient number of prostate cancer cases to be of practical interest. While an inverse association was shown or suggested for serum retinol in two reports[22,23], a third study[24] observed a lower incidence of prostate

cancer among those in the lowest quintile of serum retinol relative to those in the highest. In the only previous study[25] to examine serum vitamin A, per se, and prostate cancer incidence, an inverse association was reported. Please see Appendix A for a complete summary of epidemiologic studies of vitamin A/carotenoids and prostate cancer.

A literature review of other established and postulated risk factors for prostate cancer follows.

1.2 Literature review

AGE

While prostate cancer is very rare among Canadian males before age 45 years, incidence increases faster with age than for any other major cancer[26]. After age 45, incidence rates begin to grow in an almost exponential fashion. Whereas a Canadian male has a 4.2% chance of developing prostate cancer by the age of 70, this increases to 9.5% by the age of 80[1]. Unlike lung or female breast cancer, prostate cancer does not reach a peak age of incidence in Canada before the age of 85[26]. A similar pattern of incidence by age has been reported in the United States[27].

FAMILY HISTORY

Using genealogical records, Cannon et al.[28] found prostate cancer to have a stronger familial aggregation than either colon or breast cancer. First degree relatives of prostate cancer cases have been shown to experience statistically significantly increased risks that approach two and-a-half fold[29-32]. The risk has been shown to be higher in blacks (odds ratio (OR)=3.2) than whites (OR=1.9) though the difference was not statistically significant[31]. The closer genetically a man is to an affected relative[29,30] and the more relatives he has with the disease[29], the greater his risk. Men with three affected relatives were discovered to be at an 11-fold risk[29].

At least two Canadian studies have found evidence for a familial role in prostate cancer development[33,34]. A population-based case-control study conducted in Quebec

involving 140 francophone hospital inpatients found an OR that approached ninefold for men with one to four first-degree relatives with prostate cancer[33]. McLellan and Norman[35] have speculated that this large OR may be due to the fact that the investigators did not limit their calculations to cases with one or two affected relatives, as had been the practice in previous studies. In the other Canadian report, also a population-based case-control study, Fincham et al.[34] used the Alberta Cancer Registry to identify 382 prostate cancer cases. They reported that subjects with an affected first-degree relative were more than three times as likely to develop prostate cancer than those without.

Analysis by Carter et al.[36] strongly suggests that "hereditary" prostate cancer is the result of an autosomal-dominant inheritance of a rare high risk gene that predisposes men to the early development of prostate cancer. Their data suggested that while hereditary prostate cancer may account for a significant proportion of early onset prostate cancer, overall only about 9% of this disease in the population was due to the effects of the hereditary prostate cancer gene.

ETHNIC GROUP / COUNTRY OF RESIDENCE

The highest incidence rates for prostate cancer are among African-American men[37]. Their incidence rates are one and-a-half to almost twice those for Caucasian-American men, though rates for the latter group are among the highest in the world[37]. High incidence rates are also found in Canada and northern Europe while very low rates originate from countries in the Far East such as Japan and China[37]. Prostate cancer is

much more common in developed than developing countries, and the global range in incidence is at least 70-fold[37].

HORMONES

Sex hormones, androgens in particular, may have a role in prostate cancer development. Androgens are required for the growth, maintenance, and functional activity of the prostate gland[38]. In addition, prostate cancer growth rates can be manipulated through hormonal therapy[39]. It has been suggested that the progression of prostate cancer from histological to clinically significant forms may be partially the result of an altered hormone metabolism[40].

The principal androgenic hormone in men is testosterone[38]. It has been suggested that elevated levels of both testosterone and its metabolite dihydrotestosterone, over many decades, leads to prostate cancer[41]. However, serum testosterone levels in prostate cancer cases have been found to be elevated[42], depressed[43] and similar[44] to those of controls. Zumoff et al.[45] found that levels of testosterone were lower in prostate cancer patients than in controls among young men, but that the opposite was true for older men. Analyses of female hormones have yielded similarly inconsistent results[38] though indirect evidence suggests that estrogens do not play a role in prostate cancer development[27].

ANTHROPOMETRY

The evidence for an association between high body mass index (BMI) and prostate cancer risk is very limited. In a case-control study of 48-79 year-olds conducted in Northern Italy, Talamini et al.[46] observed that the risk of being diagnosed with prostate cancer increased with increasing BMI. The OR for men in the highest group (BMI = 28+) was nearly four and-a-half times that of the reference group (BMI < 23). Studies of Japanese [relative risk (RR)=1.33], Dutch (OR=1.5), and Seventh-day Adventist men (RR=1.17) have all reported elevated, though non-significant, risk estimates[47-49]. On the other hand, a cohort study of over 20,000 men of various ethnicities in Hawaii[50] found high body mass to be slightly protective [RR=0.7; 95% confidence interval (95% CI), 0.5-1.2] while several other studies have found no difference in mean BMI between cases and controls[51-55].

It has been suggested that previous findings of positive associations between BMI and prostate cancer might be accounted for more by muscle mass than by fat tissue[47,56]. Severson et al.[47] found the muscle, not the fat area, of the upper arm to be significantly related to prostate cancer risk. Increased muscle mass may be a marker for higher levels of androgens[38].

SOCIOECONOMIC STATUS

Whether or not low socioeconomic status is a risk factor for prostate cancer has been difficult to test because ethnic minorities are overrepresented in low socioeconomic

groups in many studies. While both positive and negative results have been found, in general, the data support the concept that socioeconomic status is not an important risk factor in the development of prostate cancer[40].

OCCUPATION

Many industries, occupations, and exposures have been studied in relation to prostate cancer. The focus, however, has primarily been on cadmium exposure, work in the rubber industry, and farming. Farming was associated with increased risk of prostate cancer in 17 of 24 studies examined in a 1993 review[57]. In 10 of these studies the results were statistically significant. In a retrospective cohort study, Morrison et al.[58] found an association between number of acres sprayed with herbicides and risk of prostate cancer mortality after 17 years of follow-up. The National Academy of Science's committee to review the health effects of exposure to herbicides in Vietnam veterans concluded that there was limited suggestive evidence linking herbicide exposure to prostate cancer[59].

Analyses based on the rubber industry as a whole have found both positive and negative associations with prostate cancer. The International Agency for Research on Cancer has concluded that while there was "limited" evidence for an excess occurrence of prostate cancer in rubber workers, the data were inadequate to establish a causal association[60].

A review of studies conducted to determine whether exposure to cadmium places a man at greater risk for prostate cancer concluded that cadmium exposure may weakly increase risk[40]. It has been suggested that cadmium interferes with the zinc-hormone relationships in the prostate[61]. Zinc is required by several enzymes involved in the replication and repair of DNA and RNA and the prostate contains the highest concentration of zinc of any organ in the body[62]. As occupational exposures to zinc and cadmium usually occur together, it is difficult to evaluate their separate or interactive effects[63]. Elghany et al.[63] failed to find an increased risk of prostate cancer among welders or electroplaters though high levels of cadmium exposure are experienced by people working in such jobs. Additional sources of cadmium exposure include alkaline batteries and cigarette smoke.

PHYSICAL ACTIVITY

It has been proposed that physical training may act to lower both body fat and testosterone levels and hence possibly reduce prostate cancer risk for men who are very active[64,65]. The physical activity of a cohort of college alumni was assessed twice by Lee and Paffenbarger[66], once during the period from 1962 to 1966 and again in 1977. They concluded that while the biologic basis for a protective effect of increased activity on cancer risk appears plausible, physical activity was not significantly associated with the risk of prostate cancer. Previous studies had reported no association between physical activity and prostate cancer risk[67,68].

Recently conducted studies in both China[65] and Turkey[69] indicated that individuals who worked in sedentary jobs were at an increased risk for prostate cancer. The results were independent of whether physical activity was measured by total energy expenditure or percentage of occupational time spent sitting. However, a study of the lifetime occupational physical activity levels among Hawaiian men concluded that physical activity may be positively associated with the risk of prostate cancer[53]. The association was unrelated to socioeconomic status, diet, or job-related chemical exposures and, in the opinion of the authors, likely to be weak and indirect.

SEXUAL ACTIVITY

Although extensively studied, the role of sexual activity in the development of prostate cancer is still unclear. Both hormonal factors and infectious agents have been proposed to increase prostate cancer. Key[70] summarized a number of studies and found the relative risks for early first intercourse, large number of sexual partners and a history of any sexually transmitted disease to be elevated. However, it has also been reported that celibate men develop prostate cancer as frequently as the general population[71].

VASECTOMY

Cohort studies examining the relationship between vasectomy and prostate cancer have yet to demonstrate a pattern. Giovannucci and colleagues found significantly elevated relative risks of approximately 1.6 in both a retrospective[72] and a prospective cohort[73]. However, Sidney[74] found no association, a result that was confirmed in a second

report based on additional years of follow-up[75]. The results of two other cohort studies proved inconclusive because of insufficient follow-up time and because they were based on too few cases among the exposed[76,77].

The results with respect to case-control studies have been inconsistent. In a very large multiethnic case-control study conducted in the United States and Canada, a history of vasectomy was not significantly associated with prostate cancer risk[78]. A similar conclusion had been reached in three previous reports[79-81]. Though their study included only five prostate cancer cases who reported a history of vasectomy, Ross et al.[82] found vasectomy to be associated with lower risk. On the other hand, a study conducted in China[83] reported a strong positive association using neighbourhood controls while Rosenberg and colleagues[84], as part of a hypothesis generating exercise, found large risk estimates regardless of whether cases were compared to cancer or non-cancer controls. Other studies have reported increased risks ranging from 40 to 70 percent[85-87].

A major concern in the study of vasectomy and prostate cancer has been detection bias[78]. Vasectomized men may have been more likely to subsequently visit a urologist, resulting in an increased chance of being diagnosed with prostate cancer[88]. In addition, while most studies have used self-reported history of vasectomy, no study to date has validated this against medical records[78]. Many studies have also used self-reported disease status though it has been suggested that a history of prostate cancer is not always accurately reported[89]. In a review of possible mechanisms, Howards[90] came to the

conclusion that it seems highly unlikely that there is a biological mechanism supporting a relationship between vasectomy and prostate cancer.

SMOKING

As reported in a 1991 review paper, smoking has largely not been found to be a risk factor for prostate cancer[38]. Using never-smokers as a referent group, seven cohort studies[49,68,91-95] failed to detect an association among former or current cigarette smokers. Similar results were found in another study[96] whose referent group included non-cigarette smokers who smoked pipes and/or cigars. Of these eight studies, three[93,94,96] also considered the number of cigarettes smoked by current smokers but still found no association. In addition, Whittemore[92] did not detect a difference in prostate cancer risk for those who smoked more than 10 cigarettes per day in comparison to those who did not. Only two[85,97] of fifteen case-control studies[51,52,85,97-108] had detected a statistically significant association.

The possibility of a positive association between smoking and prostate cancer, however, should not be quickly dismissed. Four recent cohort[109-112] and three recent case-control studies[113-115] have all reported statistically significant results of some form. Both Coughlin et al.[111] and Hsing et al.[112] reported finding increased risks of approximately 25% for prostate cancer mortality among current smokers as compared to non-current smokers. In one of these studies[112] a trend in effect was noted with the highest risk experienced by those who smoked 40 or more cigarettes per day (RR=1.5; 95% CI, 1.2-

1.9). A lesser effect was found for former smokers (RR=1.13; 95% CI, 1.03-1.24). Earlier examinations of this same cohort on 16 and eight and-a-half years of follow-up[116,117] yielded higher estimates of relative risk.

In a population-based case-control study conducted in Sweden, Andersson et al.[114] found an increased risk of prostate cancer among current smokers when compared to non-smokers (OR=1.8; 95% CI, 1.1-3.0). Van der Gulden et al.[113] found that ever-smokers experienced more than twice the risk as non-smokers (OR=2.1; 95% CI, 1.2-3.6). However, neither study observed a relationship with the number of cigarettes smoked, the number of years as a smoker, or the age at which smoking was commenced[113,114]. Despite reporting increased risks for current (OR=1.5; 95% CI, 1.0-2.4) and former smokers of 40 or more cigarettes per day (OR=1.4; 95% CI, 1.0-1.5), the lack of consistent findings in population subgroups and the lack of a clear trend in effect led Hayes et al.[115] to doubt the existence of a causal association.

In early 1996 an international consensus conference on smoking and prostate cancer was held in Australia. It was unanimously agreed that there is inadequate evidence that smoking is associated with prostate cancer incidence[118].

ALCOHOL

A biologically plausible protective role for alcohol in prostate carcinogenesis originated from work which reported that alcohol may increase metabolic clearance of

testosterone[119]. However, virtually all studies conducted have demonstrated an absence of an overall relationship[49,50,52,92,98,99,101,102,109,110,113,120,121]. One exception was a recent case-control study[122] wherein significantly elevated risks were seen for those who had 22 to 56 drinks per week (OR=1.4; 95% CI, 1.0-1.8) and 57 or more drinks per week (OR=1.9; 95% CI, 1.3-2.7) in comparison to never-users. The absence of evidence demonstrating that the effect of alcohol on circulating testosterone levels is long-lasting may explain the failure of studies to show the anticipated protective outcome.

DIET

A dietary etiology for prostate cancer is consistent with the descriptive epidemiology including observations on migrants, geographic variations, and temporal trends, making it a promising area of research[123]. A high positive correlation has been reported between prostate cancer incidence rates and the corresponding rates of several other cancers thought to be related to diet (eg. breast and colon cancer)[124]. To date, epidemiologic studies have not provided consistent evidence concerning the relationship between specific dietary factors and prostate cancer risk[125]. Attention has been focused primarily on the roles of vitamin A and fat intake.

DIETARY FAT

Ecological correlation studies from the 1970's showed strong positive associations between prostate cancer incidence or mortality and fat consumption among a number of countries and within the United States[126-128]. Based on a correlation coefficient of 0.74

between national consumption levels of fat and national mortality rates of prostate cancer, Armstrong and Doll[126] hypothesized that dietary fat may be a major cause of prostate cancer.

At least 14 case-control studies have examined the association between fat and prostate cancer[46,52,54,55,67,99,125,129-135]. These studies have differed in terms of study design (hospital or population controls) and method of dietary assessment (direct or indirect). In some cases, fat intake was inferred from the frequency of consumption of meat, dairy products, and other foods known to have a high fat content[46,99,130,132,135]. Other studies assessed fat intake in a more comprehensive manner using food composition data to approximate actual fat intake[52,54,55,67,125,129,131,133,134].

Despite these methodological differences, only three case-control studies[125,129,132] failed to show a positive association with total fat intake. Two of the three[125,129] were part of a larger Pan-Canadian investigation. Both may have suffered from selection bias as the interview response rate was very low for both cases and controls in each study. The other study[132] was conducted in Japan where fat consumption is known to be quite low in comparison with the western world and the United States in particular.

The majority of cohort studies[49,50,136-138], like the case-control studies, have shown an association between fat intake, or the consumption of foods high in fat, and prostate cancer incidence or mortality. Three studies[68,91,109], two with limited food frequency

data[91,109], failed to detect an association though Severson et al.[68] did detect an association with eggs and with margarine, butter, and cheese as a group. Any inconsistencies in the results cannot be linked to size of study, whether fatal or incident cases were used, or whether direct or indirect measures of fat intake were used.

The relationship between specific components of fat and prostate cancer were examined in detail in two recent prospective studies[136,137]. Both studies found a strong positive association between α-linolenic acid, an essential polyunsaturated fatty acid, and prostate cancer risk; no clear linear relationship across quartiles of exposure suggesting a threshold effect; low levels of linoleic acid, another polyunsaturated fatty acid, may further exaggerate the effect; an independent association with red meat but no association with dairy foods. The findings, in regard to polyunsaturated fat, of two case-controls studies[129,131] add further support to this hypothesis.

DIETARY VITAMIN A

Interpretation of the epidemiological literature relating to vitamin A/carotenoids and prostate cancer can be difficult and somewhat confusing. The main difficulty lies in the inconsistency of the application of the term vitamin A. Care has not always been taken by researchers to explicitly define what they mean when they refer to this term. Where some explanation has been given, the term has been used in reference to preformed vitamin A, carotenoids, and a summary measure of both. Please see appendix A for a complete summary of epidemiologic studies of vitamin A/carotenoids and prostate cancer.

A number of studies[52,54,109,125,129,131,133,134,139-141] have used an index of vitamin A that combines the dietary intake of both preformed and provitamin A. Results from these studies are difficult to interpret because associations related to carotenoids do not necessarily imply a mechanism involving conversion to vitamin A[123]. It is also difficult to compare the results of these studies because different studies tend to weight the two components differently. It may be more useful to examine the relationship between preformed vitamin A and prostate cancer separately from that of carotenoids and prostate cancer.

The relationship between dietary intake of carotenoids (primarily β-carotene) and risk of prostate cancer has been extensively investigated in both case-control[46,52,100,125,129-133,135,139] and cohort[49,68,109,138,141-144] studies. The majority of these studies have been nutrient-based, though several looked at the consumption of fruits and vegetables, both individually and as food groups. Nutrient-based studies are preferred because they protect against the potential confounding effects of other nutrients contained in the same food item[134]. Such studies have reported positive[130], negative[52,132,133] and null[125,141-143] associations. In two reports the direction of the association was found to differ by the age group studied[109,131]. Serum β-carotene has been shown to be positively associated with prostate cancer risk[24] in one study but to have no association in two others[22,23].

The relationship between preformed vitamin A intake and prostate cancer has been specifically examined in at least seven studies. In five of these studies[109,130,139,141,143] a positive association was reported though in two studies[109,139] it was restricted to a certain age range. Slightly decreased risks with increased consumption were found in two studies[125,129] but, as has been noted previously, these two case-control studies were part of a larger study and suffer from low response rates.

1.3 Relevance and objective of study

Prostate cancer is a leading cancer in terms of both incidence and mortality in Canada. Prostate cancer promises to become an increasing concern in the future. Morrison et al.[145] have forecasted that by the year 2016 the annual number of newly diagnosed cases will exceed 35,000 and the annual number of deaths will approach 7,800. Because little is known about the etiology of prostate cancer, further research in this area is of great importance in order to allow the development of primary preventive intervention strategies.

A role has been postulated for vitamin A in the etiology of prostate cancer, though the exact nature of that role has yet to be determined. The objective of this study was to assess the relationship between serum vitamin A measurements, taken as part of the Nutrition Canada Survey (1970-1972), and the subsequent development of prostate cancer among study participants, as identified by the record linkage of the survey cohort to the Canadian Cancer Registry (1971-1986).

2. METHODS

2.1 Sources of data

Information regarding the Nutrition Canada Survey was obtained from several sources[146-148]. The survey was conducted between September 1970 and December 1972 using a three-stage stratified cluster design. Enumeration areas representing regions of low income were oversampled. A total of 12,795 people responded to the initial invitation to participate (46% response rate); 3,295 unsolicited volunteers also participated. In-house visits were used to collect basic demographic information on the subjects. Approximately one week later, each participant received a two-hour examination at the local survey centre that included an anthropometric examination and a dietary interview. The dietary interviewer asked each participant to recall all the foods and beverages consumed on the previous day (24-hour food recall) and the frequency with which certain foods were consumed over the previous month. Blood and urine samples were collected from all participants who were able and willing to give samples.

The principal objective of the Nutrition Canada Survey was to examine the mean consumption of selected food groups and their contribution to the nutrient intake of Canadians. It was hoped that the collected data could be used as a basis for the development of nutrition programs, construction of food guides, evaluation of changes of food consumption patterns in Canada over a period of time, and as a basis for food legislation. This cohort has been used to study the relationship between a variety of physical, dietary, and lifestyle factors and various chronic disease outcomes[149-152].

The mortality and cancer incidence history of the survey cohort had already been established and was made available in ASCII file format by Health Canada. This file did not contain information on subjects interviewed as members of specially targeted populations (i.e. Native Indians and Inuit). Incident cases of cancer from 1970 to 1986 had previously been identified through record linkage with the Canadian Cancer Registry. Only the year of diagnosis was available. The mortality of the cohort, up to and including 1985, had already been determined by record linkage to the Canadian Mortality Data Base at Statistics Canada. All record linkage was accomplished by means of the Generalized Iterative Record Linkage Computer System[153], specific details of which have been documented elsewhere[149].

Men were deemed eligible for the present study if they met the following criteria:

1) at the time of the survey interview (baseline), they were 35 years of age or older;
2) they were not identified by the record linkage process as having been diagnosed with cancer, excluding non-melanoma skin**, before the interview or during the calendar year of the interview;
3) they did not die in the calendar year of their interview;
4) a serum vitamin A value was recorded.

** For the purpose of this study, skin cancer (8th revision of the International Classification of Diseases[155], rubric 173) was not included in the list of cancers.

The first criterion was met by a total of 3,245 men. Criteria two through four excluded a further 231 subjects; 23 from criterion two, 20 from criterion three, 178 from criterion four, and 10 from multiple criteria. Thus, the analysed cohort consisted of 3,014 men, 100 of whom subsequently developed prostate cancer (8th revision of the International Classification of Diseases[154], rubric 185).

It was necessary to exclude those diagnosed with cancer in the year that they were interviewed because it was not possible, with the available data, to determine whether a man was diagnosed pre- or post-interview. Subjects, therefore, could not contribute to the prostate cancer case total during the calendar year of their interview, hence any person-time accumulated during this time period was discounted. A consequence of this was that men who died in the same calendar year as their interview could not contribute to either the case or person-time total and were disregarded.

Men with previously diagnosed prostate cancer were removed because they were not at risk of developing the disease. Other prevalent cancer cases were excluded from the study because there is evidence that low serum retinol levels may be a metabolic consequence of cancer rather than a precursor[24,155].

Individuals began to contribute person-time to the study on the first day of the year following their interview. Follow-up continued until the subject died, was diagnosed with cancer (excluding non-melanoma skin), or December 31, 1986, whichever came first.

Subjects diagnosed with cancer, other than in their year of interview, were assumed to have been diagnosed at the midpoint of the year of their diagnosis with one exception. If the individual also died during this year then they were assumed to have been diagnosed halfway between the start of the year and the date of their death.

Because the mortality record linkage did not include 1986, it was necessary to use an expected value of person-time contributed for certain individuals for this year. Men who remained free of cancer during the entire study period, including 1986, and who were alive at the beginning of 1986 were assumed to contribute person-time for this year based on the following calculation:

$$\text{person-months} = 12[1\text{-asmr}] + 6*\text{asmr}$$

where asmr is the age-specific, 1986 Canadian mortality rate for all causes excluding cancer of males 35 years and older. The calculation assumes that deaths in 1986 will have occurred, on average, at the midpoint of the year.

2.2 Variables

Serum vitamin A values were determined via blood samples taken during the physical examination. Once collected, blood samples were centrifuged to obtain serum and then immediately frozen and shipped to a central laboratory for further biochemical analyses. Individual serum vitamin A values were determined by fluorometric measurement in ultraviolet light[147,156] and reported in μg/100ml.

A measure of dietary vitamin A intake was available but only as part of the 24 hour food recall portion of the survey. In general, this method of collecting dietary information is not considered appropriate for estimating individual dietary intake[157]. In particular, vitamin A is one of the most difficult nutrient intakes to measure as it appears in high concentration in only a few foods which are not consumed consistently from day to day[146]. Thus, no reliable information existed on individual dietary vitamin A intake. The survey also inquired about the use of vitamin supplements including vitamin A and zinc. However, as only a very small minority of the men in the cohort reported using such supplements these variables were also not given further consideration.

Variables, identified by the literature review as having been previously studied as potential risk factors for prostate cancer, were included in at least the preliminary analysis given that such information was collected by the Nutrition Canada Survey. These variables were age, daily fat intake, daily energy intake, daily fibre intake, body mass index, monthly alcohol intake, highest educational level obtained, cigarette smoking status

and number of cigarettes smoked each day. The source and units of these variables are displayed in Table 1.

TABLE 1. Source and units of covariates, Nutrition Canada Survey, 1970-1972.

Variable	Source	Units
age	survey	years
fat	24 hour dietary food recall	grams/day
fibre	24 hour dietary food recall	grams/day
energy	24 hour dietary food recall	calories/day
body mass index	physical examination	weight (in Kgs) / height (in metres) squared
alcohol	one month food frequency	drinks/month
education	survey	highest grade obtained
smoking	survey	never, former, or current
cigarettes	survey	average number smoked/day

Cigarette smoking status was determined by individual responses to the following survey questions. Do you smoke cigarettes? If you do not smoke daily, did you ever in the past? The men who answered yes to the first question were considered current smokers. Current smokers were further categorized based on the number of cigarettes they reported smoking each day; < 1, 1 to 20, or > 20. The '< 1' level was reserved for individuals who admitted smoking cigarettes, but not on a daily basis. Men who answered no to the first question, but yes to the second, were classified as former smokers. Those who answered no to both questions were classified as never-smokers. Due to the wording of the questions, never-smokers may include non-daily former smokers. A failure to respond to the initial question resulted in a missing value being assigned to that individual for this variable.

Monthly alcohol intake was derived as the sum of the number of 12 ounce servings of beer or ale, three ounce servings of wine and 1.25 ounce servings of spirits, consumed during the previous month. The variable representing highest level of education attained was categorized into three levels: no high school, at least some high school and at least some post secondary training. The cut points were chosen to correspond to naturally occurring breaks in the educational system.

2.3 Analysis

Baseline demographics, including five-year age group, educational attainment, employment status, and whether or not the study participant was a volunteer or part of the original sampling frame, were determined. The mean, standard deviation, quartile values, and number of non-missing records were computed for serum vitamin A and each of the covariates excluding educational attainment and smoking status.

Analyses were conducted using categorical forms of the study variables. In many cases, this meant dividing distributions into quartiles. In other cases, the choice of cut points was based on both common reference points and the distribution of the data.

The statistical analysis was divided into three parts, a preliminary analysis, a non model-based analysis, and a Poisson regression analysis. One reason for choosing the Poisson model over the Cox proportional hazards model was that the former readily incorporates updated information concerning baseline variables. While participants of the Nutrition Canada Survey were never resampled, we can infer their future age at any point during follow-up based on their baseline age (i.e. the age of the subject at the time of his interview). The term attained age was introduced to distinguish between a subject's age at a given point during follow-up and their age at baseline. For example, a man with a baseline age of 65 years would have an attained age of 75 after 10 years of uncensored follow-up.

Age groups used in the preliminary analysis corresponded to age at baseline (i.e. the age of the subject at the time of his interview). The non model-based and Poisson regression analyses used age groups that corresponded to attained age. The use of attained age permits individuals to contribute person-time to different exposure/age strata. For example, an individual who was 67 at baseline and who contributed nine person-years, would contribute person-time to each of the 65 to 69, 70 to 74 and 75 to 79 age groups. If this individual ceased to contribute person-time because he was diagnosed with prostate cancer, the case would have been registered in the 75 to 79 age group.

2.3.1 Preliminary analysis

A preliminary analysis was conducted to gauge the necessity of controlling for any of the covariates, besides age, in the main analysis of serum vitamin A and prostate cancer. The association between serum vitamin A and each of the covariates was explored first. Then, using BMDP's logistic regression program[158] and controlling for age group, an estimate of the association between each of the covariates and risk of prostate cancer was computed. Covariates found to be a risk or protective factor for prostate cancer and to be associated with serum vitamin A would likely need to be controlled for in the main analysis.

To corroborate the above findings, a stratified analysis was conducted using Epi Info[159]. Four categories of serum vitamin A were formed based on quartile values determined from the serum vitamin A distribution of the 100 prostate cancer cases. The

first quartile of serum vitamin A was considered the reference group and the fourth quartile the exposure group.

In the preliminary stratified analysis and all subsequent analyses of serum vitamin A, quartile values were based on the case distribution as opposed to the entire distribution. When there are considerably fewer cases than non-cases, as in this study, it is reasonable to expect the size of the case cell counts to be the limiting factor in terms of power, and hence expect percentiles based only on the case exposure distribution to outperform percentiles based on the total sample[160]. More broadly, the use of a categorical measure of serum vitamin A as opposed to a continuous one was motivated by the desire to observe the presence or absence of a trend over various levels of exposure. Such observations can provide insight into the biology of the relation under study and guidance for any public health intervention[161]. In addition, categorical variables are more robust to the influence of extreme data points.

Crude risk ratios were compared with adjusted risk ratios for meaningful differences. Crude risk ratios were determined by dividing the prostate cancer cumulative incidence rate in the fourth quartile by the rate in the first quartile. The Mantel-Haenszel summary estimator for cohort studies with count denominators[162] was used to adjust for each potential confounder in turn. By default, each adjusted risk ratio was calculated using only the records for which data were available for that variable. In order to make

a comparison of adjusted and crude risk ratios that would be unbiased by missing values, the crude risk ratio for each variable was also calculated using only non-missing records.

The potential confounding effect of many of the control variables was assessed using a varied number of strata. For example, the effect of controlling for fat intake was assessed by dichotomizing this variable at its median value and also by dividing it into four strata based on its quartile values. In the case of age, as many as five strata were used. Where the effect was similar, the results corresponding to the lesser number of strata were reported.

As age was known to be an important risk factor for prostate cancer, joint confounding was assessed for baseline age together with each variable in turn. Age-adjusted risk ratios were compared with risk ratios adjusted by baseline age and another variable. A similar procedure to that described previously was used to manage the problem of missing values. That is, age-adjusted risk ratios were calculated using only the non-missing records of the variable whose joint confounding was to be assessed.

The potential effect modifying influence of each variable was not assessed in the stratified analysis due to the difficulty of incorporating records from the middle quartiles of serum vitamin A in such an analysis. Instead, logistic regression, using all records, was used for this purpose. Models consisting of serum vitamin A quartile, the potential effect modifier, and an interaction term for these two variables were constructed. In each

case, the likelihood ratio (improvement) χ^2 along with the corresponding degrees of freedom and P-value (two-sided) associated with the addition of the interaction term to the main effects model were recorded.

2.3.2 Non model-based analysis

Using insights gained from the stratified analysis, further analysis was conducted that made use of the person-time data available. As previously discussed, serum vitamin A was divided into quartiles based on the distribution of the 100 prostate cancer cases. The second quartile contained 26 cases due to tied serum vitamin A values. Incidence rates of prostate cancer for each quartile of serum vitamin A were calculated by dividing the number of incident cases by the number of person-years accumulated by men in that quartile. The risk ratio for each of the upper three quartiles of serum vitamin A was computed as the incidence rate for the particular quartile divided by the incidence rate in the lowest, or referent, quartile. Ninety-five percent CIs were calculated using approximate interval estimation with follow-up data[163].

Using the person-years adaptation of the Mantel-Haenszel procedure for cohort studies[164], age-adjusted risk ratios and corresponding 95% CIs were obtained without specification of an underlying model. Three age groups were used in the age adjustment process (i.e. < 70, 70-79, and 80+). These attained age groups were chosen to roughly correspond to the three baseline age groups used in the preliminary analysis given that the median follow-up time for cases in this study was approximately eight years. In

calculating the risk ratios, a 'one-step' correction towards the maximum likelihood estimate was used[165].

The relationship of serum vitamin A level to prostate cancer was then examined separately for two age groups using an attained age of 80 years as the cut point. Because a subject's attained age increased with increased follow-up time, men could potentially contribute person-time to both analyses. It was necessary to adjust for age in the under 80 analysis due to the presence of residual confounding. In this case, attained age was dichotomized into two categories (< 70 and 70 to 79) and the adjustment was done in an identical manner to that used in the overall analysis.

2.3.3 Poisson regression analysis

A model-based analysis of the data was performed using Poisson regression. The Poisson model is appropriate for situations where the dependent variable is a count within a series of subdivisions of the sampled data[166]. It is used to model cohort data, standardized mortality ratios, and, in general, count data in which the response is rare[167]. Person-time type denominators are usually, but not necessarily, used in conjunction with the counts. Poisson regression has been used in a previous analysis of the Nutrition Canada cohort[152].

The general form for Poisson regression links a count and an optional rate multiplier with a set of fixed covariate values[167]. The logarithm of the expected rate at

which countable responses occur is modelled as a weighted sum of the independent variables. The resulting regression coefficients, upon exponentiation, provide estimates of the relative risks for the independent variables. The use of a rate multiplier permits an adjustment to be made to account for different person-time totals corresponding to the various covariate patterns. If no rate multiplier is used then all of the observed Poisson counts are assumed to originate from populations of roughly the same size[167].

Under certain conditions, Poisson regression is analogous to logistic regression. In logistic regression the analysis is based upon the binomial distribution[168]. Poisson regression is based on the premise that the dependent variable follows a Poisson distribution. The Poisson distribution serves as an approximation for the binomial distribution when the population is sufficiently large and the binomial probability parameter is sufficiently small[169]. In practice, if the person-time accumulated in the cells corresponding to the counts used in a Poisson regression is large enough and of approximately the same size, then the estimates obtained for the coefficients of the variables will be similar to those obtained by using logistic regression[167].

As alluded to above, use of the Poisson distribution is suggested when modelling rare events. Typically, Poisson regression is applied to data consisting of rates of less than 0.01[166] (i.e. one case in one hundred person-years). As such, it is well suited for studies of chronic disease like prostate cancer.

Poisson regression modelling was conducted using the statistical software package Egret[170]. Estimation of the regression coefficients was based on the maximum likelihood principle[171]. The regression coefficients associated with serum vitamin A provided, upon exponentiation, estimates of the relative risks for men in the second through fourth quartiles of this variable relative to men in the first (referent) quartile while controlling for potential confounders. Ninety-five percent CIs were calculated as described for the non model-based person-year analysis. The goodness-of-fit of all models was assessed using minus two times the likelihood which has an approximate chi-square distribution when the data deviate from the model only because of random variation[166]. Tests for linear trend in relative risk were conducted by entering directly into the model a quantitative measure of serum vitamin A[166]. The quantitative measure used was a new variable which was assigned the median values of the quartiles. P-values associated with tests for goodness-of-fit and for linear trend were based on two-sided tests of hypotheses.

An overall age-adjusted Poisson model was created first. Age-adjustment was accomplished using five-year age groupings, though the first three age groups were collapsed into one (i.e. 35 to 49) due to the absence of a case of prostate cancer in an individual under the age of 45 years at time of diagnosis. Finer divisions of age categories were used in the model than had been used in previous analyses. This was done in order to more fully meet a subtle property of the Poisson model that requires that the exposure/stratum subdivisions cover sufficiently small ranges of units so that the

probability of occurrence of an event is at least roughly constant for all observations within each cell[166].

In addition to the overall age-adjusted model, two age-specific Poisson models were also created using an attained age of 80 years as the cut point. The age-specific models were adjusted for age using the same age divisions employed in the overall model. The serum vitamin A, prostate cancer association was also examined by periods of follow-up. The initial period consisted of the first three years of follow-up, the second period covered the fourth through eleventh years, and the third follow-up period corresponded to the twelfth through sixteenth years. These time periods were chosen because they best reflected the nature of the follow-up data.

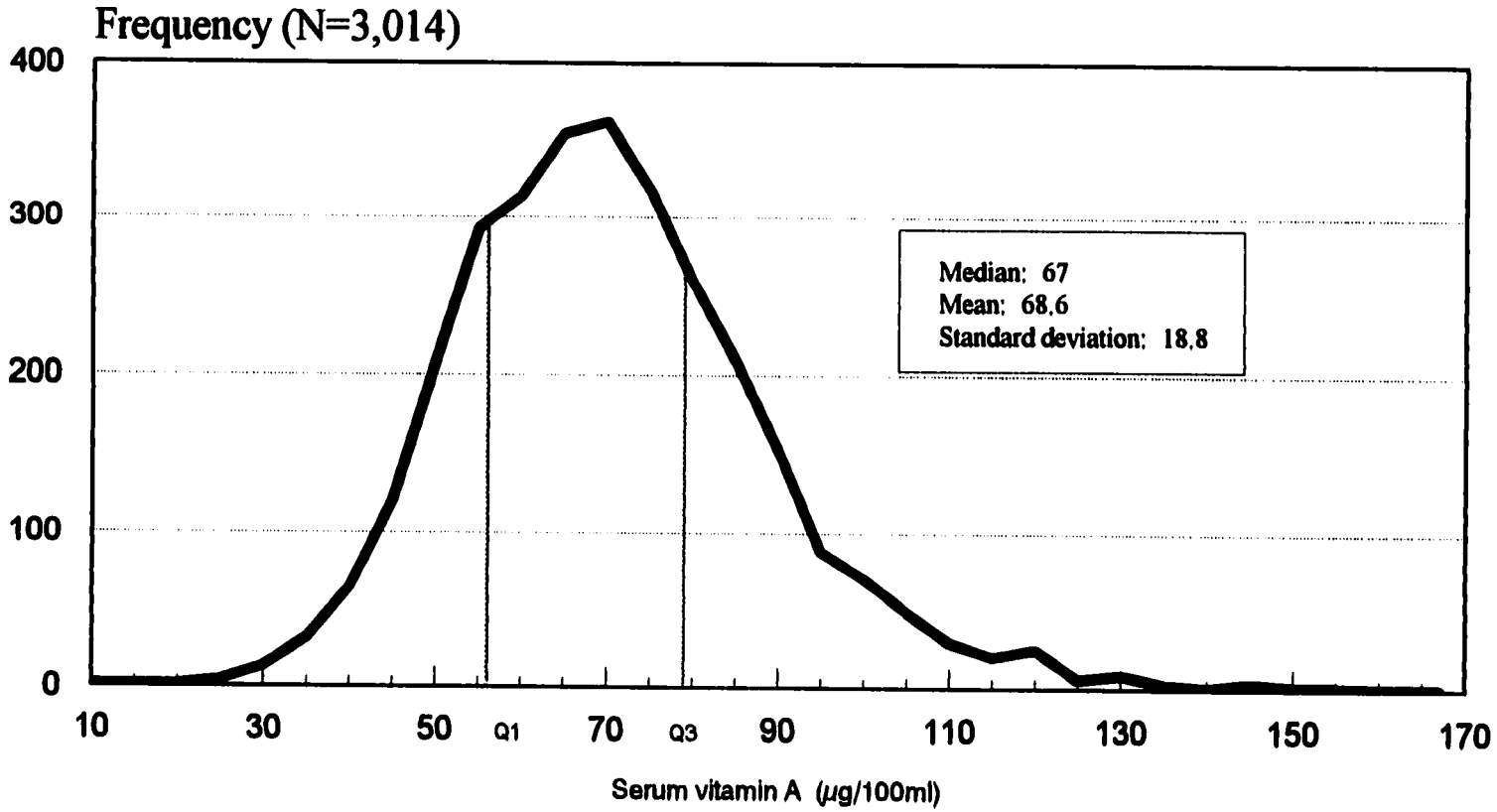
3. RESULTS

3.1 General observations

The frequency distribution of the baseline serum vitamin A values of the 3,014 men included in the present study was found to be skewed to the right with a mean value of 68.6 μg/100ml and a median of 67 μg/100ml (Figure 1). Values ranged from a low of 10 to a high of 327 μg/100ml, though the second highest value was 168 μg/100ml.

Demographic information regarding the cohort is presented in Table 2. In this cohort of 3,014 men aged 35 years or older at time of interview, 42.5% were elderly (i.e. 65 or older). In comparison, figures from the 1971 Canadian census indicated that just under 30% of Canadian men 35 or older were elderly[172]. Those who volunteered to be part of the survey were much more likely to be elderly (61%) than those who were part of the original sample (37%). Similar to the 35 and older, Canadian male population[173], just over half of the cohort had not completed at least one year of high school. Descriptive statistics of the continuous covariates studied in this cohort are given in Table 3. Quartile and median values depicted in this table were those used to categorize variables in subsequent analyses.

FIGURE 1. Frequency distribution of serum vitamin A, males, 35+ years, Nutrition Canada Survey, 1970-72



Q1 and Q3 represent the first (56) and third (79) quartiles, respectively. Depicted distribution excludes one subject with a baseline serum vitamin A value of 327 µg/100ml.

TABLE 2. Baseline demographics of study population, Nutrition Canada Survey, 1970-72.

Variable	Level	Number	% of Total
age group (years)	35-39	318	10.6%
	40-44	336	11.1%
	45-49	292	9.7%
	50-54	274	9.1%
	55-59	255	8.5%
	60-64	260	8.6%
	65-69	479	15.9%
	70-74	367	12.2%
	75-79	231	7.7%
	80-84	145	4.8%
	85+	57	1.9%
	Total	3,014	100%
educational attainment (grade)	< 9	1,532	53.5%
	9 to 13	953	33.7%
	> 13	358	12.8%
	Total	2,843	100%
employment status	Full Time	1,546	51.5%
	Part Time	95	3.2%
	Unemployed	145	4.8%
	Retired	1,146	38.2%
	Other	70	2.3%
	Total	3,002	100%
volunteer status	No	2,337	77.5%
	Yes	677	22.5%
	Total	3,014	100%

TABLE 3. Baseline descriptive statistics for covariates*, Nutrition Canada Survey, 1970-72.

Variable	N	Mean	Standard Deviation	First Quartile	Median	Third Quartile
age[a]	3,014	58.9	14.1	46	60	70
fat[b]	2,922	113.1	63.3	70.7	100.2	140.4
fibre[b]	2,922	4.0	2.6	2.3	3.6	5.2
energy[c]	2,922	2,528	1,083	1,778	2,340	3,098
body mass index[d]	2,932	25.4	3.8	22.8	25.2	27.7

* Frequency distribution of educational attainment, cigarette smoking and alcohol intake appear as part of Table 2.

[a] years; [b] grams/day; [c] calories/day; [d] weight (in kilograms) / height (in metres) squared

3.2 Preliminary analysis results

The relation between baseline levels of serum vitamin A and covariates possibly linked to prostate cancer risk is shown in Table 4. From a visual inspection of this table, cohort members 70 years of age or older at baseline tended to have lower levels of serum vitamin A, while those under 60 years at baseline tended to have higher levels. Body mass index, cigarette smoking, and alcohol consumption all appeared to be positively associated with serum vitamin A. To a lesser extent, so too were energy, fat, and fibre intake as well as education.

The age-adjusted relationship between each of the covariates and prostate cancer development was examined using logistic regression (Table 5). Age itself, as expected, was strongly associated with prostate cancer risk. None of the remaining covariates was found to be associated with prostate cancer risk in this data set.

Tables 6 and 7 depict the results of a stratified analysis undertaken to corroborate the above findings. The variable exhibiting the greatest confounding effect was age group. With the possible exception of alcohol intake, no other covariate showed evidence of being a confounder to the relationship under study (Table 6). Though not shown, an assessment of single variable confounding was also conducted using finer cut points than depicted in Table 6. In general, there was little difference in the adjusted risk ratios by number of strata used. Where the effect was similar, the result corresponding to the lesser number of strata was given.

Control for additional covariates beyond age group did not appear to be warranted (Table 7). In particular, the alcohol and age-adjusted risk ratio for serum vitamin A and prostate cancer did not meaningfully differ from the corresponding age-adjusted risk ratio. Only age group appeared to modify the effect between serum vitamin A and prostate cancer. A statistical test of interaction for age at baseline, dichotomized using a cut point of 70 years, resulted in a two-sided P-value of 0.04 (Table 8).

TABLE 4. Baseline characteristics of cohort in relation to quartiles of serum vitamin A, Nutrition Canada Survey, 1970-72.

		% of cohort in quartiles of serum vitamin A (µg/100ml)			
Variable	N	< 56	56-66	67-78	79+
age group[a]					
35-59	1,475	20.1	23.5	26.6	29.9
60-69	739	23.5	25.3	27.5	23.7
70+	800	32.9	27.6	22.4	17.1
education[b]					
< 9	1,532	26.6	26.4	25.4	21.7
9 to 13	953	19.9	25.5	25.0	29.6
> 13	358	21.2	19.8	29.1	29.9
fat[c]					
< 70.7	733	27.4	25.0	25.2	22.4
70.7 - 100.1	730	26.4	26.2	24.9	22.5
100.2 - 140.3	729	21.3	23.6	27.6	27.6
> 140.3	730	21.0	25.3	26.2	27.5
energy[d]					
< 1778	730	27.4	25.9	23.6	23.2
1778 - 2339	731	25.3	24.6	26.1	23.9
2340 - 3097	730	23.0	24.4	28.4	24.2
> 3097	731	20.4	25.2	25.9	28.6
fibre[c]					
< 2.3	715	27.3	23.1	28.3	21.4
2.3 - 3.5	802	23.4	24.8	25.7	26.1
3.6 - 5.1	695	21.6	26.6	26.5	25.3
> 5.1	710	23.8	25.6	23.5	27.0
body mass index[e]					
< 22.77	732	32.4	26.6	22.3	18.7
22.77 - 25.22	734	23.7	24.8	28.9	22.6
25.23 - 27.66	732	19.7	23.0	28.3	29.1
> 27.66	734	21.0	25.2	23.8	30.0
smoking[f]					
Never	842	29.0	25.5	25.3	20.2
Former	761	21.7	24.3	26.3	27.7
Current					
< 1	80	22.5	27.5	35.0	15.0
1-20	702	25.5	26.9	24.8	22.8
21+	522	19.0	21.3	26.6	33.1
All	1,304	22.7	24.7	26.2	26.5
alcohol[g]					
0	721	31.9	26.1	23.6	18.4
>0-29	1,258	25.0	27.3	25.4	22.4
30+	948	17.0	21.3	28.3	33.4

[a] years; [b] highest grade obtained; [c] grams/day; [d] calories/day; [e] weight (in kilograms) / height (in metres) squared; [f] cigarette smoking status including average number smoked/day for current smokers; [g] drinks/month

TABLE 5. Odds ratios of prostate cancer for baseline covariates.

Variable	Cases	Odds Ratio[#]	95% CI
age group[a]			
35-59	20	1.00	-
60-69	37	3.83	(2.21-6.66)
70+	43	4.13	(2.41-7.08)
education[b]			
< 9	58	1.00	-
9 to 13	28	1.06	(0.66-1.70)
> 13	9	0.95	(0.46-1.96)
fat[c]			
< 70.7	30	1.00	-
70.7 - 100.1	31	1.15	(0.68-1.92)
100.2 - 140.3	19	0.82	(0.45-1.50)
> 140.3	14	0.74	(0.38-1.44)
energy[d]			
< 1778	34	1.00	-
1778 - 2339	31	1.06	(0.64-1.76)
2340 - 3097	15	0.57	(0.30-1.07)
> 3097	14	0.68	(0.35-1.33)
fibre[c]			
< 2.3	29	1.00	-
2.3 - 3.5	26	0.81	(0.47-1.39)
3.6 - 5.1	20	0.78	(0.44-1.40)
> 5.1	19	0.74	(0.41-1.35)
body mass[e]			
< 22.77	23	1.00	-
22.77 - 25.22	25	1.16	(0.65-2.07)
25.23 - 27.66	30	1.42	(0.81-2.47)
> 27.66	17	0.78	(0.41-1.48)
smoking[f]			
Never	31	1.00	-
Former	26	1.01	(0.59-1.73)
Current			
< 1	1	0.35	(0.05-2.63)
1-20	23	1.00	(0.57-1.74)
21+	12	0.89	(0.45-1.80)
All	36	0.91	(0.55-1.51)
alcohol[g]			
0	27	1.00	-
>0 - 29	43	1.05	(0.64-1.73)
30+	26	1.06	(0.60-1.85)

[#] Computed by means of unconditional logistic regression adjusting for age group at baseline (i.e. 35-59, 60-69, 70+ years); [a] years; [b] highest grade obtained; [c] grams/day; [d] calories/day; [e] weight (in kilograms) / height (in metres) squared; [f] cigarette smoking status including average number smoked/day for current smokers; [g] drinks/month

TABLE 6. Single variable assessment of confounding in the serum vitamin A and prostate cancer association[a].

Control Variable	Number of Strata[b]	Crude Risk Ratio[c]	Adjusted Risk Ratio[d]
age group	3	1.54	1.69
education	2	1.60	1.63
fat	2	1.65	1.72
energy	2	1.65	1.71
fibre	2	1.65	1.68
body mass index	2	1.66	1.60
smoking status	3	1.68	1.63
alcohol	3	1.65	1.79

[a] Highest quartile of serum vitamin A (> 82.5 µg/100ml) versus the lowest (≤ 58.5 µg/100ml). Quartiles based on cases only.
[b] age group at baseline (35-59, 60-69, 70+ years), education (< 9, ≥ 9 grade attained), fat (< 100.2, ≥ 100.2 grams/day), energy (< 2,340, ≥ 2,340 calories/day), fibre (< 3.6, ≥ 3.6 grams/day), body mass index (< 25.2, ≥ 25.2 kg/m^2), cigarette smoking status (never, former, current), alcohol (0, >0-29, 30+ drinks/month);
[c] Crude risk ratios were calculated using non-missing records for each particular variable in turn and hence may differ.
[d] Adjusted using Mantel-Haenszel method.

TABLE 7. Assessment of joint confounding in the serum vitamin A and prostate cancer association[a].

Control Variables	Number of Strata[b]	Adjusted Risk Ratio[c]
age group	3	1.78
age group, education	6	1.78
age group	3	1.82
age group, fat	6	1.84
age group	3	1.82
age group, energy	6	1.82
age group	3	1.82
age group, fibre	6	1.85
age group	3	1.83
age group, body mass index	6	1.79
age group	3	1.84
age group, smoking status	9	1.80
age group	3	1.81
age group, alcohol	9	1.85

[a] Highest quartile of serum vitamin A (> 82.5 μg/100ml) versus the lowest (≤ 58.5 μg/100ml). Quartiles based on cases only.
[b] See Table 6 for strata cut points.
[c] Age-adjusted risk ratios were calculated using non-missing records for each particular variable in turn and hence may differ. Mantel-Haenszel adjustment method was used.

TABLE 8. Assessment of two-way interaction involving serum vitamin A.

Baseline Variable	Likelihood Ratio χ^2	Degrees of Freedom	P-value
age group[a] (35-59,60-69,70+)	11.40	6	0.08
age group[a] (35-69,70+)	8.10	3	0.04
education[b]	3.40	6	0.76
fat[c]	1.75	3	0.63
energy[d]	2.42	3	0.49
fibre[c]	0.82	3	0.84
body mass index[e]	3.37	3	0.34
smoking status[f]	7.90	6	0.25
alcohol[g]	1.77	3	0.62

Logistic regression model consisted of serum vitamin A, the interaction variable, and the interaction term for these two variables. The continuous form of the variables for fat, energy, fibre, and body mass index were used.
[a] at baseline in years; [b] highest grade obtained;
[c] grams/day; [d] calories/day; [e] weight (in kilograms) / height (in metres) squared;
[f] cigarette smoking status (i.e. never, former, current); [g] drinks/month

3.3 Non model-based analysis results

Tables 9 through 11 show the results of a non model-based analysis of the association between serum vitamin A and prostate cancer using person-time data. The crude risk ratios for the second through fourth quartiles of serum vitamin A, using the first (lowest) quartile as a referent group, are given in Table 9. No effect was evident for the second and third quartiles. An increase in prostate cancer risk was suggested for those in the fourth quartile. The excess risk of prostate cancer in the fourth quartile increased to 73% after an adjustment was made for age (Table 10). A lesser effect was suggested for the middle quartiles.

The association between serum vitamin A level and the subsequent development of prostate cancer was examined separately for two age groups using an attained age of 80 years as the cut point (Table 11). A total of 685 men turned 80 at some point during their follow-up and hence contributed person time to both groups. Regardless of which quartile of serum vitamin A was used as a basis for comparison, the risk of prostate cancer was found to be considerably stronger for men 80 years of age or older. For these men, statistically significantly increased risks were evident in both the third and fourth quartiles. Prior to the age of 80, only men with a baseline serum vitamin A level in the fourth quartile were found to be at any increased risk. This increased risk was observed to be weak and statistically non-significant (RR = 1.37; 95% CI, 0.72-2.63).

TABLE 9. Crude risk ratios for prostate cancer by serum vitamin A quartile.

Quartile[a]	Cases	Person- years	Risk Ratio	95% CI
1	25	9,915.0	1.00	-
2	26	9,194.9	1.12	(0.65-1.94)
3	24	9,019.6	1.06	(0.60-1.85)
4	25	6,862.1	1.44	(0.83-2.52)

[a] Boundary values for serum vitamin A quartiles were 58.50, 69.00, and 82.25 μg/100ml and were based on records of prostate cancer cases only.

TABLE 10. Age-adjusted risk ratios for prostate cancer by serum vitamin A quartile.

Quartile[a]	Cases	Person-years	Risk Ratio	95% CI
1	25	9,915.0	1.00	-
2	26	9,194.9	1.27	(0.73-2.20)
3	24	9,019.6	1.28	(0.73-2.25)
4	25	6,862.1	1.73	(0.98-3.04)

[a] Boundary values for serum vitamin A quartiles were 58.50, 69.00, and 82.25 μg/100ml and were based on records of prostate cancer cases only.

TABLE 11. Age-specific risk ratios for prostate cancer by serum vitamin A quartile.

Attained Age	Quartile[a]	Cases	Person-years	Risk Ratio	95% CI
< 80[b]	1	19	8,123.4	1.00	-
	2	16	7,963.0	0.95	(0.49-1.84)
	3	13	7,965.9	0.80	(0.39-1.62)
	4	18	6,231.1	1.37	(0.72-2.63)
80+	1	6	1,791.5	1.00	-
	2	10	1,231.8	2.42	(0.88-6.67)
	3	11	1,053.7	3.12	(1.15-8.43)
	4	7	631.0	3.31	(1.11-9.86)

[a] Boundary values for serum vitamin A quartiles were 58.50, 69.00, and 82.25 μg/100ml and were based on records of prostate cancer cases only.
[b] Results were age-adjusted (i.e. < 70, 70-79).

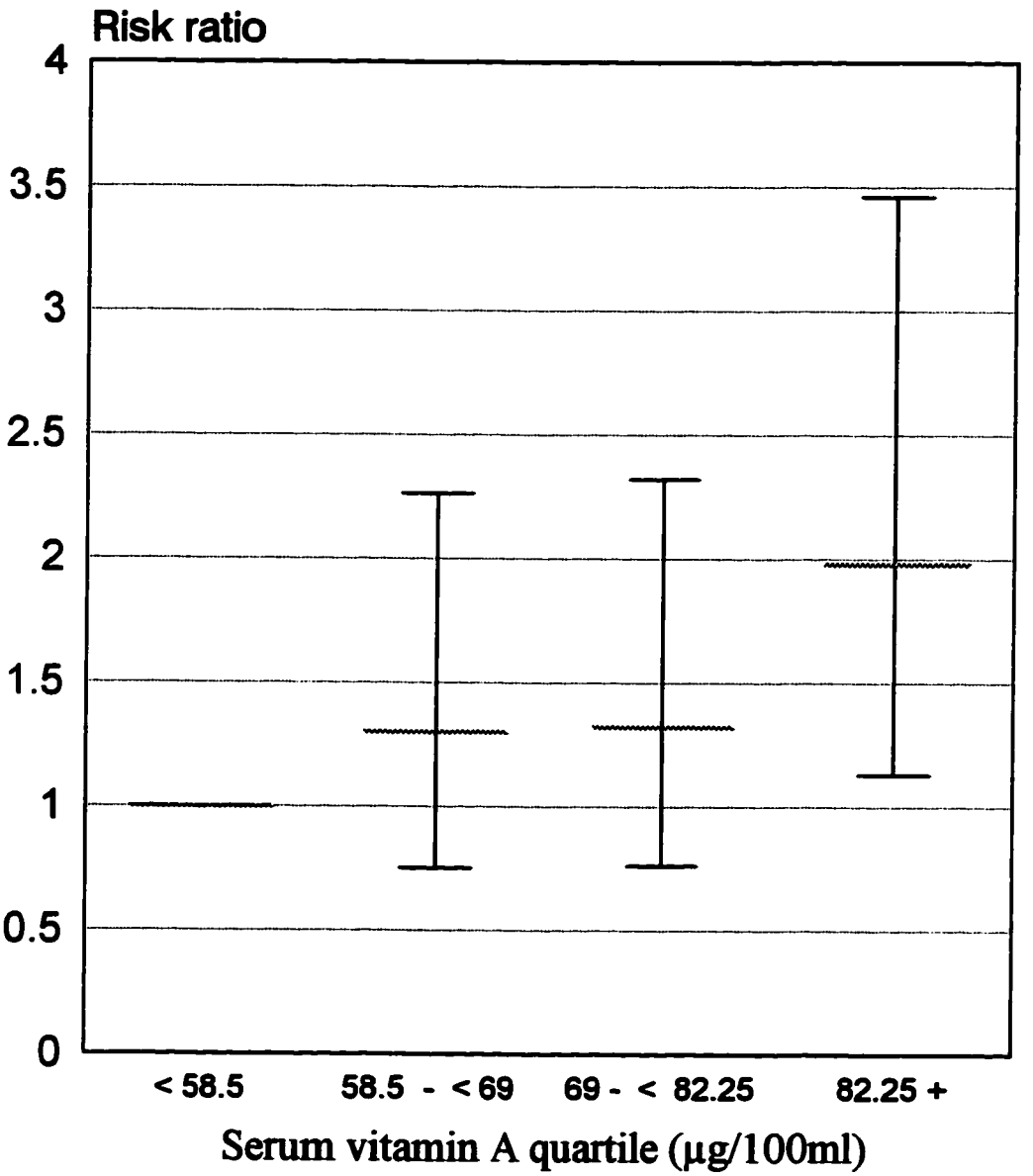
3.4 Poisson regression analysis results

The results of a Poisson regression analysis of the data are presented in Figure 2 (also see Appendix B) and Table 12. Overall, the risk of prostate cancer was observed to increase monotonically with increasing quartile of serum vitamin A (Figure 2). A test for a linear trend was statistically significant. Men with serum vitamin A levels in the upper quartile were found to be at twice the risk as those in the lowest quartile (RR = 1.98; 95% CI, 1.13-3.46).

The risk ratios and corresponding 95% CIs were found to be very similar in the second and third quartiles of serum vitamin A. As such, the two categories were combined into one and the analysis redone (results not shown). The resulting 95% CI for the combined category (0.81-2.13) was tighter than was calculated for each of the individual quartile categories, though it still included the null value of 1.00. The P-value associated with the test for a linear trend was slightly reduced at 0.016.

The interaction between serum vitamin A and attained age (i.e. less than 80 or 80 plus years) was examined. As previously mentioned, 685 men contributed person-time to both age strata. The relationship was found to be stronger among those 80 years of age or older (Table 12). In this age group, men in the second quartile of serum vitamin A experienced an increase in risk of prostate cancer nearly two and-a half times that experienced in the reference (first) quartile. For those in the third and fourth quartiles, the increase in risk exceeded three-fold. Even with the relatively small number of cases

FIGURE 2. Poisson regression analysis of the association of baseline serum vitamin A level with subsequent development of prostate cancer



Results adjusted for age. Vertical lines represent 95% CIs.
Test for linear trend P-value = 0.02.

TABLE 12. Poisson regression analysis of the age-specific association of baseline serum vitamin A level with subsequent development of prostate cancer.

Attained Age	Serum Vitamin A Quartile[a]	Cases	Person-years	Risk Ratio	95% CI
< 80	1	19	8,123.4	1.00	-
	2	16	7,963.0	0.98	(0.50-1.90)
	3	13	7,965.9	0.84	(0.42-1.71)
	4	18	6,231.1	1.57	(0.82-2.99)
Goodness-of-fit P-value = 0.48 (deviance = 18.451 on 18 degrees of freedom).					
80+	1	6	1,791.5	1.00	-
	2	10	1,231.8	2.38	(0.86-6.55)
	3	11	1,053.7	3.08	(1.14-8.32)
	4	7	631.0	3.26	(1.10-9.70)
Goodness-of-fit P-value = 0.23 (deviance = 10.753 on 9 degrees of freedom). Test for linear trend P-value = 0.02.					

Results were age-adjusted by five-year age groups.
[a] Boundary values for serum vitamin A quartiles were 58.50, 69.00, and 82.25 μg/100ml and were based on records of prostate cancer cases only.

in this age group, the increase in risk was statistically significant for the third and fourth quartiles and nearly so for the second quartile. As with the overall model, the risk of prostate cancer increased monotonically with increasing quartile of serum vitamin A and the test for a linear trend was statistically significant.

An analysis similar to the one reported above was also conducted that followed men from age 70 onward (results not shown). Relative to the lowest quartile of serum

vitamin A, increased risks of 70 to 80% for prostate cancer incidence were observed in the second through fourth quartiles. These RR estimates approached but did not achieve statistical significance (i.e 95% CIs included one in each case).

Prior to the age of 80 years, men in the highest quartile of serum vitamin A experienced a 60% increased risk of prostate cancer (RR = 1.57; 95% CI, 0.82-2.99). In this same age group, men in the second quartile experienced virtually the same risk as those in the referent category while a very slight protective effect was noted for those in the third quartile (RR = 0.84; 95% CI, 0.42-1.71). The absence of any semblance of a monotonic relationship between disease and exposure precluded the need of a test to determine the presence of a linear trend in this instance.

The overall association between serum vitamin A and risk of prostate cancer was found to be strongest in the first three years of follow-up though estimates of RR were based on only 19 cases (Table 13). While reduced in comparison to the first follow-up period, RR estimates for the period which covered the fourth through to the eleventh year of follow-up remained elevated. For this period of follow-up, those in the highest serum vitamin A quartile experienced a two and-a-half fold increased risk of prostate cancer in comparison to those in the lowest quartile (RR = 2.56; 95% CI, 1.22-5.37). No association between serum vitamin A and prostate cancer was evident when attention was restricted to more than 11 years of follow-up.

TABLE 13. Association of baseline serum vitamin A level with subsequent development of prostate cancer by duration of follow-up.

Years of Follow-up[a]	Serum Vitamin A Quartile[b]	Risk Ratio	95% CI
0.0 - 3.0			
	1	1.00	-
	2	3.54	(0.94-13.37)
	3	2.37	(0.53-10.63)
	4	3.24	(0.72-14.56)
Goodness-of-fit P-value = 0.58 (deviance = 15.409 on 15 degrees of freedom).			
3.1 - 11.0			
	1	1.00	-
	2	1.30	(0.60-2.82)
	3	1.49	(0.70-3.18)
	4	2.56	(1.22-5.37)
Goodness-of-fit P-value = 0.56 (deviance = 25.587 on 27 degrees of freedom).			
11.1-16.0			
	1	1.00	-
	2	0.61	(0.20-1.81)
	3	0.76	(0.27-2.14)
	4	0.82	(0.27-2.47)
Goodness-of-fit P-value = 0.46 (deviance = 24.296 on 24 degrees of freedom).			

Results were determined using a Poisson regression model adjusting for age by five-year age groups.

[a] For each subject, follow-up commenced at the beginning of the year following the year of interview. Period 1 had 19 cases; period 2, 56 cases; and period 3, 25 cases.

[b] Boundary values for serum vitamin A quartiles were 58.50, 69.00, and 82.25 μg/100ml and were based on records of prostate cancer cases only.

The association between serum vitamin A and prostate cancer was observed to be consistently stronger among men with an attained age of 80 years or more across the three follow-up periods (results not shown). Older men in the highest quartile of the second follow-up period (3.1 to 11.0 years) were shown to be at 4.3 times the risk of those in the lowest quartile (95% CI, 0.95-19.05). The corresponding figure for the third follow-up period (11.1 to 16.0 years) was 1.5 (95% CI, 0.24-8.93). Results for the initial follow-up period (0.0 to 3.0 years) could not be reported as the model failed to converge.

4. DISCUSSION

An analysis of the Nutrition Canada Survey cohort was undertaken to examine the relationship between individual serum vitamin A (retinol and retinyl ester) levels and prostate cancer risk. Men with serum vitamin A levels in the highest quartile were found to be at twice the risk of developing prostate cancer as those whose levels were in the lowest quartile. For men 80 years or older, the observed relative risk exceeded three. These results may reflect the true effect of serum vitamin A levels on the development of prostate cancer. Alternative explanations such as chance, bias, or confounding must also be considered and deemed unlikely before the presence of a valid statistical association can be concluded[174]. The question of causality will then be assessed based on accepted epidemiological criteria[174].

4.1 Evaluation of the presence of a valid statistical association

4.1.1 Role of chance

The 95% CI associated with the overall estimate of prostate cancer risk, highest versus lowest quartile of serum vitamin A, excluded 1.00. The same was true for the subgroup analysis of older men. Thus, chance may be viewed as an unlikely explanation for each of these results.

4.1.2. Role of bias

Two main types of bias can exist in an epidemiological study, observation bias and selection bias[174]. Selection bias is seldom a concern in prospective cohort studies as it is unlikely that the outcome could influence the classification of exposure since exposure is assessed prior to the occurrence of the outcome[175]. While the current study is a retrospective cohort study, it has much in common with prospective cohort studies***. Serum vitamin A levels were determined and fixed prior to follow-up and both the inclusion/exclusion criteria and the method of categorization of serum vitamin A levels were set prior to data inspection (i.e. knowledge of exposure-disease status).

Observation bias was thought to be more of a concern than selection bias in this study. It will be discussed here in terms of the possible misclassification of exposure and/or disease status of study subjects.

***A similar study of serum vitamin A and prostate cancer[25] was referred to by the investigators as a prospective cohort study.

Misclassification of disease status

Follow-up in this study was passive rather than active. As a consequence, uncensored individuals were assumed to have contributed person-time to the conclusion of the follow-up period. A limitation of using passive follow-up was that it may have been incomplete for cancer-free men who emigrated from Canada during the study period. Exactly how many and which study subjects this applied to could not be determined, though the number was likely to have been small and unrelated to prostate cancer incidence.

The current study relied on computerized record linkage of the cohort to the Canadian Mortality Data Base and the Canadian Cancer Registry to identify deaths and cancer cases respectively. The potential for deaths having been missed has been shown to be small due mainly to the quality of the personal identifiers, the completeness of the Canadian Mortality Data Base, and the accuracy of the record linkage process used by Statistics Canada[176]. The potential for cancer cases, in particular prostate cancer cases, to have been missed is also expected to have been small, although it is recognized that the Canadian Cancer Registry is not as complete as the Canadian Mortality Data Base[177]. Unrecorded deaths or cancer cases would likely not be related to exposure status and hence should only serve to attenuate any observed association between serum vitamin A and prostate cancer.

Misclassification of exposure status

Serum vitamin A is under homeostatic control by the body and is largely unaffected by dietary intake of preformed or provitamin A except when liver stores are depleted or at capacity[15]. Serum levels of this vitamin reflect the mean vitamin A intake over an extended period rather than its daily fluctuation[178]. Serum measurements taken for the Nutrition Canada Survey should therefore provide an accurate representation of subjects' usual levels. An exception would occur if a subject had consumed a meal rich in vitamin A shortly before having their blood drawn. Under these circumstances the concentration of retinyl esters in the serum would be temporarily increased[179] leading to an overestimation of the serum vitamin A level for that individual. Such misclassification, if present, was likely to be nondifferential (i.e. unrelated to future prostate cancer risk) and hence should have only served to attenuate the true effect.

Due to the nature of the Nutrition Canada Survey, no data were collected on serum vitamin A levels after the initial baseline measurements. It was therefore necessary to assume, for the purposes of this study, that individual serum levels of this vitamin remained relatively constant throughout follow-up. In this respect, it is fortunate that individual serum vitamin A levels appear to be relatively stable[15]. It is known that serum retinol levels are only very minimally related to vitamin A intake[13]. Studies[180,181] have shown very small (2%) to non appreciable increases in retinol levels after programs of increased vitamin A and supplementation use. Daily supplementation of vitamin A for four weeks resulted in a small (9%), statistically significant mean increase in serum

retinol in a group of healthy women previously identified as having relatively low serum retinol levels[182]. It should be noted that serum vitamin A levels may be depressed in certain rare circumstances such as the development of liver disease or protein-calorie malnutrition[15].

4.1.3 Role of confounding

It is possible that the observed effect between serum vitamin A and prostate cancer reflected some other factor not controlled for in this study. For a covariate to be a confounder, it would have had to have been related to serum vitamin A and, independent of this association, it would also have had to have been a risk or protective factor for prostate cancer. Aging is known to be a risk factor for prostate cancer and was found to be associated with serum vitamin A levels in this study. To control for this potential source of bias, estimates of RR were age-adjusted.

Besides age, the only other established risk factors for prostate cancer are heredity and ethnic group/country of residence[70]. While the Nutrition Canada Survey did not collect information on either of these factors, the fact they were uncontrolled for in the analysis is unlikely to have biased the results. There is no evidence to suggest that a hereditary predisposition to prostate cancer is associated with high serum vitamin A levels. As well, any bias introduced by the failure to control for heredity should have been restricted to younger age groups as hereditary predisposition to prostate cancer is usually realized at a relatively young age[36]. The effect in this study, however, was found

to be greatest for those 80 years or older. The number of black subjects in this study is quite likely to have been extremely small due to the ethnic distribution of the Canadian population in the early 1970's[183]. Hence any bias introduced into this study by not controlling for this factor would most likely have been correspondingly small. If it were to exist, it would likely have served to reduce the magnitude of the observed effect as available evidence suggests that serum vitamin A levels are lower in blacks than in whites[184,185].

While epidemiologic evidence suggests that fat, or some component of fat, may be a weak risk factor for prostate cancer, no such relationship was observed in this study. This finding, however, does not preclude the possibility that the results concerning serum vitamin A and prostate cancer were confounded by dietary fat. The Nutrition Canada Survey used a 24-hour food recall to assess dietary fat intake. While useful for estimating population characteristics, this method is not considered appropriate for estimating individual dietary intake[157]. Any bias introduced by the inability to adequately control for dietary fat intake is reasoned to be quite small. If dietary fat is a risk factor for prostate cancer, it does not appear to be a strong one. As well, serum retinol levels are only weakly related to preformed vitamin A intake, hence one would not expect serum vitamin A levels to be anything more than minimally related to dietary fat intake.

Although the Nutrition Canada Survey did not collect information on them, factors such as physical activity, sexual activity, hormonal levels, and vasectomy have all been

postulated as risk factors for prostate cancer. However, the evidence linking these variables to prostate cancer is inconsistent at best and they are generally not considered to be risk factors for this disease. In addition, none of these factors have been associated with serum vitamin A. Body mass index, highest level of education attained, alcohol intake, and cigarette consumption have also been studied as risk factors for prostate cancer. While information was available on these variables, they were not controlled for in the multivariate analysis because they were not found to be risk factors for prostate cancer in this cohort.

A bias could have been introduced if there was differential health care use by study subjects according to serum vitamin A status. In theory, men who visited their doctors more frequently may have been more likely to have been diagnosed with latent prostate cancer[6]. The current study was unable to distinguish between clinically significant and latent cases. As such, health care use could have been a confounder, conditional on it being associated with serum vitamin A level. To date, however, there is no evidence to suggest that serum vitamin A levels are related to health care use.

Because little is known about the etiology of prostate cancer, it remains possible that the current results reflect, at least partially, the confounding effect of some unknown risk factor(s).

In summary, chance, bias, and confounding were all determined to be unlikely alternative explanations for the effect observed in this study. It is therefore appropriate to conclude that a valid statistical association between serum vitamin A and prostate cancer exists in these data.

4.2 Causal inference

The presence of a valid statistical association, while very important, does not necessarily imply a causal relationship exists between serum vitamin A and prostate cancer. A number of criteria have been proposed for assessing causality including the strength of the association, the biologic credibility of the association, the consistency of the findings, the presence of a trend in effect, as well as the proper temporal sequence[174].

4.2.1 Strength of association

The strength of the association observed between relatively high serum vitamin A levels and the incidence of prostate cancer, especially for men 80 years or older, is weak evidence in favour of a causal inference.

4.2.2 Consistency of association

It is difficult to assess the consistency of the relationship between serum vitamin A and prostate cancer. While some studies, such as the present one, used serum vitamin A as an exposure of interest, others have restricted their attention to serum retinol. The exposure variable used, has mainly been a function of the time period in which the serum samples for a particular study were analysed in the laboratory. Since 1975, high-pressure liquid chromatography (HPLC) has become the method of choice for determining serum levels. With HPLC, retinol and its esters can be easily separated[186].

The Nutrition Canada Survey quantified serum vitamin A levels using fluorometric measurement in ultraviolet light[156]. In the National Health and Nutrition Examination Survey I, the source of exposure data for Reichman and colleagues'[25] study of serum vitamin A and prostate cancer, a colorimetric method[187] was used. These older analytic techniques were not specific enough to separate retinol and retinyl esters[186]. In general though, serum vitamin A levels obtained by colorimetric and ultraviolet methods are comparable to those obtained by HPLC with fluorometric detection[178].

The current study represents only the second study to specifically examine the relationship between serum vitamin A and prostate cancer. In the study by Reichman et al.[25], men with a baseline serum vitamin A level in the lowest quartile were found to be at a significantly increased risk of developing prostate cancer in comparison to those men in the highest quartile. The investigators reported that the observed effect was stronger among men 70 years or older.

Why the findings of the current study should contradict those of Reichman et al.[25] remains unclear. The two cohort studies were similar in many respects including the time period of the study, the length of follow-up, the overrepresentation of elderly and low income individuals, and the adjustment for the confounding effects of age. Differences included method of follow-up, age range studied, and most likely the proportion of black subjects included.

In the study by Reichman and colleagues[25], approximately 30% of the prostate cancer cases were among blacks. However, a slightly stronger inverse relationship with serum vitamin A was observed among whites than among the combined cohort. Reichman et al.[25] restricted their analysis to men 50 to 74 years of age at baseline. Given that the inverse effect they observed was strongest among the oldest group they studied, it is unlikely that the absence of even older men would account for the inconsistent results between this study and the present one. Finally, while the method of follow-up differed in the two studies under consideration, each method was thought to introduce only nondifferential bias to their respective studies. Such a situation would act to attenuate the observed effect in each study and hence lessen the magnitude of the difference in results.

The relationship between serum retinol and prostate cancer has been the focus of three previous epidemiologic studies. An increased risk of prostate cancer was associated with lower serum retinol levels in a hospital-based case-control study conducted in the Netherlands[22]. Given the design of the study, however, a treatment effect or an effect from the disease process itself could not be easily dismissed. This is an especially relevant consideration given that low serum retinol levels may be a metabolic consequence of cancer rather than a precursor[155]. The findings from two nested case-control studies differed with regard to serum retinol and prostate cancer incidence. While one study suggested an inverse relationship[23], a weak positive association was observed in the other[24] though the latter study consisted of only 32 prostate cancer cases. While serum retinol and serum vitamin A may be similar (serum retinol constitutes

approximately 90% of serum vitamin A under normal physiologic conditions) they are not identical. As such, some caution should be used in the interpretation of any comparison of studies involving these two entities.

The relevance of dietary vitamin A studies to studies based on serum levels is unclear. Still, a number of dietary studies of preformed vitamin A have found a positive association with the development of prostate cancer[109,130,139,141,143]. Like the present study, some of these studies[130,139,143] found this effect to be enhanced or restricted to subjects over the age of 70 years. Three reports concerning total vitamin A and prostate cancer[54,131,134] also observed a positive association, and two of these[54,131] noted a heightened effect among older study subjects.

4.2.3 Biological plausibility of association

One explanation for why the wide international variation in prostate cancer incidence is confined to its clinically overt invasive form[4] is that there is variation in the prevalence of exposure to some unknown cancer promoter. The enhancement of carcinogenesis by retinoids in animal models has been demonstrated experimentally[188-191] and appears to be promotional in nature[191]. In humans, vitamin A has been shown to enhance the proliferation of prostatic epithelial cells[192] and thus may stimulate the progression of latent prostate cancer.

Although a mechanism by which vitamin A may enhance prostate cancer risk has yet to be established, a role for testosterone has been suggested. Vitamin A has been shown to be positively associated with testosterone in rats[193,194] and it has been postulated that elevated levels of testosterone are involved in the development of prostate cancer[40]. Kolonel et al.[139] have further stated that if the association between vitamin A and testosterone holds for humans then the effect may be more significant in older men because their natural levels of testosterone are declining.

A second possibility is an interaction between vitamin A and zinc. Zinc has been shown to be involved in the metabolism of retinol in rats[195] and may also play a role in the development of prostate cancer[18,196]. Heshmat et al.[134] hypothesized that increased consumption of vitamin A over many years would require increased amounts of retinol-binding protein for its transport, which in turn would require increased amounts of zinc for its synthesis in the liver. They speculated that this process could result in a chronic lowering of the proportion of zinc available for prostatic tissue, eventually promoting the development of cancer.

4.2.4 Biologic gradient (trend in effect)

In this study there was evidence of a biological gradient (a trend in effect) between serum vitamin A and prostate cancer. The risk of prostate cancer was observed to increase monotonically with increasing level of serum vitamin A. Tests for linear trend

were statistically significant for both the overall model and the model restricted to older men.

4.2.5 Temporal sequence

Because prostate cancer has a long latency period, a potential concern was that some subjects had undiagnosed prostate cancer at the time of blood collection. If prostate cancer was known to elevate serum vitamin A levels in men and the positive association observed between these levels and this disease was restricted to the first few years of follow-up, then the temporal sequence of events would have to be seriously questioned.

While the effect of prostate cancer, per se, on serum vitamin A levels is not known, there is evidence to suggest that cancer in general acts to lower serum retinol levels[155]. In addition, a statistically significant increased risk of two and-a-half fold was observed for the period which covered the fourth through to the eleventh year of follow-up. It is therefore unlikely that the positive association observed in this study between serum vitamin A and prostate cancer can be explained by the presence of undiagnosed prostate cancer at baseline. The lack of an association beyond 11 years of follow-up is thought to be due, at least in part, to the effects of nondifferential misclassification. Such misclassification almost always increases in magnitude with increasing duration of follow-up.

5. CONCLUSION

This study suggests that serum vitamin A levels in men are positively associated with risk of developing prostate cancer. The results indicate that this effect is greatest among men 80 years of age or older. Chance, bias, and confounding were all viewed as unlikely explanations for these findings. However, because little is known about the etiology of prostate cancer, it remains possible that the current results reflect, at least in part, the confounding effect of some unknown risk factor(s). In addition, if health care use is associated with serum vitamin A level, it could have confounded the observed association as this study was unable to distinguish between clinically significant and latent prostate cancer cases.

While a biological mechanism has yet to be established, the strength of the observed association, evidence of a trend in effect, and the establishment of a proper temporal sequence, all argue towards a causal association between serum vitamin A and prostate cancer. However, because this is the first study to report such an association, the findings must be interpreted with caution. This is especially true given that a comparable study from the United States[25] reported results that contradict the present study. Further research is needed to clarify the role of serum vitamin A in prostate cancer etiology.

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APPENDIX A

Summary of epidemiologic studies of vitamin A/carotenoids and prostate cancer.

TABLE A1. Case-control studies

Investigator	Place	Number of Subjects	Summary of Findings
Ghadirian[129]	Montreal, Quebec, Canada	232 cases 231 population controls	No association for total vitamin A or β-carotene. Very weak association for retinol (OR = 0.77).
Rohan[125]	Ontario, Canada	207 cases 207 population controls	Reduced risk for total vitamin A (OR = 0.73) and for retinol (OR = 0.66). No association was seen for β-carotene intake.
Talamini[130]	Northern Italy	271 cases 685 hospital controls	Increased risk for retinol (OR = 2.2*), especially liver (OR = 6.9*), and β-carotene (OR = 1.5) among men 70 years or older but not among younger men.
West[131]	Utah, USA	358 cases 679 population controls	Highly suggestive increased risk for β-carotene (OR = 1.4) and total vitamin A (OR = 1.6) among older men (68-74 years). A protective effect for total vitamin A (OR = 0.7) and β-carotene (OR = 0.6) intake was suggested among younger men (45-67 years) with aggressive tumours.
Mettlin[132]	Buffalo, NY, USA	371 cases 371 hospital controls	Decreased risk (OR = 0.3*) for β-carotene intake among men less than 69 years-old.

Odds ratios (OR) are based on the extreme categories.
Total vitamin A includes preformed and provitamin A.
* Indicates a statistically significant result.

TABLE A1. Continued

Investigator	Place	Number of Subjects	Summary of Findings
Hayes[22]	Rotterdam, Netherlands	134 cases 130 hospital controls	Increased risk for lower serum retinol (OR = 2.8*, linear trend P = 0.04). No association for serum β-carotene (OR = 1.3, linear trend P = 0.47).
Ohno[133]	Kyoto, Japan	100 cases 100 hospital controls	Increased risk for lower β-carotene intake (OR = 2.9). The association is suggestive for those aged 50-69 years and significant for those 70-79. Increased risk for lower β-carotene intake from green and yellow vegetables (OR = 2.2*). Increased risk for higher β-carotene intake from fruits (OR = 2.0*).
Kolonel[139]	Oahu, Hawaii, USA	452 cases 899 population controls	Increased risks among men 70+ years for total vitamin A including supplements (OR = 2.0*, trend with age) and retinol including supplements (OR = 1.4, linear trend P = 0.1). No association for carotenoids except papaya[197].
Ross[52]	Los Angeles, USA	142 black cases 142 black controls 142 white cases 142 white controls	Decreased risk, among blacks, for β-carotene (OR = 0.6). Protective effect for β-carotene among men with low fat. Decreased risk (OR = 0.5*) for consumption of carrots among whites.
Middleton[140]	Buffalo, NY, USA	219 cases 1,238 hospital controls	Suggested increased risk for total vitamin A noted as being essentially β-carotene (OR = 1.3).

Odds ratios (OR) are based on the extreme categories.
Total vitamin A includes preformed and provitamin A.
* Indicates a statistically significant result.

TABLE A1. Continued

Investigator	Place	Number of Subjects	Summary of Findings
Talamini[46]	Pordenone, Italy	166 cases 202 hospital controls	Weak positive association with green vegetable intake (OR = 1.2).
Mishina[100]	Kyoto, Japan	100 cases 100 population controls	Increased risk (OR = 2.0) for infrequent consumption of green and yellow vegetables.
Heshmat[134]	Washington, DC, USA	180 cases 180 hospital controls	Increased risk for total vitamin A among men 30-49 year-olds (P<0.01) and those 50+ (P<0.07).
Graham[54]	Buffalo, NY, USA	262 cases 259 hospital controls	Increased risk for total vitamin A among men < 70 years-old (OR = 1.6) and those 70+ (OR = 2.0, linear trend P < 0.05).
Schuman[135]	Minnesota, USA	223 cases 223 neighbourhood controls	Decreased risk for consumption of carrots (OR = 0.45), liver (OR = 0.54), peas (OR = 0.68), tomatoes (OR = 0.71), and cabbage (OR = 0.72).

Odds ratios (OR) are based on the extreme categories.
Total vitamin A includes preformed and provitamin A.
* Indicates a statistically significant result.

TABLE A2. Cohort studies

Investigator	Place	Number of Subjects	Summary of Findings
Daviglus[142]	Chicago Illinois, USA	1,899 Western Electric Company male employees; 132 cases.	No association for β-carotene.
Giovannucci[141]	USA	47,894 health professionals; 773 cases.	No association with total vitamin A or β-carotene. Increased risk for retinol (RR = 1.3*, linear trend P = 0.004) especially for men older than 70 years of age (RR = 1.7*, linear trend P = 0.002).
Hsing[23]	Washington County, Maryland, USA	25,802 men; 103 cases, 103 population controls (nested case-control study).	Decreased risk for serum retinol (OR = 0.40) and serum lycopene (OR = 0.50) especially among men less than 70 years-old at baseline (OR = 0.26 and 0.35). No association for serum β-carotene.
Knekt[24]	Finland	21,172 men; 32 cases, 59 neighbourhood controls (nested case-control study).	Increased risk for serum β-carotene (RR = 5.0*) and a weak association for serum retinol (RR = 1.4).
Reichman[25]	USA	2,440 men; 84 cases.	Increased risk for lower serum vitamin A level (RR = 2.4*), especially for those 70+ years (RR = 3.6*).

Relative risks (RR) are based on the extreme categories.
Total vitamin A includes preformed and provitamin A.
* Indicates a statistically significant result.

TABLE A2. Continued

Investigator	Place	Number of Subjects	Summary of Findings
Hsing[109]	Minnesota and northeastern USA	17,633 Lutheran men; 149 fatal cases.	Increased risk for total vitamin A (RR = 2.8*), retinol (RR = 1.7) and β-carotene (RR = 1.9*) among those less than 75 years-old. Among those 75+ years, decreased risk for total vitamin A (RR = 0.4*), and β-carotene (RR = 0.2*); no association for retinol. Test for linear trend was significant in each case.
Severson[68]	Oahu, Hawaii, USA	7,999 Japanese men; 174 cases.	Increased risk for fruit intake (RR = 1.6).
Mills[49]	California, USA	14,000 Seventh-day Adventist men; 180 cases.	No association with an index of fruit consumption. Decreased risk for dried fruits (RR = 0.6, P = 0.06) and for tomatoes (RR = 0.6*).
Paganini-Hill[143]	Laguna Hills, California, USA	4,280 men from a retirement community; 83 cases.	No association for β-carotene. Increasing risk for vitamin A supplements (RR = 1.64, linear trend P = 0.04).
Hirayama[144]	Japan	122,201 men; 183 fatal cases.	Decreased risk with intake of green-yellow vegetables in men less than 75 years-old (RR = 0.55). Suggested positive association for men 75 years and older.
Snowden[138]	California, USA	6,763 Seventh-day Adventist men; 99 fatal cases.	No apparent association with fruit and vegetable intake.

Relative risks (RR) are based on the extreme categories.
Total vitamin A includes preformed and provitamin A.
* Indicates a statistically significant result.

APPENDIX B

Poisson regression analysis of the association of baseline serum vitamin A level with subsequent development of prostate cancer.

Serum Vitamin A Quartile[a]	Cases	Person-years	Risk Ratio	95% CI
1	25	9,915.0	1.00	-
2	26	9,194.9	1.30	(0.75-2.26)
3	24	9,019.6	1.32	(0.76-2.32)
4	25	6,862.1	1.98	(1.13-3.46)

Goodness-of-fit P-value = 0.28 (deviance = 33.915 on 30 degrees of freedom).
Test for linear trend P-value = 0.02.

Results were age-adjusted by five-year age groups.

[a] Boundary values for serum vitamin A quartiles were 58.50, 69.00, and 82.25 μg / 100ml and were based on records of prostate cancer cases only.