Université de Montréal

Sunlight exposure and prostate cancer risk: a case-control study in Montreal, Canada

par

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Présenté par

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a été évalué par un jury composé des personnes suivantes:

Sami Haddad……président-rapporteur

Jérôme Lavoué……directeur de recherche

Marie-Élise Parent……co-directrice de recherche

Maryse Bouchard……membre du jury

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Résumé

Objectifs: Évaluer l'association entre l'exposition récréative, professionnelle et globale au soleil et le risque de cancer de la prostate (CaP). **Méthodes:** Dans le contexte d'une étude cas-témoins sur le CaP menée à Montréal, Canada, des entrevues ont été complétées auprès de 1371 cas incidents de CaP diagnostiqués en 2005-2009, et 1479 témoins de la population générale. Des questionnaires détaillés ont permis d'obtenir de l'information sur la fréquence et la durée de participation à toute activité extérieure lors des loisirs durant l'âge adulte, ainsi qu'une description de chaque emploi tenu au cours de la vie. Une matrice emploi-exposition canadienne a été appliquée à chaque emploi afin d'assigner un niveau d'exposition professionnelle au soleil. Des indices cumulatifs de l'exposition au soleil basés sur le nombre d'événements récréatifs, la durée d'exposition professionnelle, ainsi qu'un indice d'exposition global ont été développés. La régression logistique a été utilisée pour estimer l'association entre chaque indice d'exposition et le CaP, en ajustant pour des variables de confusion potentielles. **Résultats:** Globalement, il n'y avait pas d'association entre chacun des indices d'exposition et le risque de CaP. Certaines tendances en accord avec un risque légèrement plus faible chez les hommes exposés au soleil ont été observées mais les résultats n'étaient pas statistiquement significatifs et il n'y avait pas de relation dose-réponse. **Conclusion:** Notre étude apporte peu de soutien à l'hypothèse d'une association entre l'exposition au soleil et le risque de développer un cancer de la prostate.

Mots-clés: Epidémiologie, cas-témoins, cancer, prostate, soleil, loisir, travail

Abstract

Objectives: To investigate the association between sunlight exposure during leisure time, at work and globally, and prostate cancer (PCa) risk. **Methods:** In the context of a case-control study conducted in Montreal, Canada, interviews were conducted with 1371 incident PCa cases diagnosed between 2005 and 2009, and 1479 population controls. Detailed questionnaires were used to elicit the frequency and duration of engagement in any outdoor recreational activity during adulthood, as well as a description of each job held over the lifetime. A Canadian job-exposure matrix was applied to attribute a sunlight exposure level to each job. Cumulative indices of sunlight exposure were developed based on the number of outdoor leisure-time events, the duration of occupational exposure, separately and combined. Logistic regression was used to estimate the association between each sunlight exposure index and PCa, adjusting for potential confounding factors. **Results:** As a whole, there was no association between any of the exposure indices, and PCa risk, or PCa aggressiveness. Some trends for slightly lower PCa risks among men exposed to sunlight were observed, but results were not statistically significant and there was no dose-response pattern. **Conclusion:** Our findings provide little evidence for an association between sunlight exposure during adulthood and prostate cancer development.

Keywords: Epidemiology, case-control, cancer, prostate, sunlight, leisure, occupation

Table of Contents

List of tables

List of figures

List of abbreviations

AIC	Akaike Information Criterion
BCR	biochemical recurrence
BMI	body mass index
BPH	benign prostatic hyperplasia
CanSIC80	Canadian Standard Industry Classification of 1980
CAREX	Carcinogen Exposure - Canada
CCDO	Canadian Classification and Dictionary of Occupations 1971
CDuration	Cumulative duration of sunlight exposure during leisure-time in hours
CEvents	Cumulative number of leisure-time events entailing sunlight exposure
CHUM	Centre Hospitalier de l'Université de Montréal
CO	Cumulative occupational sunlight exposure index
DRE	digital rectal examination
GSE	Global sunlight exposure index
GWH	General work history
IARC	International Agency for Research on Cancer
MMA	Montreal metropolitan area
NCI	National Cancer Institute
NHANES	National Health and Nutrition Examination Survey
NO	nitric oxide
NOC-S	National Occupational Classification - Statistics (2006)
OR (95% CI)	Odds ratio (95% Confidence Intervals)
PCa	prostate cancer
PIN	prostatic intraepithelial neoplasia
PROtEuS	Prostate Cancer & Environment Study
PSA	prostate specific antigen
SEER	Surveillance, Epidemiology and End Results
SO	Simplified occupational sunlight exposure index
TEMIS	Tropospheric Emission Monitoring Internet Service
TOMS	Total Ozone Mapping Spectrometer
UV	Ultraviolet
UVI	UV index
VDR	vitamin D receptor

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This thesis is dedicated to my loving mother, who nourishes my life;
and to my deceased father, who looks over me from Heaven.

1.0 Structure of the thesis

In sections 1 and 2 of this thesis, we provided a general introduction and motivation for this work and in section 3, the objectives of the project. Section 5 presents a brief general portrait of the case-control study on which the analysis was performed. Section 6, formatted as a scientific manuscript, presents the results of the analysis of sunlight exposure during leisure time and prostate cancer. Section 7 presents the methods and results specific to the analysis of sunlight exposure at work and prostate cancer, taking leisure exposure into account. Finally, section 8 contains an integrated discussion of the results.

2.0 Introduction

Prostate cancer (PCa) is the leading cause of cancer and the third cause of cancer death among the male population in Canada, as well as in Quebec. [1] It is a major public health concern and yet its risk factors remain unclear. The only well-established factors linked to PCa are increasing age, being from African ancestry and having a positive first-degree family history of PCa.

Migrant studies have suggested that immigrants acquire the prostate cancer risks of their adoptive countries [2, 3], suggesting a possible etiological role of environmental factors. Many modifiable risk factors have been studied, but results have been controversial. Ecological studies [4, 5] have linked an increased risk of PCa to geographical regions further away from the equator, suggesting that differences in sun exposure may explain differences in PCa risks. Some analytical epidemiological studies [6, 7] have also found a decreased risk of PCa among individuals with higher sunlight exposure. The potential biological mechanism most often called upon to explain these findings involves vitamin D levels. Experimental research on vitamin D has indeed demonstrated anti-tumour properties such decreasing cell proliferation and increasing apoptosis. However, epidemiological findings to date on this topic are not consistent, with some recent studies reporting instead a positive relationship between sunlight exposure and PCa risk [8, 9]. No clear underlying biological mechanism has been evoked to explain a positive association. More research aimed at clarifying the role of sunlight exposure in prostate cancer development is thus warranted.

We present here findings from the Prostate Cancer & Environment Study (PROtEuS), a large population-based case-control study conducted in Montreal. To our knowledge this is the first Canadian study to assess the association between sunlight exposure and prostate cancer risk.

3.0 Literature review

3.1 Prostate cancer

3.1.1 Clinical description

The prostate is a gland located anterior to the rectum and below the urinary bladder. Its base is linked to the bladder by the prostatic urethra where prostatic fluids are discharged to be part of the seminal fluid. The prostatic secretion is an alkaline fluid necessary for a viable sperm. [10, 11] First described by McNeal [12], the prostate is made of four zones with different embryonic origins, different composition and different susceptibility to pathologies: fibromuscular zone, the transition zone, the central zone and the peripheral zone. Benign prostatic hyperplasia (BPH) typically develops in the transition zone; around 75% of the prostate cancers forms in the peripheral zone, of which 95% are adenocarcinoma [10], and prostatitis occur generally in the central zone where the ejaculatory ducts are located. [11]

Required for the normal development and maintenance of the prostate gland, androgens, mainly testosterone, induce terminal differentiation of prostate epithelial cells and promote proliferation of these cells by inducing secretory growth factors in the stroma [13]. Testosterone also regulates the gene for prostate specific antigen (PSA) [14], which is a serine protease part of the seminal fluid involved in the liquefaction of the semen.

It has been suggested that a proliferative inflammatory atrophy is a precursor to prostatic intraepithelial neoplasia (PIN) and to PCa [15]. It has also been thought that PIN is a precursor to PCa [16]. Since proliferative inflammatory atrophy is frequently associated with chronic inflammation, it has been thought that the lesion arises from a regenerative proliferation of prostatic epithelial cells caused by a prostatic injury precipitating an inflammatory response. Proliferative cells in those atrophic areas were shown to have molecular signs of stress, such as high levels of glutathione S-transferase A1, for which the loss of genetic expression may indicate the transition to a PIN or PCa [17-19]. Autopsies have shown that around 30% of American men were presented with PIN or small foci of histological PCa in their thirties and forties [20], suggesting that cells giving rise to PCa may be initiated in early life and that tumour progression occur over a life course.

A few hormones have been hypothesized to be involved in the development of PCa, such as androgens and insulin-like growth factors (IGF). In support of an etiologic implication of androgens in the development of PCa, this cancer has been shown to be less prevalent in castrated men [21], and laboratory studies have demonstrated that PCa is induced by administration of testosterone in rats [22]. Despite this, no conclusive role of androgens on the development of prostate cancer has been found in epidemiologic research [23-29]. Research results on the relationship between the IGF pathway and PCa are more consistent. A handful of epidemiologic studies have shown a positive association between PCa and IGF-1. In addition, IGF binding protein 3, which can inhibit activation of IGF receptor and thus mediates IGF effects, has been shown to be inversely associated with decreased PCa risk. [30-35]

The most widely used grading system for PCa is the Gleason system developed by Dr. Donald Gleason, based on the structural growth patterns of the prostate adenocarcinoma. The Gleason score is assigned by a pathologist based on tissue extracted from a prostate biopsy or resection. A grade of 1 to 5 is given to the two most predominant area of the biopsy, as primary and secondary scores. A grade of 1 is assigned to the most differentiated pattern and a grade of 5, to the least. The primary and secondary scores are then summed up to give the final Gleason score. In general practice, a PCa with a score of 7 or higher is considered to be aggressive [36], however a Gleason score of 7 with primary score of 4 (4+3) is considered to be more aggressive than with primary score of 3 (3+4). [37] Men with a Gleason score of 4+3 have a higher occurrence of biochemical recurrence (BCR), defined as a PSA level of 0.4ng/ml or higher after a radical prostatectomy [38], than men with a Gleason score 3+4. Men with BCR have a worse prognosis of PCa, i.e. higher risk of cancer progression [39]. Also, men with BCR and short PSA rising time or a fast occurrence of BCR after a primary treatment have an even worse outcome in terms of prostate-cancer specific mortality [40]. After a radical prostatectomy, men with Gleason score of 6 or less, 3+4, 4+3 and 8 to 10, the 15-year prostate cancer specific mortality rates have been shown to be 0.2% to 1.2%, 4.2% to 6.5%, 6.6% to 11% and 26% to 37% respectively [41].

Staging of the disease makes use of the TNM system developed by the American Joint Committee on Cancer. This system includes the description of the extent of the tumour (T),

the involvement of the lymph nodes (N) and the presence of distant metastases (M). [10] Assigning a PCa stage thus requires additional clinical evaluations following an initial positive pathology finding.

Two commonly-used screening tools for PCa detection include digital rectal examination (DRE) and PSA testing. Due to the proximity of the peripheral zone of the prostate to the rectum, DRE has been extensively used to detect lumps that could indicate a tumour. In blood tests, PSA levels >4.0 ng/ml may indicate the presence of a malignant tumour, but the value of the test remains controversial because increased levels could also be a result of BPH, infections, ejaculation within 48 hours of the test, trauma and age [10].

Treatment options vary on a number of factors such as age, grade and stage of the cancer. These options include prostatectomy, androgen deprivation, radiotherapy, chemotherapy and when bone metastasis is present, bone-directed therapy. When the PCa tumour is less aggressive, active surveillance can be another disease management option. [42]

3.1.2 Descriptive epidemiology

Approximately 23 600 PCa cases are predicted for 2013 in Canada, representing 25% of all male incident cancer cases, with an age-standardized incidence rate of 104 per 100 000 people and 3,900 deaths. In Quebec, around 5,400 men will be diagnosed and 830 will die from PCa in 2013. This makes PCa the first cause of cancer incidence and third cause of cancer mortality in the male population in Canada and in Quebec. The 5-year survival rate estimated for 2006-2008 is 96%. [1]

In the world, PCa is the second most diagnosed cancer for men, after lung cancer, with about 75% of the cases concentrated in developed countries. The highest incidences are found in Australia/New Zealand, Western and Northern Europe and North America for the developed regions; the Caribbean, South America and sub-Sahara Africa for the developing regions. The lowest age-standardised incidence rates are found in South-East Asia. [43]

PCa is the 6th leading cause of death among male cancers patients worldwide with higher mortality rates among populations of Black men and lower rates among the Asian population, especially in Eastern Asia. While incidence rates between developed countries and developing

countries can vary by as much as 25 fold, the mortality rates appear less variable (up to 10 fold differences across countries). Higher variations for incidence might be explained by the extensive practice of screening by PSA and biopsy in developed countries, although is it thought that PCa detection would not be the sole factor underlying these variations [43].

3.1.3 Well-established risk factors

Only three etiological factors for PCa have been clearly identified. The factor most strongly associated with PCa is increasing age. The cancer is rare under the age of 50, with an exponentially increasing incidence thereafter [44]. As such, most diagnoses occur in men over 65 years of age [45]. Some autopsy data showed that prevalence rates of PCa for men between 70 and 90 years could be as high as 90%. Since PCa doesn't account for 90% of mortality, a large proportion of men likely die from other causes while having a PCa [10].

A second well established risk factor for PCa is ancestry. It is well recognized that the risk of developing PCa is higher in men of African ancestry than in men of European ancestry while Asian men have the lowest risk. In the United States (USA) according to the Surveillance, Epidemiology, and End Results (SEER) program, the age-adjusted incidence rate per 100,000 persons from 2001 to 2005 for African-Americans was 248.5, 156.7 for Non-Hispanic White Americans and 93.8 for Asians. African-Americans are also more likely to be diagnosed with advanced PCa [46]. Genetic factors, as well as factors associated with being an African-American such as the socio-economic position are hypothesized to be responsible for the observed increased risk. However no firm conclusion has been reached yet [47].

Another risk factor in the development of this cancer is a family history of PCa. A meta-analysis showed that, compared with the absence of a family history of PCa, men with any relative with PCa have a relative risk estimate of 1.93 [95% confidence interval (CI): 1.65–2.26]; and men with a first-degree relative with PCa, have a relative risk estimate of 2.22 (95% CI: 2.06-2.40). [48]. Increased risks due to family history have also been observed for different ethnic groups. A study found ORs of 3.2, 1.9 and 2.7 for Black men, White men and Asian-American men with a family history of PCa compared to the absence of any family history, respectively [49].

3.1.4 Suspected risk factors

Conflicting results have been found regarding the association between obesity and PCa. The inconsistencies may be explained by a lack of consideration of PCa aggressiveness. Indeed, results from a meta-analysis suggest that obesity is negatively associated with risk of localized tumour, but positively related to advanced stage cancer. [50] Less aggressive PCa might thus have etiologies that differ from more aggressive cancers. One possible explanation is that on one hand, obese men have lower levels of testosterone, protecting them from developing PCa. On the other hand, obesity is associated with higher serum levels of estradiol, insulin, free IGF-1, and leptin, which have all been linked to a higher risk of advanced PCa [51]. Detection issues such as the challenging performance of DRE, the lower levels of PSA in obese men with PCa [52] and less accurate biopsy for finding a PCa because of larger sized prostates [53], may delay diagnosis and allow cancer progression.

The effect of physical activity on PCa is still unclear, with about a third of the studies suggesting a protective effect in the order of 10% to 20% [54]. This protection from cancer could be mediated by decreased levels of testosterone, likelihood of obesity and stronger immune system. Inconsistencies between studies may relate to methodological issues. For instance, active men are more likely to be screened for PCa [54] and are thus more likely to get diagnosed. This phenomenon would therefore artificially create a “higher risk” in active subjects and counter balance any real protective effect.

Some occupations may present higher risk of PCa such as farmers, workers in heavy industry, rubber manufacturing and newspaper printing [55]. This suggests that exposure to some chemicals or other factors from these working environments might contribute to the development of PCa. Studies on specific chemical agents present in these industries, such as agricultural pesticides, cadmium and nitrosamines, have not shown consistent associations [56].

Other potential risk factors associated with PCa include socio-economic position, hormones and growth factors, diet, chronic inflammation, sexually transmitted infections, sexual behaviour and vasectomy. No clear conclusions have yet been drawn for these factors [47, 55].

In summary, despite previous research and some suggestive findings, no modifiable risk factor for prostate cancer has been clearly identified to date. This therefore represents an important research avenue.

3.1.5 Genetic susceptibility

Two of the strongest risk factors associated with PCa are family history and ancestry. This suggests that genetic make-up may play a role in the development of this cancer. Several studies have been conducted to elucidate the various allelic polymorphisms and the genes most likely to be associated with an increased or decreased risk. Most reports focused on those involved with the androgenic metabolism pathway, which are necessary for the growth of prostate epithelial cells. [57] Other genes may also influence the development of PCa such as the glutathione S-transferase theta-1 and n-acetyltransferase 2 genes involved in the metabolism of carcinogens [58].

Gene polymorphisms for different players in the vitamin D pathway have also been studied in association with PCa risk. A case-control study assessing the association between PCa risk and different vitamin D pathway gene variants found inconclusive evidence for possible roles of the *CYP27B1 hydrolase*, *vitamin D receptor (VDR)* and *CYP24A1 hydroxylase* genes. [59] In another study where the sunlight exposure was also taken into account, men with the *CDX-2* AG polymorphism of the VDR had twice the risk of the men the *CDX-2* GG polymorphism when exposed to the sun for more than 1,000 hours per year; and men with *Fok1* ff genotype had almost three times the risk of those with *Fok1* FF for the same sunlight exposure. [60]

3.2 Sunlight exposure and cancer

Extensive studies have linked sunlight exposure, particularly ultraviolet (UV) radiation exposure, with increased risks of melanoma and non-melanoma skin cancers, lip and eye cancers [61]. However, recent studies suggest a protective effect of sunlight exposure on several internal cancers such as breast [62-66], colorectal [65, 67-69] and prostate cancers [6, 70]. Possible mechanisms for the harmful effects of sunlight exposure are DNA damage [71] and UV-induced immunosuppression [72]. The protective effects of sunlight exposure may be mediated by the vitamin D synthesis in the skin and its action in internal organs [73], and UV-induced nitric oxide (NO) [74].

Solar radiation intensity can be determined by the geographical location, defined by the latitude and longitude. The latitude is the coordinate parallel to the equator; and the longitude is the coordinate perpendicular to the equator and parallel to the prime Greenwich meridian. When the latitude increases, solar radiation intensity decreases for a given longitude [75]. Aside from latitude, other factors affect the solar radiation received in a certain geographical location such as the season, the cloud coverage, the altitude, i.e. the elevation from the sea level, and the reflectance of the surfaces. Taking these factors into account, solar radiation intensity is generally higher in the Southern hemisphere than in the Northern hemisphere for the same season and latitude [76] as measured by the Total Ozone Mapping Spectrometer (TOMS).

Solar radiation is composed of a spectrum of different electro-magnetic wavelengths such as UV, visible light and infrared [61]. DNA-weighted UV-B, expressed in J/m^2, is the part of the UV spectrum that directly alters the DNA, which peaks at around 300 nm and this coincides with the spectrum where vitamin D synthesis occurs [4, 77]. UV index (UVI), 1 unit per 25 mW/m^2, is the clear-sky effective UV irradiance reaching the Earth's surface for the local solar noon [78].

Skin cancer has a strong association with UV, but its relation differs depending on the sub-types of the cancer. Melanoma skin cancer has been more associated with intermittent sunlight exposures, squamous cell carcinoma with a lifelong sunlight exposures and basal cell carcinoma with a mix of both [79].

3.2.1 Sunlight exposure assessment

Geographical-based and individual-based sunlight exposure assessments have been used in studies on the association of PCa and sunlight exposure. For geographical-based sunlight exposures, the latitude and the UV dose or intensity were employed [4, 5, 77, 78, 80-90]. Given the high association between skin cancer and sunlight exposure, non-melanoma and melanoma skin cancer mortality rates [85] were used as proxy to sunlight exposure. A study that used the basal cell carcinoma [91] as outcome suggested the absence of protective effect from sunlight exposure against PCa.

While the advantage of using geographical locations as surrogate to sunlight exposure is that they are easy to obtain and relatively inexpensive, a limitation in using this measure is the lack of individual behaviour information [75]. The methods used have included the data collection through questionnaires of self-reported sunlight exposure [92, 93], of detailed information of acute exposures such as holidays in sunny countries and/or sunbathing history, and of chronic exposures, such as the cumulative sunlight exposure or the frequency of exposure [7, 94, 95]. Occupation has also been used to determine the level of sunlight exposure [65, 67]. The difference between the constitutive and facultative pigmentation has also been used as a measure of lifetime cumulative exposure [92]. The constitutive pigmentation is the skin pigmentation that is not generally exposed to the sun and the facultative pigmentation that is generally exposed.

3.2.2 Studies on the association between prostate cancer and sunlight exposure

The relationship between sunlight exposure and PCa is to-date not as well understood as the link between sunlight exposure and skin cancer. As early as 1941, a protective effect of sunlight exposure for non-skin cancers was suspected [96]. The results of an ecological study suggested that cancer mortality in general decreased as the solar radiation index increased. In 1990 it was first proposed that sunlight exposure was protective against prostate cancer, via the action of vitamin D [97].

The main focus of our study is sunlight exposure, as the main predictor, and PCa risk, as the outcome, and therefore this is the focus of the literature review that follows. The association between PCa and vitamin D will not be discussed here because vitamin D remains a hypothetical mechanism for the protective effect of sunlight exposure. As well, other sources of vitamin D include diet [98-100] and supplementation [101], which are not the main focus of our study.

There are three possible outcomes that studies have used to study PCa: incident cases, prevalent cases and mortality from PCa. Twelve studies [4, 5, 8, 9, 70, 87-90, 92, 93, 102] have used incident cases as their outcome, which has the advantage for studying the factors related to the development of PCa over using prevalent or mortality cases. The drawback of

using incident cases of PCa is the challenge to get new cases, such as time constraints [103]. Nine studies [6, 7, 94, 95, 104-108] have used PCa prevalent cases, who may be individuals with a first diagnosis of PCa or recurrent cases. Using prevalent cases is advantageous when studying for a degenerative disease with no clear onset time [109]. It biggest limitation is the higher likelihood of capturing less severe cases of PCa, because these cases have better survival and are therefore more likely to be captured. Therefore, factors studied would be more related to less aggressive disease. When using the PCa mortality as the outcome, as was done in 16 studies [4, 5, 65, 67, 77, 78, 80-87, 89, 110], factors related to survival of the cancer are studied. The main advantage for using mortality cases is the readily available data from registries or death records.

Three types of study designs have been used to study sunlight exposure and PCa: ecological, case-control and cohort studies. Ecological studies are inexpensive and simple to conduct, but have limitations over study designs where individual-level data are collected and the difficulty in controlling for confounding factors [109]. Therefore, when interpreting the literature, greater weight should be placed on the results obtained from case-control and cohort studies.

Details of the studies are presented in Appendix 1, in Table 1 for ecological studies, Table 2 for case-control studies and Table 3 for cohort studies.

3.2.2.1 Ecological studies

Nearly half (n = 15) of the 33 studies conducted to-date on the association between PCa and sunlight exposure are ecological studies [4, 5, 77, 78, 80-90]. Nine ecological studies used PCa mortality as the outcome, whereas 4 studies used both incidence and mortality, and 2 studies focused on PCa incidence. One article written in Spanish was identified but it is not described here [111]. The majority (n = 7) of the studies were conducted in the USA [4, 5, 77, 80, 84, 86, 87]. One was conducted in Japan [82], one in Spain [85], one in France [89] and one in Australia [90]. There were 4 multi-country studies, and Canada was included in 3 of them [78, 81, 88].

One approach to assess the sunlight exposure in ecological studies was to use the latitude of the different geographical regions studied [80, 83-85, 89]. Solar radiation between different geographical locations differs not only by the latitude, and therefore some studies have used a

UV dose or intensity [4, 5, 77, 78, 80, 81, 84, 86-88], the mean solar radiation expressed in MJ/m^2 [90] or the mean annual hours of solar radiation [82], collected from meteorological departments or from the TOMS. Given the high association between skin cancer and sunlight exposure, non-melanoma and melanoma skin cancer mortality rates were used [85] in one study as proxy to sunlight exposure.

One multi-country study showed that the 5-year PCa survival rate was negatively associated with the latitude of the country [83]. In the USA, both the incidence and mortality rates were increased by around 20% if the residence was in the Northern part of the country [4], and increasing latitude was linked to an increase of PCa mortality [84]. In Spain, a study showed that mortality by PCa was not correlated with the latitude ($r=0.06$, $p>0.05$), but slightly negatively correlated with the non-melanoma skin cancer mortality rate ($r=-0.21$, $p>0.05$) and positively correlated with melanoma mortality rate ($r=0.52$, $p<0.01$) [85]. A French study demonstrated a much stronger correlation between latitude and PCa mortality ($r=0.68$, $p=0.001$). [89] As previously mentioned, latitude may not be the best indicator of sunlight exposure, because other factors could affect the level of solar radiation. Populations were different in the French and Spanish studies as well and other risk factors may play a role in the associations.

In multi-country studies, PCa mortality and incidence rates showed a weak inverse association with UVR exposure (either UVI or measured UV-B) [78, 81, 88] while another study in the USA demonstrated a significant decreased PCa incidence and mortality for the 10^{th} UVI decile compared to the 1^{st} decile [5]. By contrast, an investigation observed a positive correlation between PCa mortality and measured UV-B dose [84].

In analyses stratifying by race [87], White Caucasian men were at lower risk of being diagnosed with or dying of PCa at higher UVI. Meanwhile, the PCa incidence for African Americans was inversely correlated with the UVI, but they were at higher risk of dying from the cancer at higher UVI, although results were not statistically significant.

3.2.2.2. Case-control studies

Overall methodology

Thirteen published case-control studies were found [6-9, 67, 91, 92, 94, 95, 104-108]. One case-control study [67] used the PCa mortality as outcome, whereas 9 studies [6, 7, 94, 95, 104-108] used prevalent cases of PCa, and 3 studies, the incident PCa cases [8, 9, 92]. Eight studies were conducted in the United Kingdom (UK) [6, 7, 94, 95, 104-107], 3 in the USA [67, 92, 108], one in Singapore [8], and one in Australia [9]. No case-control study has yet been done in Canada.

The discussion that follows applies to the 12 case-control studies that did not use PCa mortality as outcome. Ten studies had a sample size (sum of cases and controls) of less than 1,000 and the two other case-control [9, 107] studies less had than 1,100 cases. In 10 studies, cases were recruited from hospital settings [6-8, 94, 95, 104-108], and in the other 2 studies, from cancer registries [9, 92], all with histologic confirmation of PCa. In two studies [94, 95], cases with advanced or aggressive PCa, were compared to controls with less aggressive or advanced PCa, Seven studies compared PCa cases with hospital controls [6-8, 104-107] and three studies between PCa cases and population controls [9, 92, 108]. One study primarily focused on African-Americans, a high-risk population [108], one on Asians, a low-risk population [8] and eight on Caucasians, more specifically on White Northern Europeans [6, 7, 94, 95, 104-106] or non-Hispanic Caucasian men [92]. The Australian study [9] assessed the ancestry of the participants, but did not find an association with PCa risk.

All of these, 12 studies controlled for age, but only six studies controlled for first-degree family history of PCa [7, 8, 92, 104, 105, 108]. Two studies [94, 106] assessed the first-degree family history of PCa, but the latter was not found associated with the outcome. In relation to sunlight exposure, eight studies controlled for skin type or skin colour [8, 9, 92, 95, 104-107]. Three studies assessed solar protection [9, 106, 107], but only one of them adjusted for it [107]. Since the main potential mechanism explaining the protective effect of sunlight exposure on PCa is via vitamin D, two studies have controlled for dietary factors involving vitamin D [6, 70]. One study assessed gene polymorphisms for VDR but found no association

with PCa [6], while in two studies, these factors were included in their analyses as modifying factors to sunlight exposure [92] or as predictive factors [95].

Eight studies [6, 7, 95, 104-108] have assessed acute episodes of sunlight exposure such as sunbathing, childhood sunburn and holidays in foreign countries, the latter implying warm and sunny countries. Chronic sunlight exposure could also be assessed as a frequency of exposure [8, 92, 94, 95, 104, 106] or a cumulative sum of exposure [6, 7, 9, 94, 95, 105, 107, 108] or the self-reported occupational and recreational exposures [92]. Frequency and cumulative sum of exposures was typically retrieved from questionnaire by asking the number of hours spent outdoors. Eight studies assessed occupational exposures using the number of hours of exposure occurring on weekdays, and separately, exposures during leisure, by assessing hours of exposure on weekends [6, 7, 9, 94, 95, 104-106]. Different measures of exposure frequency have been used in other studies such as the mean number of months of exposure per year during adulthood [94], mean number of hours of exposure per year during adulthood [104], the number of hours of occupational and recreational exposure per week during adulthood [8, 106] or during lifetime [92], or the proportion of the occupation spent outdoors [95]. Cumulative measures of exposure used in the past include: mean number of years of exposure during three adulthood age-periods [95] or during the 10, 20 and 30 years prior diagnosis [94], the cumulative number of months of exposure during adulthood (based on the sum of hours of weekday and weekend exposure during three age-periods) [105], mean number of weeks of exposure [6, 7], number of hours spent outside during summer in lifetime [107], number of hours of exposure at work, during recreational time, during vacation and residence in the tropics over lifetime [108], and the number of hours of exposure for weekdays or weekend or both in the warmer months from ages 30 to 50 [9].

Inverse relationship between sunlight exposure and PCa risk

Of the 12 case-controls studies, 8 studies [6, 7, 92, 94, 104-106, 108], 6 from the UK and 2 from the USA, found an inverse relationship between PCa risk and sunlight exposure. One study [94] focused on advanced-stage, according to the TNM staging system, or on aggressive PCa, according to the Gleason score, as outcome. When using a continuous index of chronic sunlight exposure, the beneficial effect of the exposure ranges from 0.1% to 69% decreased

PCa risk for each increase of exposure unit, expressed by the number of months per year [94, 105], the mean number of weeks [6, 7], the number of hours per year [104, 108] and the number of hours per day [106]; and results were statistically significant except for the risk of advanced stage/aggressive PCa [94]. A protective effect of 4% to 69% decreased risk was observed for categorical chronic exposures, but overall results were not statistically significant. The sunlight exposure categories used were the mean number of weeks of sunlight exposure [6, 7], the duration of residence in low solar radiation state [92], the lifetime number of hours per week during leisure and work [92] and the difference between constitutive pigmentation and facultative pigmentation as measure of cumulative sunlight exposure [92]. For acute sunlight exposures (sunbathing, childhood sunburn and foreign holiday), there was a decreased PCa risk of 10% to 82%, with overall statistically significant results [6, 7, 94, 104-106]. It should be noted that all these studies had a sample size less than 1000. While 5 of the studies [7, 92, 104, 105, 108] adjusted for family history of PCa, only one had information on use of protective measures against solar radiation [106].

Inconclusive results on the relationship between sunlight exposure and PCa risk

Two studies reported no association between PCa and sunlight exposure, one focused on overall PCa [107] and the other one on PCa with bone metastasis [95]. Both of the studies, based in UK, used the cumulative number of hours spent outdoor over the life course and acute sunlight exposures in their analyses. One of the studies had a large sample size (1,020 cases of PCa and 5,044 controls) [107] while the other study had a much smaller one (72 cases with bone metastasis and 110 controls with PCa but no bone metastasis) [95]. In both studies, they used prevalent cases and hospital controls. Controls without PCa may have another disease that could be inversely associated with sunlight exposure, for example colorectal cancer [65, 67-69] or multiple sclerosis [112], and therefore sunlight exposures between cases and controls could have been similar.

Positive relationship between sunlight exposure and PCa risk

Two studies, one from Singapore [8] and the other from Australia [9] reported a positive association between sunlight exposure and risk of PCa. Compared to study participants with low exposure, the risk increase ranged from 30% to 107% for the more exposed, when using a

chronic sunlight exposure. In the Singapore study, they also found an increase of 30% to 330% of the risk for those who get sunburnt compared to those who did not. Statistically significant results were only found in the most exposed group in both studies.

In the Singapore study [8], they had a small sample size (240 cases and 268 controls), an Asian population and their exposure assessment was the average frequency of exposure per week over lifetime, collected through questionnaire. The Australian study [9] had a larger study sample (1,084 cases and 234 controls) and used the cumulative number of hours of sunlight exposure between 30 and 50 years old as the assessment of exposure. Since the majority of the studies on sunlight exposure and PCa risk found an inverse relationship, the Australian study [9] stated that their results were different because their study was conducted in the Southern hemisphere, where solar radiation intensity is higher. The Singapore study was also conducted in a high solar radiation intensity region [113] because it is located near the equator. Only the Singapore study controlled for the family history of PCa, while the Australian study did not. Both studies did not assess the solar protection, which could affect the amount of sunlight received [114].

3.2.2.3 Cohort studies

Overall methodology

The literature search yielded 5 cohort studies, three from the USA [70, 93, 102] and two from Norway [65, 110]. The studies in the USA used incident PCa as the outcome and the Norwegian studies used PCa mortality. Two of the studies in the USA used the NHANES I cohort (National Health and Nutrition Examination Survey) [93, 102] and the other one used the NIH-AARP cohort (National Institutes of Health – American Association of Retired Persons) [70]. In the NHANES I studies, in which the first interviews were conducted between 1971 and 1975 and the last follow-up interviews in 1992, yielded respectively 153 PCa cases out of 3414 men [102] and 161 PCa cases out of 3528 men [93], ascertained by either or both self-report of PCa, or confirmed by hospital records or by death certificate. In the NIH-AARP study, 272,796 men were followed from 1995 until end of 2006 or until loss to follow-up or death or diagnosis of PCa; and 21,439 PCa cases were identified through probabilistic linkage with cancer registries [70].

Results

The American studies found an inverse association between sunlight exposure and PCa risk, with a beneficial effect of 6% to 51%, and results were only significant for the NIH-AARP study [70]. The Norwegian studies found a beneficial effect of sunlight exposure in the survival of PCa of 1% to 51%, with overall statistically non-significant results. All the cohort studies used the residence of the study participants as proxy for sunlight exposure, while one study [65] also used the occupation (mainly indoor, mainly outdoor or mixed), and one other study [93] also used the self-reported recreational and occupational sunlight exposures (never/rarely, occasional, frequent) and the physician-assessed sun exposure and skin damage by sun exposure. The NHANES I studies had a small number of cases (153 and 161 cases respectively) [93, 102] while the other three studies had over 10,000 cases. While all the studies controlled for age and some of them controlled for family history of PCa [102], dietary factors [70], birth cohort, childbearing patterns, education, PCa diagnosis factors, occupation, physical activity and household income, none of them assessed solar protection.

3.2.3 Summary

Most of the presented studies on PCa risk and sunlight exposure demonstrated an inverse relationship, but few are inconclusive and some showed a positive relation. Therefore whether sunlight exposure would protect men from PCa remains unclear. Only three case-control studies used incident PCa cases as outcome, which is preferred for studying the etiology of the cancer and none of them were conducted in a Northern climate. Of these three case-control studies, the largest sample size had 1,084 cases and 234 controls [9]. Also most of the case-control studies have restricted their study sample to a certain population. For cohort studies, two were focused on PCa mortality while the other three used PCa incident cases as outcome. These three studies has all used the residence of the study participants as proxy to sunlight exposure while only one also used the occupation for sunlight exposure at work [93].

4.0 Research objectives

The overall objective was to assess the relationship between sunlight exposure and the risk of incident PCa in a population-based case-control study in Montreal, Canada. This study was conducted in the context of PROtEuS (Prostate cancer & Environment Study), a research program targeted to clarify the potential etiological role of a wide range of factors in PCa development.

Specific objectives included (1) assessing the association between PCa and sunlight exposure incurred during leisure time; (2) assessing the association between PCa and sunlight exposure at work; and (3) assessing the association between PCa and sunlight exposure during leisure and at work.

5.0 Description of the overall study

This investigation is part of PROtEuS, a large-scale research program aimed at elucidating the possible roles of occupational, environmental, anthropometric and lifestyle factors, either alone or with genetic susceptibility biomarkers, on the development of prostate cancer.

5.1 Study sample

Cases were actively ascertained through pathology departments across seven out of nine Francophone hospitals representing over 80% of all prostate cancer patients diagnosed in the Montreal metropolitan area (MMA). Eligible cases for the study were men under the age of 76 with a first diagnosis of primary prostate adenocarcinoma between September 2005 and December 2009. Concurrently, population controls were selected from Quebec's permanent electoral list and frequency-matched to cases by age (± 5 years). They never had a diagnosis of PCa at the time of interview and resided in the same electoral districts as the cases. To be eligible, both cases and controls had to be Canadian citizens registered on the provincial electoral list, and to reside in the MMA.

Response rates were 84% among eligible cases and 61% among eligible controls. Reasons for non-participation among cases and controls were refusal (93% and 86% respectively), unable to trace (2% and 11% respectively), death with no proxy available (2% and 1% respectively), language barrier (2% for both); too sick with no proxy available (1% for controls only); and other (0.1% for controls only). Proxy respondents provided information for 3% and 4% of cases and controls, respectively. The study was approved by the ethics committees of all participating institutions and all participants provided informed consent.

Overall, PROtEuS called upon the participation of almost 4,000 participants. The present analyses focused on the first 1,391 cases and 1,505 controls interviewed because information on remaining participants was still being entered electronically. A further 19 cases and 26 controls were excluded because of missing information on covariates such as ancestry, education level, solar protection during leisure, occupational sunlight exposure, solar protection at work or BMI, and 1 case was removed because information on self-reported sunlight exposure during leisure was missing, leaving 1,371 cases and 1,479 controls for analyses for both recreational and occupational sunlight exposures.

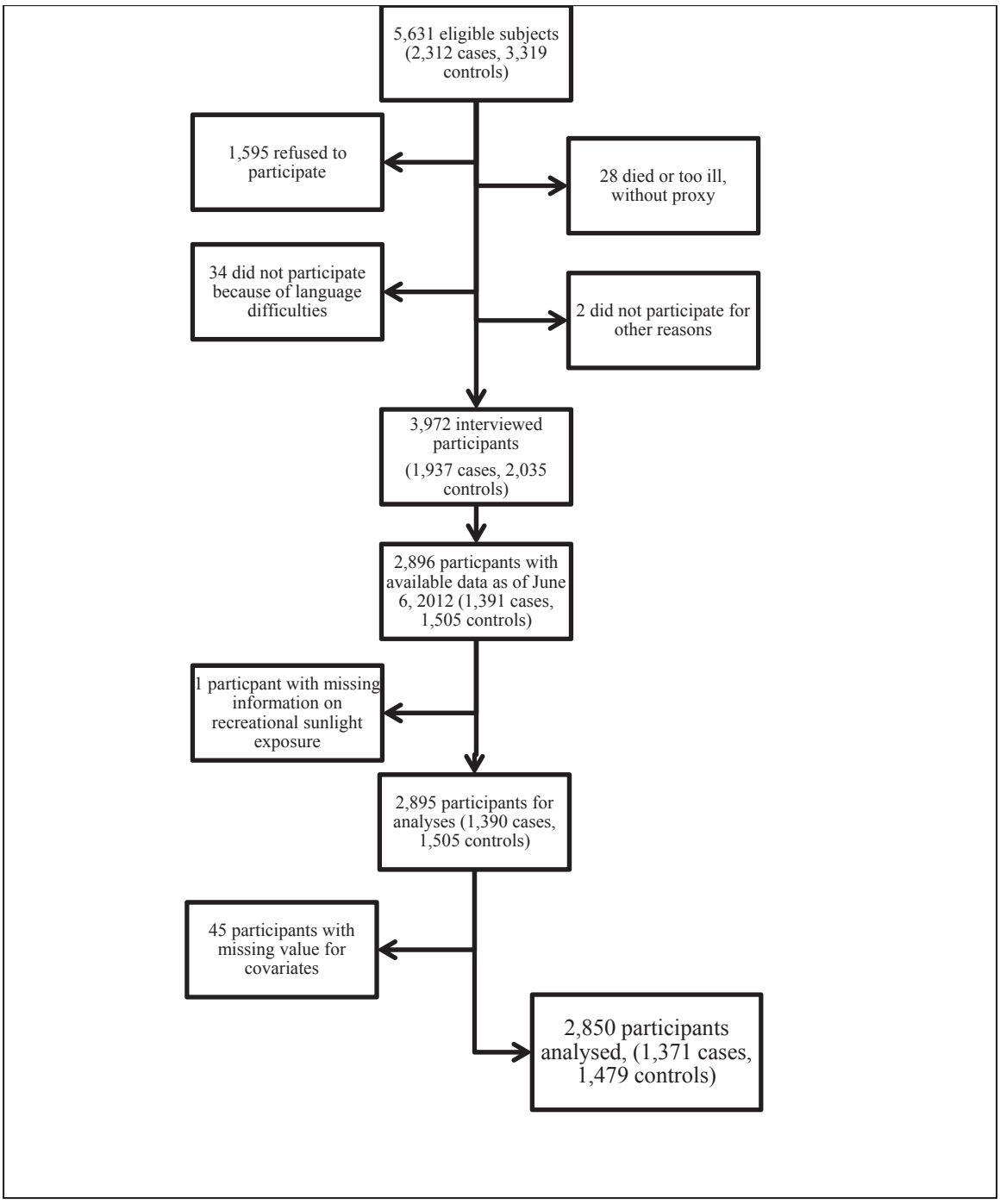

Figure 1 - Steps for establishing the final study sample

5.2 Data collection

Face-to-face interviews with subjects or proxy respondents were conducted, mostly at home, by trained interviewers. A structured questionnaire elicited detailed information on socio-demographic characteristics and several lifestyle habits including engagement in specific hobbies and leisure activities during adulthood, as well as the use of sunlight exposure and solar protection during leisure and at work. Participants were also asked to describe their overall physical activity levels as an adult at home, during leisure-time, and at work (very active, moderately active, not very active, do not know). Anthropometric and medical information, along with biological specimens were collected. Prostate cancer screening history (PSA tests and/or DRE) was elicited.

Sunlight exposure was derived from questionnaire information on hobbies and leisure time activities. The questionnaire elicited whether participants had participated regularly, for at least 6 months, in any of 16 common leisure activities including sports, hobbies and household activities, since they were 18 years of age (adulthood). Other performed leisure activities could be added to the pre-defined list. Information collected for each activity included the ages when participants started and stopped doing the activity, the number of months per year, the frequency per day, week or month, and the total number of years of engagement in the activity. Interruptions and changes in frequency were also recorded.

In the second part of the interview, a semi-structured questionnaire was used to obtain a detailed work history. Participants were asked to provide a list of each job held for at least one year. In addition, a General Work History (GWH) questionnaire was administered to elicit details of each job held for at least 2 years. Each job reported was assigned occupational and industry codes according to different Canadian and international classification schemes. For the purpose of the present project, we used codes from the Canadian Classification and Dictionary of Occupations 1970, updated till 1986, and which comprises 7 digits [115]. If for some period of time between the year the participant started a job and the index year, the participant was in a particular situation other than occupying a paid job such as if they were retired, disabled and/or sick, homemaker, unemployed, student, refugee/prisoner, volunteer worker, unknown/never worked or was occupying a job position for less than 2 years (n=76),

a special code was attributed. 2,052 jobs of less than 2 years have been assigned with a CCDO code.

The degree of aggressiveness of prostate cancers, as defined by the Gleason score (http://gleasonscore.net/), was extracted from the pathology reports.

5.3 Exposure to sunlight

We assessed lifetime exposure to sunlight from two main sources. The first represented exposure during leisure-time, based on outdoor leisure-time activities during adulthood. The second captured occupational sunlight exposure over the entire work history. These were then further combined to obtain a global sunlight exposure index. Details of the approaches used to derive the respective indices are described in section 6.0 for recreational sunlight exposure, and in section 7.0 for occupational exposure, as well as for the global sunlight exposure. We summarize them here briefly.

5.3.1 Leisure-time sunlight exposure

Leisure-time sunlight exposure was derived from the information from the questionnaire on recreational activities subjects engaged on during adulthood. Activities used to assign sunlight exposure were those considered to have been performed outdoors most of the time. In addition, some activities were carried out on a seasonal basis. However, information on this was not collected initially in the questionnaire and was only introduced one year into the study, by requesting the number of months of participation in each activity over the year. Imputations were applied for seasonality based on usual patterns in the Montreal area.

Two recreational sunlight exposure indices were created based on this. The first represented the cumulative number of leisure-time events entailing sunlight exposure (*CEvents*) during adulthood. The second represented the cumulative duration of sunlight exposure during leisure-time, in hours (*CDuration*), after assigning a typical duration to each of the leisure activities.

The equations to calculate these two indices were:

$$CEvents = \sum_{i=1}^{m}(Frequency\ of\ event_i\ x\ Seasonality_i/12\ x\ Duration\ in\ years_i) \quad (1)$$

and

Cumulative duration of exposure ($CD_{uration}$):

$$CDuration = \sum_{i=1}^{m}(Frequency\ of\ event_i\ x\ Duration\ of\ event\ in\ hours_i\ x\ Seasonality_i / 12\ x\ Duration\ in\ years_i) \quad (2)$$

where CE_{vents} is expressed in events and $CD_{uration}$ is expressed in hours, i is an individual event, m is the total number of different types of events, *Frequency of event* is the number of events per year, *Seasonality* is the number of months per year the event occurred, *Duration in years* is the total number of years of engagement in the event, and *Duration of event in hours* is the typical number of hours of engagement attributed to each event.

5.3.2 Occupational sunlight exposure

In order to assess occupational exposure to sunlight, we assigned occupational exposure levels to each job held by each study subject using a job-exposure matrix, the SunJEM, developed under CAREX Canada [116].

We calculated two indices of occupational exposure to sunlight. One is referred to as the cumulative index (*CO*) and a simplified index (*SO)*. The first index (*CO*) was calculated as the sum of the products of the duration in years of the job and of the respective weighted exposure level. The second index (*SO*) was created to segregate participants with a substantial amount of sunlight exposure from the other less exposed or never-been-exposed participants.

5.3.3 Global index of exposure to sunlight

A global sunlight exposure index (*GSE*) was derived, combining the cumulative number of leisure-time events entailing sunlight exposure (*CEvents*) and the cumulative occupational sunlight exposure index (*CO*).

5.4 Statistical analyses

Unconditional logistic regression was used to assess associations between sunlight exposure during leisure time, occupational sunlight exposure, global exposure to sunlight, and PCa risk. Regression models built on a set of *a priori* variables, to which a number of covariates were added after being tested for potential confounding.

5.4.1 Outcome variable

The outcome variable studied was a binary variable categorized according to the status of "PCa case" or "control". Analyses were also conducted with stratification of PCa aggressiveness. Low aggressiveness is defined by a Gleason score of 6 or less, or 7 with a primary grade of 3 and high aggressiveness by a Gleason score of 8 or more, or 7 with primary grade of 4.

5.4.2 Covariates included *a priori* in regression models

The well-established risk factors for PCa, age, ancestry and first-degree family history of PCa, were included in all models. Age, a continuous variable, for cases was the age at the diagnosis of PCa, and for controls, the age at the interview. The ancestry variable was made of four categories: French, Black, Asian and Other. For the first-degree family history of PCa, participants were classified according to whether they had at least one first-degree relative diagnosed with PCa or not, or they didn't know.

PCa screening is linked to prostate cancer detection and may also relate to health behaviours and lifestyle, including sunlight exposure. It has indeed previously been recommended that PCa screening be considered as a potential confounder of associations between lifestyle factors, such as diet, and PCa risk [117]. We thus included in our models a variable indicating whether subjects had undergone prostate cancer screening within two years prior the index date, i.e. the year of diagnosis for cases or the year of interview for controls. Subjects were classified in one of four categories: screened within two years prior to the index date, screened more than two years prior, never screened and do not know whether he was screened.

Education may be related to the kind of jobs participants would occupy, as well as to sunlight exposure behaviour during leisure and/or at work. Therefore, education level (highest level achieved) was included *a priori* in the models assessing occupational and combined sunlight exposures analyses. It was also tested as a potential confounder in the models assessing PCa risk in relation with recreational sunlight exposure. Educational level was categorized as primary school or less, secondary school, college or university.

5.4.3 Other covariates

Solar protection was considered for inclusion in the regression models based on the premise that it can affect the amount of sunlight to which the body is exposed. A variable indicating whether subjects had used solar protection, for both work-time and leisure time, could take one of three categories: "never protected", "sometimes protected" and "often protected".

The body mass index (BMI) may be associated with recreational sunlight exposure. We considered the BMI, as derived from the reported weight two years before the index date, for inclusion in the recreational and in the combined recreational and occupational sunlight exposure models, but not in the occupational sunlight exposure models.

The recreational sunlight exposure indices were created here using detailed information on recreational activities. Since these could be associated with physical activity, and the latter has been linked with PCa, it was important to control for physical activity when assessing the sunlight exposure-PCa relationship. To address this, an overall physical activity score was created by combining information derived from subjects' reports about their usual physical activity levels at work, during leisure time and at home. Possible responses were according to the following choices: "very active", "moderately active", and "not very active". The overall physical activity score, in three categories (low, medium and high) was created out of the 27 possible combinations, taking into account the fact that more days per week are normally spent at work than during leisure (tables 4).

Table 4 - Attribution of the new 3 categories of overall physical activity to the combinations of physical activity at home, during leisure time and at work

Physically active at home	**Physically active during leisure**	**Physically active at work**		
		Not very	**Moderately**	**Very**
Not very	**Not very**	low	low	high
	Moderately	low	medium	high
	Very	medium	medium	high
Moderately	**Not very**	low	low	high
	Moderately	low	medium	high
	Very	medium	medium	high
Very	**Not very**	low	medium	high
	Moderately	low	medium	high
	Very	medium	high	high

5.4.4 Variables tested for inclusion in the models but not retained

A few covariates were considered to be tested for the inclusion in the logistic regression models, but they were dropped because they were not associated with the outcome, using unadjusted logistic regression. These factors were family income, ever smoked at least 100 cigarettes during lifetime, ever having consumed alcohol beverages once a month for at least 1 year and artificial UV exposure at work.

6.0 Sunlight exposure during leisure and prostate cancer

Sunlight exposure during leisure activities and risk of prostate cancer in Montréal, Canada, 2005-2009

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6.1 Abstract

Prostate cancer is the leading cause of cancer among men in Canada and many other countries, but no modifiable risk factors have been identified. A few studies have suggested a possible etiological role for sunlight exposure. We report on the association between leisure time sunlight exposure during adulthood and prostate cancer risk in the context of a population-based case-control study. Prostate cancer cases (n=1,371) were ascertained across all main Montreal French hospitals between 2005 and 2009. Population controls (n=1,479), frequency matched to cases by age (± 5 years), were selected from French electoral lists. Interviews elicited the frequency of engagement in any leisure activity during adulthood. These were used to derive an index representing the cumulative number of sunlight exposure events. Odds ratios (OR) and 95% confidence intervals (CI) were used to estimate the association between this sunlight exposure index and prostate cancer risk, adjusting for age, ancestry, family history of prostate cancer, prostate cancer screening, education, solar protection, body mass index and physical activity.

Compared with men in the upper quartile of sunlight exposure, men never exposed during leisure time had an OR of 1.48 (95% CI: 0.87-2.53). Corresponding ORs were 1.11, 0.90 and 1.22 for the first to the third quartiles of exposure, respectively. Results were unaltered when the duration of events was considered.

There was little evidence of an association between sunlight exposure during leisure time and prostate cancer risk. Men with no sunlight exposure appeared at somewhat higher risks but none of the estimates achieved statistical significance.

Keywords: prostate cancer, sunlight exposure, leisure, epidemiology

6.2 Introduction

Prostate cancer is the leading cause of cancer among men in Canada [1], and in many other countries [2]. Despite extensive research, the only clearly established risk factors thus far are increasing age, being of African ancestry, and having a first-degree family history of prostate cancer [2, 3]. However, none of these factors lend themselves to disease prevention. One striking observation comes from migrant studies, which suggest that emigrants tend to acquire the prostate cancer risks of their host countries [4, 5]. This argues for a role of environmental influences, one of which might be sunlight exposure. While the latter has been predominantly linked to an increased skin cancer risk, a handful of studies have suggested a protective effect of sunlight exposure against breast and colorectal cancers [6-8]. The evidence for a role of sunlight exposure in prostate cancer risk remains sparse. Ecological observations suggest that populations living in lower latitudes tend to have a lower risk of prostate cancer than those residing further from the equator in the northern hemisphere [7, 9]. It has been hypothesized that greater sunlight exposure would confer a protective effect against prostate cancer development through increased vitamin D serum levels [10]. Vitamin D is thought to prevent DNA damage, epithelial cell proliferation and angiogenesis, as well as to positively regulate the immune system, all of which may be involved in preventing prostate cancer [11].

In the context of a population-based case-control study of prostate cancer and environmental factors conducted in Montréal, Canada, we assessed the relation between sunlight exposure in adulthood, as incurred during outdoor leisure activities, and prostate cancer risk.

6.3 Methods

This analysis is part of PROtEuS (Prostate Cancer & Environment Study), a large scale research project aimed at elucidating the possible role of occupational, environmental, anthropometric and lifestyle factors, either alone or in combination with genetic susceptibility biomarkers, on the development of prostate cancer. This study has been described previously [12].

Study population

Cases were actively ascertained through pathology departments in all major French hospitals, representing over 80% of all prostate cancer patients diagnosed in the Montreal metropolitan area (MMA). Eligible cases were men under 76 years of age, with a first diagnosis of primary prostate adenocarcinoma between September 2005 and December 2009. Concurrently, population controls were randomly selected from Quebec's permanent French electoral list and frequency matched to cases by age (± 5 years). They had no history of prostate cancer. To be eligible, both cases and controls had to be Canadian citizens registered on the provincial electoral list, and to be residents in the MMA.

Response rates were 84% and 61% among eligible cases and controls, respectively. Reasons for non-participation among cases and controls were refusal (93% and 86%, respectively), unable to trace (2% and 11%, respectively), death with no available proxy (2% and 1%, respectively), language barrier (2% for both), and too sick with no available proxy (1% for controls only) and other (0.1% for controls only). Proxy respondents provided information for 3% and 4% of cases and controls, respectively. The study was approved by the ethics committees of all collaborating hospitals and affiliated universities, and participants provided written informed consent.

Data collection

Face-to-face interviews were conducted, mostly at home, by trained interviewers. The questionnaire elicited detailed information on socio-demographic characteristics and a wide range of lifestyle and occupational factors.

Of relevance to the current analysis, subjects were asked to provide details about prior engagement in any activity or hobby during their leisure time, over their entire adulthood. This information was used to derive detailed cumulative indices of exposure to sunlight during leisure (see below). Specific questions first elicited whether participants had participated regularly, for at least 6 months, in any of 16 common leisure activities including sports, hobbies and household activities, since they were 18 years of age. Additional questions probed for corresponding information about any other performed hobby or leisure activity not included in the pre-defined list. For each activity reported, participants were asked when they started and stopped doing the activity, the number of months per year, the frequency per day, week or month, and the total number of years of engagement in the activity. Interruptions and changes in frequency were also recorded.

In addition, subjects were asked to self-report their overall frequency of direct exposure to sunlight, separately for leisure time and work time (never, sometimes, and often). Further questions addressed whether participants used solar protection, such as using sun cream, wearing long sleeves, seeking shelter, etc. when directly exposed to sunlight during leisure as well as at work (never, sometimes, often).

Semi-quantitative assessments of overall physical activity levels during adulthood were elicited from participants for three types of circumstances, i.e., at home, during leisure-time,

and at work (not very active, moderately active, very active). These were eventually combined into a composite index of overall physical activity level for each subject (low, medium, high), taking into account the expected duration and intensity of the physical activity in each setting, e.g. more days are normally spent per week at work than during leisure.

Anthropometric and medical information was collected, including a prostate cancer screening history covering prostate-specific antigen tests and/or digital rectal exams. The degree of aggressiveness of prostate cancers, as defined by the Gleason score (http://gleasonscore.net/), was extracted from pathology reports.

Sunlight exposure assessment

Sunlight exposure indices were derived from questionnaire information on leisure time activities. Activities used to assign sunlight exposure were those considered to have been performed outdoors most of the time. These included sports (walking for exercise, jogging, golf, racket sports, swimming, skiing/skating, cycling, etc.), as well as gardening and domestic chores (lawn mowing, snow removal, etc.).

Each leisure-time activity entailing exposure to sunlight is referred to hereafter as an "event". We calculated, for each participant, two indices of cumulative exposure to sunlight during adulthood. The first index was based on the cumulative number of events (*CEvents*), as follows:

$$CEvents = \sum_{i=1}^{m}(Frequency\ of\ event_i\ x\ Seasonality_i/12\ x\ Duration\ in\ years_i) \quad (1)$$

The amount of time participants spent during each leisure activity event varied both between and within activities, and between and within participants, thereby influencing exposure

duration per event. To better reflect important differences in duration per event, and to estimate the cumulative number of hours of engagement in activities, we assigned a typical duration for each activity. For example, 1 hour was assigned for walking, jogging, swimming and domestic chores requiring physical effort, 2 hours for racket sports, cycling and gardening, 3 hours for skiing or skating and 4 hours for golf. This enabled us to derive a second index based on the cumulative duration of exposure (*CDuration*):

$$CDuration = \sum_{i=1}^{m} (Frequency\ of\ event_i\ x\ Duration\ of\ event\ in\ hours_i\ x\ Seasonality_i/12\ x\ Duration\ in\ years_i) \quad (2)$$

where *CEvents* is expressed in events and *CDuration* is expressed in hours, *i* is an individual event, *m* is the total number of different types of events, *Frequency of event* is the number of events per year, *Seasonality* is the number of months per year the event occurred, *Duration in years* is the total number of years of engagement in the event, and *Duration of event in hours* is the typical number of hours of engagement attributed to each event.

Some activities were carried out on a seasonal basis. However, information on this was only introduced in the questionnaire one year into the study, by requesting the number of months of participation in each activity over the year. Imputations were thus applied for seasonality for the 286 cases and 187 controls with a missing value, and restrictions in number of months were applied to the rest of the participants, reflecting usual patterns from the study base: 12 months per year for walking and domestic chores demanding physical efforts, 6 months per year for jogging, golf, biking and gardening, and 4 months per year for swimming, skiing and skating.

Statistical analysis

Overall, PROtEuS called upon the participation of almost 4,000 subjects. The present study focuses on the first 1,391 cases and 1,505 controls concurrently interviewed and for which all relevant questionnaire and medical information had been collected and treated electronically. A further 19 cases and 26 controls were excluded because of missing information on covariates such as ethnic origin, education level, solar protection during leisure, occupational sunlight exposure, solar protection at work or BMI, and 1 case was removed because information on recreational activities was missing, leaving 1,371 cases and 1,479 controls for analyses.

Unconditional logistic regression was used to estimate odds ratios (OR) and corresponding 95% confidence intervals (CI) for the association between the two sunlight exposure indices and prostate cancer risk. Participants were categorized into five sunlight exposure groups, i.e., unexposed subjects, and exposed subjects distributed into quartiles according to the distribution among exposed controls. The upper quartile of exposure was chosen as the reference category because of the small number of unexposed participants.

Models were adjusted on a set of *a priori* variables, along with variables by empirically-based inclusion. Age (continuous), first-degree family history of prostate cancer (no, yes, don't know), ancestry (French, Black, Asian, Other), and timing of the last prostate cancer screening (last 2 years, more than 2 years, don't know whether screened within 2 years, not screened) were included *a priori* in all models. A step-wise forward approach and the Akaike Information Criterion (AIC) were used to identify other covariates to be included in the final models. Variables tested included educational level (elementary, high school, college,

university), body mass index (BMI) 2 years before the index date (continuous), solar protection during leisure (never, sometimes, often) and at work (never, sometimes, often), self-reported occupational sunlight exposure (never, sometimes, often) and overall physical activity level (low, medium, high). Solar protection at work and self-reported occupational sunlight exposure were not retained since they did not appreciably improve the fit of the model.

Stratified analyses according to Gleason scores were conducted to evaluate the association between sunlight exposure and prostate cancer according to disease aggressiveness. Non-aggressive prostate cancer was defined by a Gleason score of 6 or lower, or a score of 7 with a primary score of 3, whereas aggressive prostate cancer was defined by a Gleason score of 7 with a primary score of 4, or a score of 8 or higher. [13]

Sensitivity analyses were performed by excluding 1) proxy respondents, 2) controls who had not been screened for prostate cancer in the two years before interview, 3) participants who were not asked about the number of months per year for each leisure activity, 4) study participants without a positive first-degree family history of prostate cancer, as a sub-analysis for potential genetic susceptibility and 5) using the self-reported sunlight exposure during leisure instead of the main exposure indices (*CEvents* and *CDuration*).

Statistical analyses were carried out using the R 2.15.1 statistical software (R development Core Team, Vienna, Austria) [14] with the packages vcd [15] for categorical data analyses.

6.4 Results

Selected characteristics of cases and controls are presented in Table 1-M. Cases and controls were similar in terms of age, family income, BMI, as well as smoking and alcohol consumption patterns. While the study population was primarily of French ancestry, cases were more often of French or Black ancestries, and less often of Asian ancestry, than controls. Cases tended to have a lower educational level, had a higher prevalence of skin cancer and were twice as likely as controls to have a first-degree family relative with prostate cancer. Prostate cancer screening was common in this study population, with nearly all cases and over 76% of controls having been screened in the two years preceding diagnosis or interview. Self-reported physical activity levels were similar amongst cases and controls. Education was moderately correlated to family income and to physical activity; and ancestry to alcohol consumption pattern. None of the other variables was highly correlated one to another.

Table 1-M – Selected characteristics of 1,371 cases and 1,479 controls, PROtEuS, Montreal, Canada, 2005-2009

Characteristics	Cases	Controls
Age in years, mean (SD)	63.7 (6.8)	64.8 (6.9)
Ancestry, n (%)		
French	1025 (74.8)	904 (61.1)
Black	94 (6.9)	65 (4.4)
Asian	17 (1.2)	42 (2.8)
Other	235 (17.1)	468 (31.6)
Family income in $CAD, n (%)		
<10,000	45 (3.3)	46 (3.1)
10,000-19,999	119 (8.7)	136 (9.2)
20,000-29,999	191 (13.9)	188 (12.7)
30,000-49,999	324 (23.6)	361 (24.4)
50,000-79,999	307 (22.4)	291 (19.7)
80,000-100,000	114 (8.3)	124 (8.4)
>100,000	179 (13.1)	193 (13.0)
Unknown	92 (6.7)	140 (9.5)

Education, n (%)		
Elementary	349 (25.5)	330 (22.3)
High school	410 (29.9)	440 (29.7)
College	202 (14.7)	263 (17.8)
University	410 (29.9)	446 (30.2)
BMI in kg/m^2, mean (SD)	26.7 (4.0)	27.2 (4.4)
Ever smoker[a], n (%)	1016 (74.1)	1101 (74.4)
Ever drinker[b], n (%)	1219 (88.9)	1304 (88.2)
Physical activity at work, n (%)		
Not very active	247 (18.0)	282 (19.1)
Moderately active	380 (27.7)	459 (31.0)
Very active	744 (54.3)	738 (49.9)
Physical activity during leisure time, n (%)		
Not very active	386 (28.2)	474 (32.0)
Moderately active	650 (47.4)	699 47.3)
Very active	335 (24.4)	306 (20.7)
Physical activity at home, n (%)		
Not very active	339 (24.7)	429 (29.0)
Moderately active	674 (49.2)	758 (51.3)
Very active	358 (26.1)	292 (19.7)
Had skin cancer, n (%)	42 (3.1)	39 (2.6)
First-degree relative with prostate cancer, n (%)	311 (22.7)	153 (10.3)
Timing of last prostate cancer screening, n (%)		
Within the last 2 years	1358 (99.1)	1120 (75.7)
More than 2 years earlier	3 (0.2)	178 (12.0)
None	3 (0.2)	140 (9.5)
Not sure whether screened within the previous 2 years	7 (0.5)	41 (2.8)
Gleason score, n (%)		
<6/10	12 (0.9)	
6/10	581 (42.4)	
7/10	588 (42.9)	
8/10-10/10	173 (12.6)	
Unknown	35 (2.6)	

[a] Smoked at least 100 cigarettes in lifetime. [b] Consumed at least one alcohol beverage per month for at least one year.

Table 2-M presents sunlight exposure patterns of participants. The proportions of cases and controls reporting to have never engaged in any leisure-time activities entailing sunlight exposure during adulthood were 3.4% and 2.6%, respectively. Over half of study participants reported having engaged in up to three different types of outdoor activities, while the

remaining reported between 4 and 11 different types of activities, with similar distributions between cases and controls.

The median cumulative number of sunlight exposure events, as derived from *CEvents*, was 6,482 events (range = 24 to 94,890) for exposed cases and 6,756 events (range = 24 to 79,400) for exposed controls. The median cumulative duration of leisure-time exposure to sunlight, as derived from *CDuration* was 9,511 hours (range = 24 to 103,500) among exposed cases and 9,893 hours (range = 48 to 86,820) among exposed controls. *CEvents* and *CDuration* were found to be highly correlated with one another (Spearman's $\rho = 0.97$).

When subjects were asked to rate their typical frequency of exposure to sunlight, seven percent of the cases and controls reported never having been exposed to sunlight during leisure, while about half of the subjects reported to having been often exposed. Almost two thirds of cases and controls reported having never been exposed to sunlight at work; about 17% of subjects reported having often had workplace exposure.

Regarding use of solar protection, patterns varied according to sunlight exposure circumstances. About half of sunlight-exposed participants reported never having used any protection during leisure time; 87% of men indicated having never used protection when exposed at work.

Table 2-M – Sunlight exposure patterns of 1,371 cases and 1,479 controls, PROtEuS, Montreal, Canada, 2005-2009

	Cases n=1371 (%)	**Controls n=1479 (%)**
Individual types of outdoor leisure activities		
Walking	858 (62.6)	940 (63.6)
Jogging	321 (23.4)	335 (22.7)
Golf	304 (22.2)	342 (23.1)
Racket sports	363 (26.5)	378 (25.6)

Swimming	332 (24.2)	325 (22.0)
Skiing/skating	643 (46.9)	646 (43.7)
Cycling	787 (57.4)	763 (51.6)
Gardening	541 (39.5)	582 (39.4)
Domestic chores demanding physical effort	1118 (81.5)	1207 (81.6)
Other	428 (31.2)	485 (32.8)
Number of different types of outdoor leisure activities		
0	46 (3.4)	39 (2.6)
1-3	731 (53.3)	840 (56.8)
4-11	594 (43.3)	600 (41.6)
Cumulative number of sunlight exposure events *(CEvents)*		
None: 0	46 (3.4)	39 (2.6)
Q1: 1-3,291	369 (26.9)	359 (24.3)
Q2: 3,292-6,755	307 (22.4)	361 (24.4)
Q3: 6,756-14,039	357 (26.0)	359 (24.3)
Q4: 14,040-94,890	292 (21.3)	361 (24.4)
Cumulative number of hours exposed to sunlight *(CDuration)*		
None: 0	46 (3.3)	39 (2.6)
Q1: 1-4,575	349 (25.5)	358 (24.2)
Q2: 4,576-9,892	333 (24.3)	361 (24.4)
Q3: 9,893-18,869	361 (26.3)	361 (24.4)
Q4: 18,870-103,500	282 (20.6)	360 (24.3)
Self-reported sunlight exposure during leisure		
Never	97 (7.1)	105 (7.1)
Sometimes	506 (36.9)	594 (40.2)
Often	768 (56.0)	780 (52.7)
Self-reported sunlight exposure at work		
Never	892 (65.1)	996 (67.3)
Sometimes	237 (17.3)	229 (15.5)
Often	242 (17.7)	254 (17.2)
Use of solar protection during leisure		
Never	774 (56.4)	765 (51.7)
Sometimes	322 (23.5)	372 (25.2)
Often	275 (20.1)	342 (23.1)
Use of solar protection at work		
Never	1187 (86.6)	1281 (86.6)
Sometimes	94 (6.9)	77 (5.2)
Often	90 (6.6)	120 (8.1)

Association between leisure-time sunlight exposure and prostate cancer risk

Model selection: The unadjusted model for the association between *CEvents* and prostate cancer risk yielded an AIC of 3,949. Introducing the *a priori* variables markedly improved the model fit (AIC=3,357), which was further improved (AIC=3,319) by considering the following covariates: educational level, solar protection during leisure, BMI and overall physical activity level during adulthood. This set of variables was also found to provide the best fit to our final model using the index *CDuration* ($AIC_{unadjusted}$=3,950, $AIC_{a\ priori\ adjusted}$=3,358 and $AIC_{fully\text{-}adjusted}$=3,320). There was no evidence of effect-modification according to any of the covariates (data not shown).

Table 3-M presents associations between the two indices of sunlight exposure during leisure time and prostate cancer for the whole sample, and separately by aggressiveness status. Compared to men who had ever been exposed to sunlight during leisure time activities during adulthood, those who had never been exposed had an OR for prostate cancer of 1.36 (95% CI = 0.83-2.27). Using men in the upper quartile of sunlight exposure as the referent category, no statistically significant associations emerged between both indices and prostate cancer. Nevertheless, there was a weak suggestion of a higher risk of prostate cancer among men in the lower quartile of sunlight exposure, as well as those who had never been exposed. No evidence of a dose-response pattern was found (*p* for trend for *CEvents*= 0.44, *p* for trend for *CDuration*=0.32).

Similar results were obtained upon stratifying by aggressiveness status of prostate cancer, with either *CEvents* or *CDuration* (Table 3-M).

Table 3-M – Adjusted[a] odds ratios for the association between leisure-time sunlight exposure indices and prostate cancer, for all cancers and by disease aggressiveness, PROtEuS, Montreal, Canada, 2005-2009

	1,479 controls	**All prostate cancers** 1,371 cases and 1,479 controls		**Non-aggressive prostate cancers[b]** 985 cases and 1,479 controls		**Aggressive prostate cancers[c]** 362 cases and 1,479 controls	
Sunlight exposure index	**n (%)**	**n (%)**	**OR (95% CI)[d]**	**n (%)**	**ORs (95% CI)[b]**	**n (%)**	**ORs (95% CI)[c]**
CEvents[e]							
None	39 (2.6)	46 (3.4)	1.48 (0.87-2.53)	30 (3.0)	1.59 (0.88-2.88)	15 (4.1)	1.45 (0.68-3.02)
Q1	359 (24.3)	369 (26.9)	1.22 (0.94-1.57)	277 (28.1)	1.28 (0.97-1.69)	86 (23.8)	1.00 (0.68-1.46)
Q2	361 (24.4)	307 (22.4)	0.91 (0.71-1.16)	228 (23.1)	0.94 (0.72-1.23)	72 (19.9)	0.77 (0.53-1.13)
Q3	359 (24.3)	357 (26.0)	1.11 (0.88-1.41)	245 (24.9)	1.06 (0.82-1.39)	106 (29.3)	1.19 (0.84-1.69)
Q4	361 (24.4)	292 (21.3)	1.00 (ref)	205 (20.8)	1.00 (ref)	83 (22.9)	1.00 (ref)
			p-trend=0.44		*p-trend*=0.41		*p-trend*=0.72
CDuration[f]							
None	39 (2.6)	46 (3.3)	1.52 (0.90-2.61)	30 (3.0)	1.64 (0.91-2.97)	15 (4.1)	1.51 (0.71-3.16)
Q1	358 (24.2)	349 (25.5)	1.19 (0.92-1.53)	259 (26.3)	1.25 (0.94-1.65)	84 (23.2)	1.00 (0.68-1.47)
Q2	361 (24.4)	333 (24.3)	0.99 (0.77-1.26)	239 (24.3)	0.99 (0.76-1.30)	88 (24.3)	0.97 (0.67-1.40)
Q3	361 (24.4)	361 (26.3)	1.24 (0.98-1.58)	260 (26.4)	1.26 (0.96-1.64)	95 (26.2)	1.20 (0.84-1.72)
Q4	360 (24.3)	282 (20.6)	1.00 (ref)	197 (20.0)	1.00 (ref)	80 (22.1)	1.00 (ref)
			p-trend=0.32		*p-trend*=0.31		*p-trend*=0.51

[a] Adjusted for age, first-degree family history of prostate cancer, ancestry, timing of last prostate cancer screening, education, BMI, solar protection during leisure and overall physical activity level. [b] Prostate cancer cases with a Gleason score of 6 or lower or of 7 with a primary score of 3. [c] Prostate cancer cases with Gleason score of 7 with a primary score of 4 or 8 or higher. [d] Odds ratio (OR), 95% confidence interval (CI). [e] Cumulative number of events entailing sunlight exposure during adulthood (levels: none-0 event, Q1- 1-3291 events, Q2- 3292-6755 events, Q3- 6756-14,039 events, Q4- 14,040-94,890 events). [f] Cumulative duration of leisure-time exposure to sunlight during adulthood (levels: none- 0 hour, Q1: 1-4575 hours, Q2- 4576-9892 hours, Q3- 9893-18,869 hours, Q4- 18,870-103,500 hours).

In addition, all five sensitivity analyses, i.e., excluding proxy respondents, non-screened controls for prostate cancer recently, participants without leisure activity seasonality, participants without a positive first-degree family history of prostate cancer, or using the self-reported sunlight overall exposure rating instead of the calculated cumulative exposure indices, showed results comparable with those obtained from the main analyses.

Table 4-M – Sensitivity analyses for the association between leisure time sunlight exposure and prostate cancer 1) excluding proxy respondents 2) excluding controls not screened for prostate in the previous 2 years, 3) excluding participants without seasonality information for leisure activities, 4) using the self-reported sunlight exposure during leisure. PROtEuS, Montreal, Canada, 2005-2009

Sensitivity analysis	Cases n (%)	Controls n (%)	OR (95% CI)[a]
Excluding proxy respondents	1,344 (100)	1,420 (100)	
CEvents[b]			
None	46 (3.4)	36 (2.5)	1.60 (0.93-2.77)
Q1	362 (26.9)	344 (24.2)	1.28 (0.99-1.65)
Q2	304 (22.6)	346 (24.4)	0.96 (0.75-1.22)
Q3	351 (26.1)	345 (24.3)	1.15 (0.90-1.46)
Q4	281 (20.9)	349 (24.6)	1.00 (Ref)
			p-trend =0.36
CDuration[c]			
None	46 (3.4)	36 (2.5)	1.63 (0.95-2.83)
Q1	342 (25.4)	344 (24.2)	1.23 (0.94-1.59)
Q2	329 (24.5)	348 (24.5)	1.03 (0.80-1.31)
Q3	353 (26.3)	343 (24.2)	1.28 (1.00-1.63)
Q4	274 (20.4)	349 (24.6)	1.00 (Ref)
			p-trend =0.29
Excluding controls not screened for prostate cancer in the previous 2 years	1,371 (100)	1,120 (100)	
CEvents[b]			
None	46 (3.4)	30 (2.7)	1.54 (0.90-2.66)
Q1	369 (26.9)	249 (22.2)	1.26 (0.97-1.62)
Q2	307 (22.4)	282 (25.2)	0.92 (0.72-1.18)
Q3	357 (26.0)	280 (25.0)	1.12 (0.88-1.43)
Q4	292 (21.3)	279 (24.9)	1.00 (Ref)
			p-trend =0.41

CDuration [c]			
None	46 (3.4)	30 (2.7)	1.59 (0.93-2.74)
Q1	349 (25.5)	252 (22.5)	1.23 (0.95-1.59)
Q2	333 (24.3)	279 (24.9)	1.00 (0.78-1.28)
Q3	361 (26.3)	275 (24.6)	1.26 (0.99-1.60)
Q4	282 (20.6)	284 (25.4)	1.00 (Ref)
			p-trend =0.30
Excluding participants without seasonality information for leisure activities	1,090 (100)	1,295 (100)	
CEvents[b]			
None	46 (4.2)	38 (2.9)	1.72 (1.00-2.97)
Q1	288 (26.4)	311 (24.0)	1.28 (0.97-1.69)
Q2	251 (23.0)	323 (24.9)	0.98 (0.75-1.27)
Q3	285 (26.1)	297 (22.9)	1.27 (0.97-1.65)
Q4	220 (20.2)	326 (25.2)	1.00 (Ref)
			p-trend =0.35
CDuration[c]			
None	46 (4.2)	38 (2.9)	1.72 (1.00-2.99)
Q1	267 (24.5)	312 (24.1)	1.19 (0.90-1.58)
Q2	275 (25.2)	321 (24.8)	1.06 (0.81-1.38)
Q3	287 (26.3)	302 (23.3)	1.38 (1.05-1.80)
Q4	215 (19.7)	322 (24.9)	1.00 (Ref)
			p-trend =0.31
Excluding participants without positive family history of prostate cancer	311	153	
CEvents[b]			
None	6 (1.9)	2 (1.3)	2.50 (0.44-23.45)
Q1	84 (27.0)	30 (19.6)	1.53 (0.79-2.99)
Q2	65 (20.9)	39 (25.5)	0.74 (0.40-1.36)
Q3	90 (28.9)	40 (26.1)	1.31 (0.71-2.41)
Q4	66 (21.2)	42 (27.5)	1.00 (ref)
			p-trend =0.46
CDuration[c]			
None	6 (1.9)	2 (1.3)	2.19 (0.39-20.20)
Q1	78 (25.1)	31 (20.3)	1.21 (0.62-2.36)
Q2	81 (26.0)	39 (25.5)	0.94 (0.51-1.73)
Q3	80 (25.7)	39 (25.5)	1.03 (0.55-1.91)
Q4	66 (21.2)	42 (27.5)	1.00 (ref)
			p-trend =0.47
Self-reported recreational sunlight exposure	1,371 (100)	1,479 (100)	
None	97 (7.1)	105 (7.1)	1.01 (0.71-1.42)
Sometimes	506 (36.9)	594 (40.2)	1.02 (0.85-1.21)
Often	768 (56.0)	780 (52.7)	1.00 (Ref)

[a] Odds ratio (OR), 95% confidence interval (CI). Models adjusted for age, first-degree family history of prostate cancer, ancestry, timing of last prostate cancer screening, education, BMI, solar protection during leisure and overall physical activity level. Analyses excluding controls not screened for prostate cancer in the previous 2 years are not adjusted for prostate cancer screening. [b] Cumulative number of events entailing sunlight exposure during adulthood (levels: none - 0 event, Q1 -1 to 3291 events, Q2 – 3292 to 6755 events, Q3 – 6756 to 14,039 events, Q4 – 14,040 to 94,890 events). [c] Cumulative duration of leisure-time exposure to sunlight during adulthood (levels: none - 0 hour, Q1 - 1 to 4575 hours, Q2 – 4576 to 9892 hours, Q3 – 9893 to 18,869 hours, Q4 – 18,870 to 103,500 hours).

6.5 Discussion

The environment is thought to influence prostate cancer etiology but the specific factors involved remain elusive. Given the large number of men diagnosed with this cancer each year, research towards the identification of potential modifiable risk factors is of high importance.

Some ecological studies [16-18] and a handful of analytical studies [19-21] have suggested an inverse relation between sunlight exposure and prostate cancer. A meta-analysis [22] yielded a pooled relative risk of 1.13 (95% CI=0.98-1.29) for incident prostate cancer associated with the lowest exposure compared with the highest exposure. By contrast, two other recent studies conducted in Australia [23] and Singapore [24] suggested a positive relationship between sunlight exposure and prostate cancer; subjects in the highest exposure group were twice as likely to develop prostate cancer than those in the lowest exposure group. Of the three previous studies that looked at prostate cancer aggressiveness based on the Gleason score, two showed an inverse relation between sunlight exposure and aggressiveness, [22, 25], while one reported the reverse [24].

Differences in results across studies, including ours, may well relate to methodological issues. One important aspect to consider is how sunlight exposure assessment was conducted. Markedly different assessment protocols have been applied, ranging from using skin cancer as a marker of high sunlight exposure, to some semi-quantitative measurements incorporating frequency and/or duration of exposure. The exposure circumstances under study have varied as well, covering

various leisure-time activities, or very specific activities, such as sunbathing. Finally, the timing of exposure assessment has differed between investigations, relying on specific time points or covering several years. All of these need to be taken into account when drawing inference from accumulated data.

Most ecological studies and some analytical studies focusing on prostate cancer used latitude [7, 26-29] and/or UV-B dose or UV index [9, 16-18, 21, 29-34]. In most case-control and cohort studies, chronic sunlight exposure in terms of frequency or cumulative exposure [19, 20, 22-25, 35-41] and/or acute sunlight exposure like sunbathing [19, 20, 22, 25, 35-38] were assessed. Assessment of cumulative exposure relied on the frequency of exposure based on the number of hours of sunlight exposure per year [20], per week [6, 23, 24] or per day [38], and a cumulative number of hours in the summer season [22].

Our study used a sunlight exposure assessment protocol based on the cumulative number of sunlight exposure events during adulthood, as derived from detailed questionnaire data eliciting participation in outdoor leisure activities. Changes in engagement in the different activities over the years were factored in, so were variations across seasons for most study subjects. We did not collect information on acute sunlight exposures, or on the specific number of hours involved in each outdoor activity. Nevertheless, we applied usual event durations to differentiate between typically shorter and longer exposure events and this had little impact on risk estimates. We had information on the reported overall sunlight exposure during work-time, and it was similar (less than 10% of subjects were exposed) among cases and controls. Albeit crude, this information suggested that assessing leisure-time activities likely captured the largest part of overall sunlight exposure for most study participants. Our sunlight exposure assessment did not collect data on sunlight exposure while traveling to work or elsewhere.

The vitamin D mechanism is most often put forward to explain a possible protective effect of sunlight exposure on prostate cancer. [6, 39] [42] Different pathways may be involved such as decreased cell proliferation, cell cycle regulation and increased cellular differentiation apoptosis. [11] Although the evidence for an anti-cancer mechanism of vitamin D is strongly suggested by biological studies, it has not been consistently been supported by epidemiological findings. It is thus possible that other mechanisms exist between sunlight exposure and prostate cancer.

Should a relation between sunlight and prostate cancer truly exist, and should this association involve vitamin D synthesis, then a number of factors would need to be considered for valid exposure assessment. The relation between solar UVB and vitamin D synthesis may indeed be modulated by multiple factors including skin coverage by clothing, skin type, geographical location and meteorological conditions. The amount of skin exposed to the sun can determine the rate of vitamin synthesis. However, previous data indicate that after a certain threshold, a greater exposed surface and a higher dose of UVB will not significantly increase vitamin D levels because of vitamin D [43]. While one study [44] stated that skin type does not affect the rate of vitamin D synthesis through UVB, other studies showed the contrary, where darker skins tended to allow for less vitamin D production. [45, 46] Finally, the amount of solar radiation received has been shown to differ between geographical regions, even when doing the same activity for the same amount of time [47]. Meteorological conditions such as the presence of direct, diffuse and reflected radiations (e.g. snow reflects UV radiation [48]), the time of the day and the atmospheric conditions [46] also affect the amount of solar radiation received. In addition, diet and supplementation play a role in the level of serum vitamin D, especially in the winter months when, at northern latitudes, no important vitamin D synthesis is triggered. [49] Information for

these factors was not available for our study, so each recreational sunlight event was assumed here to be equal in terms of sunlight exposure dose.

As is the case for any study evaluating risks or benefits associated with sunlight, exposure misclassification likely occurred to some extent in our data. However, it is believed to have been largely non-differential, which tends to result in conservative estimates of the association between sunlight exposure and prostate cancer. There may be less concern about misclassification of participants into the unexposed group than about the level of exposure among exposed participants. Indeed, we believe that individuals are reasonably accurate in reporting having not or very rarely engaged in outdoor activities. Our assessment of leisure activities has been shown to be reasonably reliable [50]. However, questions on these activities were primarily formulated to assess energy expenditure and subjective judgement needed to be applied in a number of occasions when assigning them as indoor or outdoor activities. Moreover, since physical activity might be associated with prostate cancer [51], we adjusted for it in our analyses.

Other than for sunlight exposure assessment, a number of methodological differences may also explain discrepant findings across previous studies. These include the ethnic background of participants, the location, the control for potential confounding factors, and the outcome. Our study was largely comprised of subjects of French ancestry. It is not clear, for instance, that a direct comparison can be drawn with findings from a study of subjects of Asian ancestry [24], which have been shown to typically have lower risks of prostate cancer [52]. Moreover, it may be that our study findings should be compared to those based on populations exposed at latitudes similar to ours. A number of British studies, which would be comparable to ours in terms of latitude, have either suggested a protective effect of sunlight exposure against prostate cancer

risk [19, 20, 38], or no association [22]. By contrast, recent studies conducted in areas considered to have high ambient solar UV environments [23, 24], suggested a positive association between solar UV and prostate cancer risk. Sunlight exposure is correlated with a number of lifestyle factors. Unlike some of the previous investigations, we were able to adjust for all recognized and several potential risk factors of prostate cancer. This included the use of solar protection, which very few studies have considered [22, 23, 38].

Finally, a number of previous studies have looked at prostate cancer mortality in association with sunlight exposure [34, 53, 54]. Since mortality can reflect both survival and etiology, findings from our study, which focused on incident prostate cancer cases, would not be expected to necessarily align with those using mortality as the outcome.

Reporting bias based on case-control status was possible, but unlikely. Exposure to sunlight was not the primary focus of the PROtEuS study. Moreover, there is no widespread belief in the population that sunlight exposure is associated with prostate cancer.

Participation rates in the study were relatively good, compared to rates often observed in similar studies, yet selection bias cannot be ruled out. The characteristics of eligible participants who declined to participate in the study (16% and 39% of cases and controls, respectively) differed slightly from those of participants. As previously reported [12], non-participants had a slight tendency to reside in areas with 1) a greater proportion of recent immigrants within the previous 10 years, 2) a higher unemployment rate, 3) a greater proportion of adults without a high school diploma, and 4) a lower median household income. Should non-participants have engaged less in outdoor activities than participants, there could have been a greater under-representation of

participants unexposed to sunlight among controls than amongst cases, which would have brought a true protective association towards the null.

The prevalence of skin cancer was slightly higher among our prostate cancer cases than among controls, as opposed to what we would expect if sunlight exposure was inversely associated with prostate cancer. Lindelof et al. (2012) have also shown that patients with prostate cancer were more likely to have a basal cell carcinoma than controls. [55] A previous finding contrary to the hypothesis of a protective effect of sunlight against prostate cancer is the common observation of higher risks of prostate cancer among agricultural workers [56], who typically have high exposure to sunlight.

Finally, the present study, the first of this type in Canada, has the largest number of incident prostate cancer cases with individually-based sunlight exposure assessment.

6.6 Conclusion

Overall, there was little evidence in our data of an association between leisure-time exposure to sunlight during adulthood, and prostate cancer development. Men with less exposure to sunlight tended to show somewhat higher risks than those highly exposed, but confidence intervals included the null value and there was no dose-response pattern. These observations applied to both non-aggressive and aggressive prostate cancers. Further studies of prostate cancer based on refined sunlight exposure assessment protocols should be undertaken. Should sunlight exposure be shown to be linked to prostate cancer risk, such a finding would have public health importance.

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6.9 Disclosure of Potential Conflicts of Interest

The authors declare that they have no conflicts of interest or competing financial interests.

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7.0 Sunlight exposure at work, global sunlight exposure (work and leisure), and prostate cancer

For most men, sunlight exposure primarily occurs during leisure time. However, based on estimates for 2006, 8.8% of the Canadian workforce population is likely to be exposed to solar UVR on the job [116]. Workplace sunlight exposures can vary in terms of the proportion of workplace hours exposed. For instance, individuals have been categorized as having "high exposure" (ex: farmers, some construction workers), "moderate exposure" (ex: carpenters, heavy equipment operators), or "low exposure" (ex: truck drivers, courier service drivers).

In the following section, we present an analysis of the association between occupational sunlight exposure and PCa. This analysis is based on the same Montreal case-control study of prostate cancer (PROtEuS), and the same study subjects, as those previously described to assess the association between leisure-time sunlight exposure and PCa.

Finally, we present an analysis of the association between a global index of exposure to sunlight during adulthood, encompassing both leisure-time and occupational exposures, and PCa risk.

7.1 Methods

7.1.1 Exposure assessment

In this study, occupational exposure to sunlight was assessed by applying a job-exposure matrix (JEM). A JEM is a tool that permits exposures to be assigned according to the occupation held by a subject. Additional dimensions can be added to a JEM, such as historical period or geographical area. For each cell of a JEM (i.e., a specific occupation), various exposure metrics can be provided. They vary from the simplest binary variable (exposed/not exposed) [134] to ordinal categories of intensity of exposure [135] to quantitative levels of exposure [134, 136, 137]. Additional information can include the proportion of workers exposed within an occupation, or the proportion of time typically spent exposed (e.g. 50% of a normal workweek).

The JEM used in this study, SunJEM [116], was recently developed in the context of the CAREX (CARcinogen Exposure) Canada project, which aims at estimating the number of Canadians exposed to carcinogenic agents, including sunlight, in the workplace and in the general environment. SunJEM is a semi-quantitative matrix providing information on sunlight exposure and artificial UV radiation for all occupations according to the National Occupational Classification for Statistics 2006 (NOC-S 2006) classification scheme. For the purpose of this study, SunJEM's occupational codes were initially converted from the NOC-S 2006 to the Canadian Classification and Dictionary of Occupations 1971 (CCDO 1971). The conversion was performed by Cheryl Peters, who took the leadership in developing the SunJEM. This was necessary in order to apply the SunJEM to occupations from the case-control study PROtEuS, which had been assigned occupational codes under the CCDO 1971 classification scheme.

There are four possible categories of sunlight exposure in SunJEM: 0 for occupations with no exposure, 1 for occupations rarely outdoor, 2 for occupations that are either mixed indoor/outdoor or that are normally indoor but could be indoor in certain industries, and 3 for occupations being outdoor at least 75% of the time. [116] Of the 7,739 CCDO occupations listed in the recoded SunJEM, 552 are associated with at least some sunlight exposure, i.e. an exposure category different from 0.

For artificial UV exposure, the four possible categories in SunJEM are: 0 for occupations with no exposure, 1 for rarely exposed occupations, 2 for moderately, and 3 for highly exposed occupations. Eighty-nine (89) of the 7,739 CCDO occupations listed in SunJEM are associated with at least some artificial UV exposure.

Based on the exposure categories assigned to each individual job, we built a cumulative exposure index corresponding to the lifetime total duration of occupational exposure to sunlight (CO). This index was calculated by assigning to each exposure category a proportion of time spent outdoors, based on the description provided in SunJEM and on judgement: these proportions were 0, 0.05, 0.5 and 0.75, for the exposure categories 0, 1, 2, and 3, respectively.

The calculation of *CO* is described by equation 3: $CO = \sum_{j=1}^{n}(N.Years_j \times P_j)$ (3)

Where n is the number of jobs occupied by the participant; $N.Years_j$ is the number of years the participant occupied job j and P_j is the proportion of time spent outdoor for job j.

For the analyses, this cumulative index was categorized into three groups: never-exposed, lowly-exposed (*CO* < exposed controls' median) or highly-exposed (*CO* ≥ exposed controls' median).

Calculating the *CO* index required assuming arbitrary proportions of time spent outdoors for each category in SunJEM, implying a potential sensitivity of the analysis to the chosen values. Therefore, we also devised a simpler index that did not rely on such assumption. This index (*SO*) was defined in three categories: never-exposed, non-substantially exposed, and substantially exposed. Participants were substantially exposed only if they had at least 5 years in occupations with level-3 exposure. The non-substantially exposed corresponded to subjects having held jobs associated with exposure but that did not meet the 'substantially exposed' criterion.

Finally we created an exposure metric combining occupational and leisure sunlight exposure into a global sunlight metric. For this metric, both the lifetime cumulative number of sunlight leisure exposure events (described in details in section 6) and the lifetime total duration of occupational exposure to sunlight (described above) were categorized using a similar approach: never exposed (0 exposure), lowly exposed (lower than controls' median) and highly exposed (higher than controls' median). The global sunlight exposure metric (*GSE*) was then defined as a 3-category variable based on table 5 below.

Table 5 - Global exposure to sunlight as a function of occupational and leisure sunlight exposure categories

		Leisure exposure[b]		
		Never	**Low**	**High**
Occupational exposure[a]	**Never**	Low	Low	Medium
	Low	Low	Medium	High
	High	Medium	High	High

[a] Cumulative occupational sunlight exposure index (*CO*), levels: never – never been exposed, low – *CO* < exposed controls' median, high – *CO* ≥ exposed controls' median). [b] Cumulative number of events in participation in outdoor leisure activities (*CEvents*), levels: never – never been exposed, low – *CEvents* < exposed control's median, high – *CEvents* ≥ exposed controls' median.

7.1.2 Statistical analyses

Unconditional logistic regression was used to evaluate the association between each of the three indices, *CO*, *SO* and *GSE,* and PCa. A number of variables were included *a priori* in all models: age (continuous), first-degree family history of prostate cancer (yes, no, don't know), ancestry (French, Black, Asian, Other), timing of last prostate cancer screening (last 2 years, more than 2 years, don't know whether screened within 2 years, not screened) and education (primary school, secondary school, college, university).

Several additional covariates were analysed for potential inclusion in the final model for each of the 3 exposure indices. They included occupational artificial UV (exposed, unexposed), recreational sunlight exposure (not exposed, low-exposed, high-exposed, as defined in 7.1.1), and self-reported solar protection at work and during leisure ("yes, often", "yes, sometimes", "no" and "don't know") for the 2 occupational exposure indices (*CO* and *SO*). For the global sunlight exposure index (*GSE*), the same covariates were tested, in addition to the BMI 2 years before the index date (continuous) and overall physical activity levels (low, medium and high). The BMI and overall physical activity variables were only tested in the global sunlight exposure models because these two variables may be related to leisure exposures and not so much to occupational exposures.

For the *CO* and *SO* analyses, potential interaction between occupational sunlight exposure and 3 covariates (recreational exposure, solar protection at work and solar protection during leisure) were also tested.

For each exposure index, the final model was selected as the combination of potential covariates leading to the lowest value of the Akaike Information Criterion (AIC). [138]

Odds ratios (OR) and 95% confidence intervals (CI) were then calculated, with reference group for both *CO* and *SO* being "never exposed", and "low exposed" for *GSE*.

Colinearity was addressed by evaluating the association between all pairs of potential predictors. Spearman's ρ was used for two continuous variables, the square-root of the unadjusted R-squared of the ANOVA for one continuous and one categorical variable, and Cramer's V for two categorical variables. For any pair of variables, if the correlation index

was greater than 0.7 (or less than -0.7 for Spearman's correlation), only one was tested in the model, selected based on judgement.

7.1.3 Sensitivity analyses

Stratified analyses according to the Gleason score were conducted to evaluate the effect of sunlight exposure on non-aggressive and aggressive prostate cancers. Low aggressiveness was defined by a Gleason score of 6 or less or 7 with a primary grade of 3 and high aggressiveness by a Gleason score of 8 or more or 7 with primary grade of 4 [37].

Several cells of the SunJEM contain comments of the form "to review" followed by conditions which, when met, would change the initial exposure rating to a higher or lower value. For example, if a construction manager (CCDO=1145-110) spent more than 25% outdoor during work, the rating would change from 0 to 2; and, on the opposite, if an attendant at a recreational facility (CCDO=3715-130) did not work outdoors, the exposure rating would decrease from 3 to 0. In our study population, 2,570 jobs (16%) from 245 different CCDO codes would have required review. Because such as review was not feasible within the timeframe of this thesis, these jobs were assigned the initial rating. As a sensitivity analysis, we recalculated the 3 exposure indices and computed new ORs by assuming the conditions were met and the sunlight exposure rating had to be changed for the 2,570 jobs needing review.

In the general questionnaire, participants were asked to report their solar exposure at work, over the lifetime, by answering the question "Have you been directly exposed to the sun at work?" with the following possible answers: yes, often; yes, sometimes; no; or don't know. A sensitivity analysis was performed using the self-reported occupational sunlight exposure as the exposure variable instead of the main occupational sunlight exposure indices (*CO* and *SO*).

Similarly, a sensitivity analysis was carried out for *GSE*, the global index integrating leisure and occupational exposure, by using this time the self-reported information on sunlight exposure at work and during leisure time. A 3-category variable was created based on table 6 below.

Table 6 - Global exposure to sunlight as a function of self-reported occupational and leisure sunlight exposure categories				
		Leisure exposure		
		No	**Sometimes**	**Often**
Occupational exposure	**No**	Low	Low	Medium
	Sometimes	Low	Medium	High
	Often	Medium	High	High

The data analyses were done using the R 2.15.1 statistical software (R development Core Team, Vienna, Austria) [122] with the package vcd [123] for analyses of categorical variables.

7.2 Results

7.2.1 Study population

Exposure at the job level

Since socio-demographic characteristics were already described in section 6.4 (details in table 1-M), we only present here some descriptive information about the results of the exposure assessment conducted with SunJEM.

855 jobs (5.2%of all jobs) held by participants of the study population corresponded to one of the 552 occupations associated with at least some sunlight exposure in SunJEM: 0.1% with low exposure, 1.7% with medium exposure, and 3.4% with high exposure. The occupations associated with low exposure were: snow-removal equipment operator in urban area (CCDO=9199-130, n=6), wrecker and salvager (CCDO=8799-266, n=5), snow-removal equipment operator (CCDO=9199-122, n=5), campground manager (CCDO=6130-115, n=3) and street sweeper operator (CCDO=9199-142, n=1). For medium exposure, the most frequent occupations were delivery person (CCDO=4177-122, n=107), heavy-duty equipment operator (CCDO=8711-110, n=27), longshore worker (CCDO=9313-110, n=23), messenger (CCDO=4177-118, n=17) and door-to-door salesperson (CCDO=5141-110, n=15), while they were logger (CCDO=7513-122, n=59), general farmer (CCDO=7111-110, n=29), general

farm worker (CCDO=7181-110, n=27), letter carrier (CCDO=4172-110, n=25) and general farm labourer (CCDO=7198-112, n=21) for high exposure.

235 jobs (1.4% of all jobs) held by participants of the study population corresponded to one of the 89 occupations associated with at least some artificial UV exposure in SunJEM: 0.1% with low exposure, 0.2% with medium exposure, and 1.1% with high exposure. The occupations associated with low exposure were: elevator repairer (CCDO=8799-114, n=12), elevator constructor (CCDO=8799-118, n=7) and transformer repairer (CCDO=8739-138, n=1). For medium exposure, the most frequent occupations were structural steel erector (CCDO=8793-114, n=13), dentist (CCDO=3113-134, n=12) and ornamental metalworker (CCDO=8793-110, n=5), while they were arc welder (CCDO=8335-138, n=65), combination welder (CCDO=8335-126, n=48), gas welder (CCDO=8335-142, n=16) and reinforcing-iron worker (CCDO=8793-126, n=12) for high exposure.

Exposure at the subject level

Table 7 presents descriptive statistics of the various indices used to assess exposure to sunlight at work among the subjects in our study. The majority of our participants (80.2% of cases and 78.8% of controls) have only had indoor jobs in their lifetime. The two occupational sunlight exposure indices, *CO* (categorical) and *SO*, were strongly correlated, with a kappa coefficient of 0.91.

The median values of the lifetime total index score of occupational exposure to sunlight (*CO*) of the exposed participants were 2.13 for the cases (range=0.09 to 4.63) and 2.25 for the controls (range=0.05 to 4.75) with low exposure and they were 10.88 for the cases (range=4.88 to 40.5) and 11.81 for the controls (range=4.88 to 38.62) with high exposure. The occupational sunlight exposure indices (*CO* and *SO*) were in fair agreement with the self-reported occupational sunlight exposure (κ=0.26 and 0.25 respectively). The majority of the participants did not use solar protection at work (86.6% for both cases and controls), but a slightly greater proportion of controls (8.1%) than cases (6.6%) reported being often protected. Sunlight exposure during leisure was not associated with sunlight exposure at work: ρ=-0.07 between the 2 continuous indices. 2.0% of cases and 1.8% of controls never had any recreational nor occupational sunlight exposures.

Table 7 - Distribution of the cases and controls according to the cumulative occupational sunlight exposure index (*CO*) groups, simplified occupational sunlight exposure index (*SO*), self-reported occupational sunlight exposure, global sunlight exposure (*GSE*) index and solar protection at work

Sunlight exposure patterns	Cases n=1,371 (%)	Controls n=1,479 (%)
CO[a]		
None	1099 (80.2)	1165 (78.8)
Low	137 (10.0)	156 (10.5)
High	135 (9.8)	158 (10.7)
SO[b]		
None	1099 (80.2)	1165 (78.8)
Low	146 (10.6)	177 (12.0)
High	126 (9.2)	137 (9.3)
GSE		
Low	583 (42.5)	600 (40.6)
Medium	615 (44.9)	664 (44.9)
High	173 (12.6)	215 (14.5)
Self-reported occupational exposure		
Not exposed	892 (65.1)	996 (67.3)
Sometime exposed	237 (17.3)	229 (15.5)
Often exposed	242 (17.7)	254 (17.2)
Solar protection at work		
Never protected	1187 (86.6)	1281 (86.6)
Sometimes protected	94 (6.9)	77 (5.2)
Often protected	90 (6.6)	120 (8.1)

[a] Cumulative occupational sunlight exposure index levels: none-never been exposed, low-exposed but lower than exposed controls' distribution median and high-exposed and equal or higher than median. [b] Simplified occupational sunlight exposure index levels: none-never been exposed, low-moderately exposed and high-substantially exposed.

7.2.2 Model selection

The unadjusted models with either sunlight exposure index (*CO*, *SO* or *GSE*) all yielded significantly worse fit in terms of AIC than the models including the *a priori* variables. Among the potential covariates tested, sunlight exposure during leisure and solar protection during leisure were retained in the final models with *CO* and *SO* exposure indices. Solar protection during leisure, BMI and overall physical activity were kept in the final model with *GSE* index. The final *GSE* model had a noticeably better goodness of fit than the *CO* and *SO* final models (AIC=3,320 compared to 3,342 and 3,342, respectively).

7.2.3 Association between occupational sunlight exposure and prostate cancer risk

Table 8 presents the unadjusted and adjusted (full model) ORs and 95% CIs for all the three exposure indices (*CO*, *SO* and *GSE*). All the exposed groups had ORs lower than 1 compared to the reference, but the results were not statistically significant. There was no clear dose-response relationship. Adjusting for the covariates in the full models consistently decreased the OR estimates, albeit by a small margin.

Table 8 - Unadjusted and adjusted ORs for the risk of prostate cancer according to the cumulative occupational (*CO*), simplified occupational (*SO*) sunlight exposure indices and global sunlight exposure (*GSE*) index

Exposure index	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
CO[a]		
None	1.00 (Ref)	1.00 (Ref)[c]
Low	0.93 (0.73-1.19)	0.85 (0.64-1.12)[c]
High	0.91 (0.71-1.16)	0.88 (0.66-1.16)[c]
SO[b]		
None	1.00 (Ref)	1.00 (Ref)[c]
Low	0.87 (0.69-1.10)	0.81 (0.62-1.07)[c]
High	0.97 (0.75-1.26)	0.92 (0.69-1.24)[c]
GSE		
Low	1.00 (Ref)	1.00 (Ref)[d]
Medium	0.95 (0.81-1.12)	0.99 (0.82-1.19)[d]
High	0.83 (0.66-1.04)	0.83 (0.64-1.09)[d]

[a] Cumulative occupational sunlight exposure index (levels: none-never been exposed, low-exposed but lower than exposed controls' distribution median and high-exposed and equal or higher than median). [b] Simplified occupational sunlight exposure index (levels: none-never been exposed, low-moderately exposed and high-substantially exposed). [c] Adjusted ORs for age, ancestry, first-degree family history of prostate cancer, education, prostate cancer screening, recreational sunlight exposure and solar protection during leisure time. [d] Adjusted ORs for age, ancestry, first-degree family history of prostate cancer, education, prostate cancer screening, solar protection during leisure time, BMI and physical activity

Stratification by PCa aggressiveness

Table 9 presents ORs and 95% CIs for the analyses stratified by degree of PCa aggressiveness. Results obtained for the association between non-aggressive PCa and occupational sunlight exposure were similar to the main results. For aggressive PCa, the middle exposure group shifted from slightly lower to slightly higher than 1 (not significant) for the 3 indices.

Table 9 - Stratified analyses for the aggressiveness of the prostate cancer according to the cumulative occupational (*CO*) and simplified occupational (*SO*) sunlight exposure indices, and global sunlight exposure (*GSE*) index

	Non-aggressive prostate cancer		Aggressive prostate cancer	
Exposure index	**Cases n=985 (%)**	**OR (95% CI)[c]**	**Cases n=362 (%)**	**OR (95% CI)**
CO[a]				
None	798 (81.0)	1.00 (Ref)[c]	279 (77.1)	1.00 (Ref)[c]
Low	91 (9.2)	0.76 (0.55-1.04)[c]	44 (12.2)	1.07 (0.71-1.58)[c]
High	96 (9.7)	0.91 (0.66-1.24)[c]	39 (10.8)	0.89 (0.58-1.33)[c]
SO[b]				
None	798 (81.0)	1.00 (Ref)[c]	279 (77.1)	1.00 (Ref)[c]
Low	96 (9.7)	0.74 (0.55-1.01)[c]	48 (13.3)	1.06 (0.72-1.54)[c]
High	91 (9.2)	0.95 (0.69-1.32)[c]	35 (9.7)	0.87 (0.56-1.34)[c]
GSE				
Low	298 (30.3)	1.00 (Ref)[d]	115 (31.8)	1.00 (Ref)[d]
Medium	433 (44.0)	0.91(0.75-1.11)[d]	166 (45.9)	1.28 (0.97-1.69)[d]
High	254 (25.8)	0.84(0.62-1.12)[d]	81 (22.4)	0.89 (0.59-1.33)[d]

[a] Cumulative occupational sunlight exposure index (levels: none-never been exposed, low-exposed but lower than exposed controls' distribution median and high-exposed and equal or higher than median). [b] Simplified occupational sunlight exposure index (levels: none-never been exposed, low-moderately exposed and high-substantially exposed). [c] Adjusted ORs for age, ancestry, first-degree family history of prostate cancer, education, prostate cancer screening, recreational sunlight exposure and solar protection during leisure time. [d] Adjusted ORs for age, ancestry, first-degree family history of prostate cancer, education, prostate cancer screening, solar protection during leisure time, BMI and physical activity

7.2.4 Sensitivity analyses

The first sensitivity test involved using the occupational exposure rating from the SunJEM assuming the review criteria were met. Except for the moderately exposed group with *GSE* index, which was marginally affected, ORs for all exposed groups shifted from slightly lower to slightly higher than 1 (Table 10). The second sensitivity analysis used self-reported occupational sunlight exposure instead of the *CO* or *SO* indices. Participants who were sometimes exposed to the sun at work had a minor increased risk of PCa compared to those without exposure; and participants who were often exposed had slightly decreased risk. Using the combined self-reported recreational and occupational sunlight showed very similar results to those obtained with self-reported occupational sunlight exposure sensitivity test. None of the ORs calculated in the sensitivity analyses were statistically significant.

Table 10 - Sensitivity analyses for occupational sunlight exposure 1) using the new sunlight exposure rating if the job review criterion was met. 2) using self-reported occupational sunlight exposure variable. 3) using the global self-reported recreational and occupational sunlight exposure.

Sensitivity analysis	Cases n=1,371 (%)	Controls n=1,479 (%)	OR (95% CI)
Jobs reviewed			
***CO* index**[a]			
None	650 (47.4)	721 (48.7)	1.00 (Ref)[d]
Low	372 (27.1)	378 (25.6)	1.06 (0.86-1.30)[d]
High	349 (25.5)	380 (25.7)	1.06 (0.85-1.32)[d]
***SO* index**[b]			
None	650 (47.4)	721 (48.7)	1.00 (Ref)[d]
Low	574 (41.9)	574 (38.8)	1.06 (0.88-1.28)[d]
High	147 (10.7)	158 (10.7)	1.04 (0.78-1.40)[d]
***GSE* index**			
Low	325 (23.7)	350 (23.7)	1.00 (Ref)[e]
Medium	553 (40.3)	606 (41.0)	0.95 (0.77-1.18)
High	493 (36.0)	523 (35.4)	1.04 (0.82-1.31)
Self-reported occupational sunlight exposure			
Not exposed	892 (65.1)	996 (67.3)	1.00 (Ref)[d]
Sometime exposed	237 (17.3)	229 (15.5)	1.12 (0.89-1.41)[d]
Often exposed	242 (17.7)	254 (17.2)	0.96 (0.76-1.21)[d]
Global self-reported sunlight exposure			
Low	420 (30.6)	520 (35.2)	1.00 (Ref)[e]
Medium	612 (44.6)	597 (40.4)	1.14 (0.94-1.38)[e]
High	339 (24.7)	362 (24.5)	0.95 (0.76-1.20)[e]

[a] Cumulative occupational sunlight exposure index (levels: none- never been exposed, low-exposed exposed but lower than exposed controls' distribution median and high-exposed and equal or higher than median). [b] Simplified occupational sunlight exposure index (levels: none-never been exposed, low-moderately exposed and high-substantially exposed). [c] Global sunlight exposure index. [d] Adjusted ORs for age, ancestry, first-degree family history of prostate cancer, education, prostate cancer screening, recreational sunlight exposure and solar protection during leisure time. [e] Adjusted ORs for age, ancestry, first-degree family history of prostate cancer, education, prostate cancer screening, solar protection during leisure time, BMI and physical activity.

8.0 Discussion

8.1 Results

We estimated the cumulative leisure-time exposure to sunlight during adulthood, cumulative occupational exposure to sunlight over the entire work history, and created a global sunlight exposure index combining the former two. Our findings provide little evidence of an association between any of these, and PCa risk.

Some weak trends were observed in our data, which would be in line with a protective effect. For instance, men never exposed to sunlight during leisure-time had a roughly 50% excess risk of the cancer, as compared to men classified in the upper quartile of exposure. Men occupationally exposed to sunlight had ORs below one compared to those unexposed at work. The global index was also consistent with a slightly lower PCa risk among men with sunlight exposure. However, none of these results were statistically significant, and there was no evidence of dose-response relationships, bringing little support for a true protective effect of sunlight exposure. Results from analyses stratifying cancers by disease aggressiveness were generally consistent with those from the main analyses. Moreover, interpretation of findings remained unchanged when considering various sensitivity analyses.

8.2 Comparison with literature

Of the 33 studies assessing the relationship between sunlight exposure and PCa, 15 were ecological studies [4, 5, 77, 78, 80-90], 13 were case-control studies [6-9, 67, 91, 92, 94, 95, 104-108] and 5 were cohort studies [65, 70, 93, 102, 110].

The majority of ecological studies found a protective effect of sunlight exposure against PCa. However, eight of these studies were based exclusively on mortality statistics. PCa incidence is preferred over mortality (reflecting both etiology and survival) when investigating etiological factors. Moreover, ecological studies typically offer little opportunity to adjust for potential confounding factors. Consequently, we will not discuss these in detail here.

Nine of the 13 case-control studies found a beneficial effect of sunlight exposure against PCa risk [6, 7, 92, 94, 104-106, 108] or PCa mortality [67], 2 showed a harmful effect [8, 9] and 2

reported no association [95, 107]. The five cohorts, three of which looked at incidence and two of them at mortality, reported a protective effect in terms of PCa risk.

The two case-control studies [95, 107] that found no association between sunlight exposure and PCa were conducted in the UK, at similar latitudes as Canada. One of the studies [95] used PCa cases with bone metastasis and controls with PCa but without bone metastasis, while we used incident cases of PCa as the outcome and controls from the population. In the other case-control study [107] reporting no association, the sample size was large (1,020 cases and 5,044 controls). They assessed both acute and chronic sunlight exposures, which consisted of summing the number of hours spent outdoors at different age groups over lifetime, childhood or adulthood depending on the particular analysis. They also controlled for age, sunscreen use and skin pigmentation as a proxy for ancestry, although the majority of their study participants were Caucasian. They did not adjust for family history of PCa, smoking, physical activity and occupational status because results did not differ when adjusting for these factors. The cases they used were prevalent cases, thus they studied risk factors that would be related to the risk of disease and survival. The controls they used were hospital-based, thus these control participants could have a disease related to low sunlight exposure, such as colorectal cancer [65, 67-69] or multiple sclerosis [112] which may have reduced the opportunity to observe an association between PCa and sunlight exposure.

In the two case-control studies [8, 9] which reported a positive association between sunlight exposure and PCa risk, there were also a number of methodological differences with our study. The first, which renders these studies difficult to compare with ours, is that the countries (Singapore [8] and Australia [9]) in which these studies were conducted are on different latitudes to Montreal, Canada. This difference in latitude means that the population living in Montreal is exposed to lower solar radiation intensity [75]. Another difference relates to the ancestries represented in the different study populations. Our study predominantly included subjects of French ancestry, which may compare to the study population in the Australian study, predominantly of European descent (97% of cases and 90% of controls). By contrast, the Singapore study focused on Asians, a population known to have lower risks of PCa. First-degree family-history of PCa, a major risk factor to this cancer, was adjusted for in the analyses of the Singapore study, but it was not assessed in the

Australian study. Although our sunlight exposure assessment may not be as precise as in the aforementioned studies where they assessed the cumulative number of hours of sunlight exposure [9] or number of hours of exposure per week [8], we had the exposure for the whole adulthood of our study participants, whereas in the Australian study, they only used the exposure at two time points, i.e., at the ages of 30 and 50 years. It should also be noted that both studies had smaller sample sizes (240 cases and 268 controls in the Singapore study, and 1,084 cases and 234 controls in the Australia study) than ours (1,371 cases and 1,479 controls).

The NIH-AARP Diet and Health cohort study [70], reporting an inverse association, had, to our knowledge, the largest sample size (21,439 PCa cases from the 272,796 men followed) for studies investigating on the relationship between sunlight exposure and PCa risk. They also controlled for a large number of factors, such as ancestry, age, BMI, dietary factors, alcohol consumption, smoking, education level, physical activity and median household income. However, they used the UV-B level generated from the total ozone mapping spectrometer (TOMS) according to the residence coordinates of the participants at baseline as their sunlight exposure index. This did not capture the individual behaviour of the participants and may not be accurate if the participants moved during follow-up period.

Our exposure assessment of sunlight exposure consisted of cumulative sunlight exposure indices for recreational exposures (*CEvents* and *CDuration*) and occupational exposures (*CO*) and a simplified index (*SO*). Our indices may not be as precise as the exposure assessment of other studies in which they had the number of hours of sunlight exposure in the recreational and occupational settings [9, 107, 108]. However, we had the precise number of events of leisure activities entailing sunlight exposure captured during the adulthood period for recreational exposures. For occupational exposures, we had two indices based on the proportion of the time spent outdoors at work, which did not confer the accurate amount of exposure, but could be used to compare between individuals with different levels of exposure. One study [95] also used the proportion of occupation spent outdoors, but they did not specify when or which occupation was assessed, whereas in our study, we had the advantage of having the entire work history for an overall occupational exposure.

A case-control very similar to ours, but with a smaller sample size (450 cases and 455 population controls) [92] also found a statistically non-significant inverse relationship between the risk of PCa and sunlight exposure. Their participants who had the highest frequency (hours/week) of overall sunlight exposure (work and leisure) or only at work over lifetime were at decreased risk of incident PCa compared to the less exposed individuals (respective ORs and 95% CIs: 0.95 [0.62-1.45] and 0.73 [0.48-1.11]). Their moderately exposed groups were however at higher risk than the non-exposed reference group. Similar to us, they assessed recreational exposure through outdoor physical activities (e.g. walking to work or school, outdoor exercise and outdoor chores) and sedentary leisure activities (e.g. sunbathing and watching sporting events), and occupational exposure through lifetime occupational histories. An additional factor that we controlled in our study was physical activity, which could be associated with a decreased PCa risk. They also did not control for solar protection, which could modulate the amount sunlight received by the skin [114]. As a measure of cumulative sunlight exposure, they used the difference between the constitutive and facultative pigmentations; and with this exposure assessment they found a decreasing risk of PCa for an increasing exposure, but results were not statistically significant, except for the most exposed group (OR and 95% CI: 0.51 [0.33-0.80]). This finding may be explained by the fact that their study was conducted in California where more sunlight could be received than in Quebec [75]. They restricted their sample population to non-Hispanic White men.

In the literature, farmers, who typically have high sunlight exposure, have been shown to have excess prostate cancer risks [133]. Freedman et al. (2002) [67] have reported that farmers have a risk increased by 16% of dying from prostate cancer compared to men who were working indoors. They were also at higher risk than men who have a mixed indoor/outdoor job and men with an outdoor job. This argues against a protective effect of sunlight. However, we didn't have the same observation in our study. Instead, a higher proportion of controls had at least one farming job in their lifetime than cases, which gives supportive evidence for a beneficial effect of sunlight exposure. The difference in observations between our study and the literature may be explained by some other underlying factors, such as pesticides, possibly involved in this association [56], and which we have not taken into account.

8.3 Mechanisms

Vitamin D synthesis is the biological mechanism most often raised to explain the protective effect of sunlight exposure on PCa observed in some studies. Better known for its implication in calcium homeostasis [73], recent studies have clarified some of the anti-cancer mechanisms of this vitamin which may be involved in the prevention of PCa. This is not the only pathway, however, through which sunlight exposure might be beneficial in the prevention of PCa. .

8.3.1 Vitamin D

Previtamin D, 7-dehydrocholesterol, synthesized in skin and gut wall cells, is isomerized by UV-B absorption into provitamin D, also called vitamin D_3 or cholecalciferol. It is then converted into 25 (OH) D_3, or calcidiol, by CYP27A1 hydrolase in the liver. Calcidiol is usually measured for the serum levels of vitamin D, but levels are also influenced by skin pigmentation, dietary factors and body fat. [139]

Calcidiol is then hydrolysed again by CYP27B1, in the kidney and other tissues like the prostate epithelial cells, into 1,25 $(OH)_2$ D_3 also called calcitriol, as the active form of vitamin D. This form binds to the vitamin D receptor (VDR) which then heterodimerizes with the retinoid X receptor before binding to the vitamin D response element of DNA. The next step is the expression of the target genes involved in different biological pathways. One of them is the induction of the CYP24A1 hydroxylase which metabolizes calcidiol and calcitriol, creating a negative feedback loop. Its expression was reported to be inhibited by the androgen dihydrotestosterone and the retinoic acid, suggesting cross-talk between the androgen and vitamin A pathways. The other effects of gene expression or function modulation by calcitriol include a decrease of c-Myc, telomerase, BCL-2, α6 and β4 integrins, CDK2, interleukin-6 and interleukin-8; and an increase of retinoblastoma protein phosphorylation, CDK inhibitors p21 and p27 and GADDD45γ. Through these genes, cell proliferation, cell cycle progression, cell invasiveness and angiogenesis are inhibited and cell differentiation and programmed cell death are induced. [73, 124, 140] Looking at these effects, vitamin D seems to be involved in both the early and late stages of tumour development.

Prostate cancer cells have been shown to harbour less VDR than normal prostate cells [141, 142], providing further evidence for protective effect of vitamin D. However, epidemiological

studies on the association of vitamin D and prostate cancer remain controversial. A nested case-control study [143] reported an increased risk of PCa in participants with either low or high serum levels of vitamin D. The conclusion about the low levels of vitamin D is well supported by experimental studies, but the conclusion about the high levels is much less well established. It was thought that the upregulation of the CYP24A1 hydroxylase would decrease levels of active vitamin D. It was shown previously that serum levels of vitamin D may reach saturation after a certain UV dose threshold. [125] Therefore no extra protection from vitamin D would be observed with more sunlight exposure.

8.3.2 Other mechanism

Sunlight exposure may bring other health benefits through other pathways than those involving vitamin D, but may not be directly related to prostate cancer. Examples [112] include mood enhancement by β-endorphin release, lupus vulgaris treatment by killing *Mycobacterium tuberculosis* and vitiligo treatment by increase of melanocytes. Another positive effect of UV exposure is cardiovascular health improvement through blood pressure decrease by UV-induced nitric oxide (NO). It has also been shown that NO is involved in prostate cancer progression. [74] Its effects are, however, concentration-dependent. At high concentrations, inhibitions of prostate cancer cell proliferation, of metastases and of epithelial-mesenchymal transition were observed. In contrast, low concentrations of NO promote angiogenesis for prostate cancer progression. In other words, low exposure may have deleterious effects and high exposure may have a protective effect on prostate cancer through NO.

8.4 Limits of the current study

8.4.1 Measurement error

To create the recreational sunlight exposure index, the hobbies and leisure activities section of the questionnaire was used. This section was not initially created to assess sunlight exposure; therefore there were activity groups in the list that contained both indoor and outdoor activities. For some activities, detail about whether it was practiced outdoors or indoors was not collected, for example, for swimming. In our study, we had considered these as outdoor activities, which could have overestimated exposure levels of some participants. However,

this would have applied equally to cases and controls, and therefore would have led to non-differential misclassification.

Although doing outdoor activities in the winter involves fewer exposed skin surfaces than in the summer, because of the cold, the exposed parts could receive the UV-B reflected by the snow, which constitute up to 94% of UV-B from the sun [144]. Also at higher altitudes, UVR levels are higher. For every 1,000 meters increase in elevation, the UVR intensity increases by 10–12%. [145] Therefore, mountain skiers could receive a non-negligible amount of UVR, even when most body surface is covered. Based on this, while our study did not collect information on the portion of body exposed to sunlight, we considered that subjects participating in winter sports in altitude as exposed in our leisure sunlight exposure index. A further issue to consider is that while solar UV-B is the major source of vitamin D, there is evidence to suggest that no important vitamin D synthesis is triggered in the winter at Northern latitudes [131] such as Canada. We did not adjust for season of exposure, which may have led to an overexposure of both cases and controls if indeed vitamin D is the mechanism through which sunlight exposure affects the risk of PCa. In Northern climates, diet and supplementation become the main sources of vitamin D during the winter months [98-101], however, information on diet and supplementation was outside the scope of this thesis and therefore was not included in the analysis

Occupational sunlight exposure was assessed using the SunJEM. The level of exposure applies to the majority of workers for a certain specific occupational code, however, it is a generalization and individual experiences may differ due to differences in tasks for the same occupational title. It was not feasible to review the job descriptions of 2,570 jobs, and therefore we did a sensitivity analysis where all the exposure levels were changed for these jobs. The statistically non-significant results show a marginally increased risk; and thus demonstrate a tendency for the absence of association between PCa risk and occupational and global sunlight exposure. In addition, we assumed that all participants worked during the day. If some participants worked at night in occupations which would normally involve sunlight exposure had they worked during day, we may have overestimated exposure levels of these individuals. It was previously shown [146] that men working at night were at risk of developing PCa. Night work would have probably occurred, at some point, in less than 15%

of the study population [146], and since this could have applied equally to cases and controls, it would have likely led to a non-differential misclassification.

Unlike other studies [6-8, 95, 104, 105] where recreational and occupational sunlight exposure were collected using the same unit of exposure, it was not possible in our study to easily combine sunlight exposure from recreational and occupational activities. We therefore created a relatively crude exposure variable by combining recreational and occupational exposures and then grouping the different combinations into three categories. This may not be the most precise exposure index, but we nonetheless found relatively consistent results with those obtained using either the occupational or recreational sunlight exposures indices.

In this study, we have only taken into account the sunlight exposure during leisure and work. Other instances of sunlight exposure can happen when traveling between locations (e.g. commuting), when receiving acute sunlight exposures such as sunbathing or when traveling to sunnier vacation locations, for which we did not collect information. However, we believe that our exposure assessment encompasses the majority of sunlight received by the participants. Also it was assumed that our cases and controls received their exposure in Quebec. We have accounted for season for some leisure activities because of the Canadian climate. Individuals who lived in a foreign country could have had a different amount of exposure, which we were not able to take into account. Also, the jobs that participants may have held outside of Canada may have involved slightly different tasks, which could result in different sunlight exposure levels.

In addition, we considered that all sunlight exposure events were equal in terms of sunlight dose, which may not have been the case in reality.

8.4.2 Confounding factors

Another issue concerning the design of this exposure variable is the potential confounding with physical activity. There is a possible association between physical activity and PCa risk as described in the introduction, and so to address this, our analyses were adjusted using an index assessing physical activity.

8.4.3 Study precision

The vast majority of both cases and controls had some recreational sunlight exposure in the course of their lifetime (96.6% and 97.4% respectively). Therefore the non-exposed group had a very small number of participants, which could lead to imprecise OR estimates for this group. To address this issue, the most exposed group was used as the reference group in the analyses.

8.4.4 Selection bias

This study focused on the French-speaking population of Montreal, which represents the majority of the population of Montreal. More than 86% of the population on the Island of Montreal and 90% in the Montreal Metropolitan area can speak French [147]. Cases were ascertained from 7 out of 9 major French hospitals, out of the 14 hospitals that diagnose prostate cancer in the region. Based on registry data, we estimate that 80% of all new PCa cases diagnosed in Montreal during the study period were eligible to participate. Although this study did not include the 20% of incident cases referred to the other hospitals, we are confident that the cases and controls were recruited from the same base population. To address the possibility of referral bias, we recruited French-speaking controls who resided in the residential areas as the cases, confirmed by a comparison of the distributions of residential postal codes, and electoral districts, between the two groups.

Response rates among the cases and controls were considered high for epidemiological research (84% and 61%, respectively). Of those who did not participate in the study, the predominant reason was refusal. As previously reported [121], non-participants had a slight increased tendency to reside in areas with 1) a greater proportion of recent immigrants within the previous 10 years, 2) a higher unemployment rate, 3) a greater proportion of adults without a high school diploma, and 4) a lower median household income. If non-participants tend to be unemployed, their sunlight exposure would originate mostly from recreational activities. Non-participants may have engaged more in outdoor activities than participants, which could have led to an under-representation of exposed participants among controls than among cases, which would have brought a true protective association towards the null.

8.4.5 Detection bias

Another concern about studies of long-latency diseases, such as PCa, is the presence of asymptomatic and/or undiagnosed cases among the control group. However, results were unchanged in our sensitivity tests in which we removed control participants who did not undergo a prostate screening within the two years before the interview. Also Canada has a universal health care system, where most controls would be screened for PCa, reducing the likelihood that controls would have undetected PCa. Therefore, a detection bias was unlikely to have occurred in this study.

8.4.6 Information bias

A major concern in retrospective studies is recall bias relating to information reported by the participant or by a proxy. The cases were diagnosed not long before the interview, and therefore they may have tried to remember the potential factors associated with the development of PCa. Modifiable risk factors to PCa have not been established, but general public health messages are mostly about eating healthy, increasing physical activity, not smoking and decreasing alcohol consumption. This could lead cases to under-estimate the frequency of participation in outdoor leisure activities, which would have led to a differential misclassification, in turn resulting in an over-estimation of the beneficial effects of sunlight exposure in leisure activities.

Recall bias is less likely to apply for occupational exposures because only the job code was used to assess the sunlight exposure.

8.4.7 Missing values

Missing values were found for some covariates and recreational sunlight exposure measures. When information was missing for only a few participants, these participants were removed from the analyses; otherwise a new category for participants with unknown information was created, to retain as many participants as possible for the analyses.

Imputations were used for recreational sunlight exposure information. Missing values were found for the seasonality and duration of leisure activity (for a subset of the participants), for which a maximum possible value was imputed. This could potentially increase the exposure of the participants. This could have resulted in a non-differential misclassification. Some

specific occupations, for example retirement, were not compiled in the SunJEM, In those cases, an occupational sunlight exposure level of zero was assigned, assuming that if the participants did get some exposure, it would have occurred during leisure time.

8.5 Strengths of the study

The present study has several important strengths over previous studies. The first is the large sample size, which included 1,371 newly diagnosed histologically confirmed cancer cases and 1,479 population-based controls. Second was our use of an individual sunlight exposure assessment, as opposed to a geographically determined index. It is, to our knowledge, the largest study to use an individual exposure assessment [8, 65, 70, 92, 102]. It is also the first study in Canada to assess the relationship between sunlight exposure and prostate cancer risk. This study also benefited from relatively high response rates from both cases and controls. We also had the advantage of doing PCa research in a country with a universal health care program. The advantage is the high prevalence of screening amongst controls which limits the likelihood of undetected PCa amongst controls.

The general questionnaire and the general work history questionnaire, used in our study, allowed us to retrieve detailed information about the participants' sunlight exposure over the entire adulthood. For recreational sunlight exposure, we had the duration, the seasonality and the frequency of exposure. We also could account for changes over the years in terms of frequency of different activities. For occupational exposures, we had the duration and the specific job that the participants occupied, for each job held over the lifetime. From these data, we were able generate detailed exposure indices and we were also able to compare the results we obtained when using different exposure indices to draw an overall conclusion. The questionnaires used in this study were designed to collect information on a number of different exposures of interest, and therefore we had the opportunity to control for multiple known and potential covariates in this study. This included solar protection, which has not often been considered.

8.6 Conclusions

This is the largest study to date to investigate the role of leisure-time and occupational sunlight exposure in prostate cancer incidence using individually-based sunlight exposure assessment protocols over the entire period of adulthood.

As a whole, our findings provide little evidence for an association between cumulative sunlight exposures during leisure time, at work, either alone or in combination, and prostate cancer development. This held true for both non-aggressive and aggressive cancers, after conducting several sensitivity analyses, as well as after taking into account a wide range of potential confounding factors.

Weak suggestions of a protective effect of sunlight exposure emerged when comparing men highly exposed to sunlight during leisure to those unexposed, as well as when comparing men occupationally exposed to sunlight to men with no occupational exposure. However, none of the risk estimates achieved statistical significance and there was no dose-response pattern, arguing against a true association.

The search for modifiable risk factors for prostate cancer is of great public health significance. Research into environmental causes of the disease should be pursued, including on the possible role of sunlight exposure.

8.7 Suggestions for future research

The relationship between sunlight exposure and prostate cancer risk still needs more investigation. As part of the PROtEuS program, genetic information is available for the majority of study participants. In upcoming studies we hope to incorporate genetic factors, which will allow for the assessment of the interaction between sunlight exposure and prostate cancer risk. Using a detailed residential history obtained for each participant, we also hope to account for is the amount time spent residing in foreign countries where sunlight exposure may differ even when doing a same activity [129], where the climate could allow a longer seasonality for outdoor leisure activities.

As was done here, future studies should use incident cases of prostate cancer, to better clarify the etiology of the disease. More studies should be conducted in the Southern hemisphere, where positive relationship between sunlight exposure and prostate cancer risk were found [8, 9]. Moreover, most research has focused on White Caucasians, one specifically on African Americans [108], and one on Asians [8]. More studies should be done with more ethnically diverse populations.

In the event that enough evidence accumulates that sunlight exposure is protective for prostate cancer, research on the sufficient amount of sunlight exposure for a healthy prostate would be needed. The duration of sunlight exposure required to reach optimal vitamin D levels has been estimated previously [148], however, the appropriate dose for reducing the risk of PCa would need to be addressed as well. Although a handful of studies have looked at vitamin D, no conclusive findings have yet been made [149]. Other potential mechanisms should also be taken into account.

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Appendix 1 – Literature review

Table 1 - Ecological studies on the association of sunlight exposure and prostate cancer					
Author (year)	**Country**	**Geographical unit, outcome sources**	**Exposure assessment**	**Results of interest**	**Notes**
Hanchette et Schwartz (1992) [80]	USA	3073 counties, mortality rates from Biometry Branch of the Health Effects Research Laboratory, EPA	Latitude, epidemiologic index (quantity of received UV including cloud cover and latitude), UV count (estimation that includes altitude and latitude)	Latitude: r=0.19, p=0.000 (n=220) Epidemiologic index: r=-0.25, p=0.0002 (n=3069) UV count: r=-0.15, p=0.0001 (n=3073)	Data period: 1970-1979 Outcome: PCa mortality Risk assessment: Pearson's correlation Population: White men

Grant (2002) [77]	USA	3053 counties and 466 SEAs, mortality rates from NIH's *Atlas of Cancer Mortality in the United States*	DNA-weighted UV-B from TOMS; UV-B from UVB monitoring stations of the U.S. Department of Agriculture, taking into account aerosols	Regression coefficient: TOMS-generated UV-B dose: r=-0.32 , p<0.001 Monitoring stations: July: r=-0.44, p=0.061 September: r=-0.63, p=0.012	Data period: 1950-1969 and 1970-1994 Outcome: PCa mortality Risk assessment: linear regression Adjustment: age Population: White American men
Grant (2004)[81]	AT, AU, BE, BG, CA, CH, DE, DK, DZ, EG, ES, FI, FR, GR, HU, IE, IR, IT, NL, NO, NZ, PL, PT, RO, SA, SE, SY, TN, TU, UK, US	31 countries, mortality rates from WHO	Annual average UV-B data reported for European ground stations. UV-B dose calculated according to the latitude for the 11 non-European countries	European countries: Adjusted R^2 = 0.40 F= 14, p=0.002 t = -3.7, p=0.002 All the countries: Adjusted R^2 = 0.51, F=33, t = -5.8, p<0.001	Data period: late 1990s (PCa),1979-1986 exposures Outcome: PCa mortality Risk assessment: linear regression Adjustment: age, diet

Mizoue (2004) [82]	Japan	47 prefectures, mortality rate from Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labor and Welfare	Average annual hours of solar radiation from Japan Meteorological Agency, data from 1961-1990 extrapolated for 2000	Adjustment for age and income r = -0.01 p>0.05 Adjustment for age and fat intake r= -0.07 p>0.05	Data period: 2000 Outcome: PCa mortality Risk assessment: Pearson's correlation Adjustment: age
Boscoe et Schymura (2006) [4]	USA	1499 counties for incidence, 3108 counties for mortality from North American Association of Central Cancer Registries' CINA Deluxe file and NCI's SEER Stat database	TOMS-generated solar UVB dose	Relative risk northern versus southern US boundary (95%CI) Incidence: 1.20 (1.19-1.22) Mortality: 1.17 (1.15-1.19)	Data period: 1993-2002 for mortality, 1998-2002 for incidence Outcome: PCa incidence and mortality Risk assessment: Poisson regression Adjustment: age, poverty, income, smoking, exercise, alcohol, outdoor occupation, urban/rural, air quality

					Restricted to non-Hispanic Whites men
Colli et Colli (2006)[78]	AR, AT, AU, AZ, BE, BG, BO, BR, BY, CA, CH, CL, CN, CO, CR, CU, CY, CZ, DE, DK, DO, DZ, EC, ES, FI, FR, GR, HU, ID, IE, IL, IN, IS, IT, JM, JO, JP, KH, KR, LA, MM, MT, MX, MY, NI, NL, NO, NZ, PA, PE, PH, PK, PL, PT, PY, RO, RU, SE, SI, SK, SY, TH, TN, TU, UA, UK, US, UY, UZ, VE, VN	Mortality rates for the 71 countries from GLOBOCAN 2000 database by IARC	UVI from TEMIS	UVI Regression coefficient (95%CI) : -0.27 (-0.583, 0.043)	Data period: 2000 or 3-5 years earlier Outcome: PCa mortality Risk assessment: linear regression Adjustment: age, diet(sugar, cereal, onions)

Grant (2006) [83]	AT, CH, DE, DK, ES, FR, IE, IT, UK	Incidence and mortality rates for 9 countries from GLOBOCAN 2000 database by IARC	Latitude of the countries	Regression coefficient (2nd order latitude), regression coefficient (latitude), adjusted correlation coefficient, F value, p 1-year survival: -16.0, 15.8, 0.52, 5.3, 0.05 5-year survival: -15.6, 15.2, 0.64, 8.0, 0.02	Data period: 1990-1994 Outcome: PCa survival Risk assessment: linear regression Adjustment: age
Grant et Garland (2006)[84]	USA	NCI's *Atlas of Cancer Mortality in the United States* for 500 SEAs	TOMS-generated solar UV-B dose by state, latitude of state	Regression coefficients (p-value): Model 1950-1969 smoking, Hispanic UVB: 0.02 (0.94) Latitude: 0.52 (0.09) Model 1950-1969 –Hispanic Latitude: 0.48 (0.01) Model 1970-1994 –smoking, Hispanic UVB: 0.38 (0.04) Latitude: 0.45 (0.01) Model 1970-1994 – smoking UVB: 0.27 (0.12) Latitude: 0.44 (0.02)	Data period: 1950-1969 and 1970-1994 Outcome: PCa mortality Risk assessment: linear regression Adjustment: age; alcohol, urban residence, poverty; and other factors specified in each model

Grant (2006)[85]	Spain	48 provinces' mortality rate from *Atlas of Cancer Mortality*	Latitude	r=0.06, p>0.05	Data period: 1978-1992 Outcome: PCa mortality Risk assessment: Pearson's correlation Adjustment: age
			Non-melanoma skin cancer mortality rate	r=-0.21, p>0.05	
			Melanoma mortality rate	r=0.52, p<0.01	
Schwartz et Hanchette (2006) [86]	USA	Mortality rate from the NCI for 55 cities, 2573 counties for 1950-1969, 2850 counties for 1970-1994	UV Index from the National Oceanic and Atmospheric Administration (National Oceanic and Atmospheric Administration)	r^2 for UVI: North of 40th parallel: 0.03 South of 40th parallel: 0.0001	Data period: 1950-1994 Outcome: PCa mortality Population: White men Risk assessment: linear trend surface analyses

<table>
<tr><td rowspan="6">Colli et Grant (2008)[87]</td><td rowspan="6">USA</td><td rowspan="6">48 states: incidence rate from State Cancer Registry and National Program of Cancer Registries Cancer surveillance. Mortality rates from SEER program of the NCI</td><td rowspan="2">UVI from National Oceanic and Atmospheric Administration/EPA(1995-2001)</td><td colspan="4">Correlation coefficients (* p<0.05)</td><td rowspan="6">Data period: 2000-2001 (incidence), 1992-2001 (mortality)

Outcome: PCa incidence and mortality

Population: White, Black

Risk assessment: Pearson’s correlation

Adjustment: age at death</td></tr>
<tr><td colspan="2">Incidence</td><td colspan="2">Mortality</td></tr>
<tr><td></td><td>White</td><td>Black</td><td>White</td><td>Black</td></tr>
<tr><td>Annual average</td><td>-0.36*</td><td>-0.30</td><td>-0.46*</td><td>0.15</td></tr>
<tr><td>Winter</td><td>-0.42*</td><td>-0.20</td><td>-0.53*</td><td>0.24</td></tr>
<tr><td>Spring</td><td>-0.38*</td><td>-0.27</td><td>-0.48*</td><td>0.18</td></tr>
<tr><td>Summer</td><td>-0.23</td><td>-0.40*</td><td>-0.31*</td><td>0.03</td></tr>
<tr><td>Fall</td><td>-0.40*</td><td>-0.26</td><td>-0.50*</td><td>0.18</td></tr>
<tr><td>Waltz et Chodick (2008)[88]</td><td>AR, AU, BE, BR, CA, CH, CN, CO, CR, CZ, DE, DK, EC, ES, FI, FR, IE, IL, IN, IS, IT, KR, NL, NO, PH, PK, PO, PR, SE, SG, TH, UK, VN</td><td>Cancer Incidence in Five Continents Vol. 3, IARC for 38 geographical regions from 33 countries</td><td>UV-B from Robertson-Berger measures calculated from the latitude and altitude of the geographical locations</td><td colspan="4">Regression coefficient (log RB): -0.013, p>0.05 (univariate regression)</td><td>Data period : 1993-1997

Outcome : PCa incidence

Risk assessment : linear regression

Adjustment : age, race, GDP per capita, health care, % workforce in</td></tr>
</table>

					agriculture, dietary intake of vitamin D
Grant (2010) [89]	France	12 continental regions, Publication of the Fédération Nationale des Observatoires Régionaux de la Santé and 12 Cancer registries	Latitude	Incidence rate: r=0.64, adjusted R^2=0.37; Mortality rate: r=0.68, adjusted R^2=0.44	Data period: 1998-2000 Outcome: incidence and mortality Risk measurement: regression
Loke et al. (2011) [90]	Australia	70 local government areas, Incidence rate from Cancer registry, standardized to the Australian Standard Population of 2001 Cancer registries	Mean daily solar radiation (MJ/m^2) averaged over 1990-2010, from the Bureau of Meteorology	Pearson's correlation r=-0.5423 Coefficient of determination R^2=0.2941 (95%CI: 0.120-0.468)	Data period: 1998-2007 Outcome: PCa incidence Risk assessment: linear regression Adjustment: age
Taksler et al. (2013) [5]	USA	336 counties, Surveillance, Epidemiology, and End Results program for incidence	UV irradiance from NASA according to latitude and longitude of the counties	Regression coefficients (p-value): PCa incidence (White and Black men): UV Index of 10 vs. 1: -23.4 (<0.001)	Data period: 1978-2005 Outcome: logs of PCa incidence and mortality

		2203 counties, National Vital Statistics System for mortality		PCa mortality (White and Black men): UV Index of 10 vs. 1: -15.9 (<0.001)	Risk assessment: linear regression Adjustment: age, median income by race, number of physicians and short-term general hospital beds, whether county was federally designated Health Professional Shortage Area in primary care less urban or rural geography and census division

Table 2 – Case-control studies on the association of sunlight exposure and prostate cancer					
Author (year)	**Country**	**Population**	**Exposure assessment**	**Results of interest**	**Notes**
Luscombe et al. (2001)[6]	UK	210 PCa cases and 155 BPH controls from urology clinics in University Hospital of North Staffordshire Restricted to non-related, white northern-European	Questionnaire: weeks of outdoor weekday and weekend activities (i.e. recreational and occupational exposures) for cumulative lifetime exposure. Acute exposure: - Number of childhood sunburn events - Sunbathing scores: 1-never, 2-rarely, 3-occasionally, 4-frequently - Yes/no holiday in sunny country over the last 10 years, duration	OR (95%CI) Chronic exposures Mean weeks cumulative exposure: 0.998 (0.997-0.999) Lowest exposure quartile: 3.03 (1.59-5.78) 25-50% quartile: 1.51 (0.83-2.76) 50-75% quartile: 1.18 (0.65-2.16) Highest quartile : 1.00 Living abroad for >6 months : 0.71 (0.45-1.14) Acute exposures: Positive childhood sunburn: 0.18 (0.08-0.38) Mean sunbathing score: 0.83 (0.76-0.89) History of foreign holiday: 0.41 (0.25-0.68) Mean weeks foreign holidays: 0.85 (0.74-0.98)	Recruitment period: October 1999-May 2000 Outcome: prevalent PCa Risk assessment: logistic regression Adjustment: age at diagnosis

Luscombe et al. (2001) [95]	UK	72 PCa cases with bone metastasis and 110 PCa controls without bone metastasis from urology clinics in University Hospital of North Staffordshire Restricted to: Northern European Caucasian	Questionnaire: childhood sunburn, sunbathing, foreign holiday, cumulative sun exposure in years, extent of occupation spent outdoor Genotype assessment of VDR	OR (95%CI) Cumulative sun exposure: 1.04/year (0.93-1.16) Sunbathing: 0.94/unit (0.82-1.08) Childhood sunburn: 1.17 (0.17-7.99) Foreign holiday: 1.28 (0.50-3.31) Proportion of occupation in outdoor: 1.02/unit (0.92-1.14)	Recruitment period: October 1999-May 2000 Outcome: prevalent PCa bone metastasis Risk assessment: logistic regression Adjustment: advanced T stage, high grade histology, age at diagnosis and skin type

<table>
<tr>
<td>Freedman et al. (2002) [67]</td>
<td>USA</td>
<td>97873 PCa cases and 83421 population controls whose information from death certificate from National Center for Health Statistics, NCI and National Institute for Occupational Safety and Health</td>
<td>- Residential sunlight exposure
- Occupational sunlight exposure (job on death certificate)</td>
<td>
<table>
<tr><th colspan="2" rowspan="2">OR (95%CI)</th><th colspan="3">Residence (solar level)</th><th rowspan="2">TOTAL</th></tr>
<tr><th>Low</th><th>Med</th><th>High</th></tr>
<tr><td rowspan="5">Occupation</td><td>Inside</td><td>1.0</td><td>1.0</td><td>1.0</td><td>1.0</td></tr>
<tr><td>Mixed</td><td>1.03 (0.97-1.09)</td><td>0.96 (0.91-1.00)</td><td>1.02 (0.96-1.08)</td><td>1.00 (0.97-1.03)</td></tr>
<tr><td>Outside</td><td>1.04 (0.93-1.15)</td><td>1.04 (0.96-1.14)</td><td>0.95 (0.86-1.04)</td><td>1.00 (0.96-1.05)</td></tr>
<tr><td>Farmer</td><td>1.28 (1.16-1.42)</td><td>1.21 (1.12-1.31)</td><td>1.01 (0.91-1.12)</td><td>1.16 (1.11-1.22)</td></tr>
<tr><td></td><td>TOTAL</td><td>1.0</td><td>0.89 (0.86-0.91)</td><td>0.90 (0.87-0.93)</td><td></td></tr>
</table>
</td>
<td>Data period: 1985-1995

Outcome: PCa mortality

Risk assessment: logistic regression

Adjustment: age, race socioeconomic status, physical activity</td>
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Bodiwala et al. (2003) [104]	UK	453 PCa cases and 312 BPH controls: from urology clinics in the University Hospital of North Staffordshire	Questionnaire: cumulative UVR exposure in hours during adult life/year, sunbathing, skin type, childhood sun burning, foreign holidays	OR (95%CI) Univariate model: Mean hours cumulative exposure/year: 0.999 (0.999-1.000)/h, p = 0.0001 Model 2 (cumulative exposure, childhood sunburn, sunbathing, foreign holiday, skin type) • Partition (i) node 3 (sunbathing score >8.0) : reference node 2 (sunbathing score >3.0 <=8.0) : 2.36 (1.64–3.39) node 1 (sunbathing score <=3.0) : 4.94 (2.97–8.24) • Partition (ii) node 3.2 (holidays yes) : reference, node 3.1 (holidays no) : 2.81 (1.45–5.41), 0.002 node 2.2 (childhood sunburn yes) : 1.59 (0.77–3.30) node 2.1 (childhood sunburn no) : 5.35 (3.03–9.44) node 1.2 (skin type 2, 3, 4) : 13.0 (6.33–26.9) node 1.1 (skin type 1) : 2.94 (1.10–7.82), 0.031 • Cumulative sunlight exposure not presented	Recruitment period: October 1999 to August 2002 Outcome: prevalent PCa Risk assessment: logistic regression Adjustment: age Recursive partitioning: Division of data into subgroups to be analyzed as original data sets, and can be further divided into more sub-groups.

Bodiwala et al. (2003) [7]	UK	212 PCa cases and 135 BPH controls: from urology clinics in the University Hospital of North Staffordshire	Questionnaire: cumulative sun exposure in weeks, childhood sunburning, adult sunbathing, foreign holidays, residence in hot climate	OR (95% CI) : Chronic exposures : Mean weeks of cumulative exposure : 0.998/week (0.997-0.999) Lowest vs. highest quartile of cumulative exposure : 3.21 (1.61-6.40) Residence in hot country : 0.89 (0.54-1.48) Acute exposures : Childhood sunburn : 0.42 (0.21-0.84) Regular foreign holidays : 0.56 (0.35-0.9) Adult sunbathing score : 0.79/unit (0.72-0.87)	Recruitment period: August 2001-April 2002 Outcome: prevalent PCa Risk assessment: logistic regression Adjustment: age
Bodiwala et al. (2003) [105]	UK	453 PCa cases and 312 BPH controls: from urology clinics in the University Hospital of North Staffordshire Participants with no two first or second-degree family history of PCa before age 55	Questionnaire: cumulative exposure in months during adult life per year, adult sunbathing, skin type, childhood sunburn, foreign holidays, living abroad in a hot climate for > 6 months, proportion of occupation spent outdoor, sunscreen use	OR (95%CI) Increased cumulative exposure per year: 0.71/month (0.60-0.84) Sunbathing: 0.80/unit (0.75-0.86) Sunbathing score ≤3.0: Skin types 2-4 vs. 1: OR=4.78 Sunbathing score >3.0≤8.0: Skin types 3 and 4 vs. 1 and 2: OR=1.78 Sunbathing score >8.0: no difference between skin type	Recruitment period: October 1999 to August 2002 Outcome: sporadic PCa prevalence Risk assessment: logistic regression Adjustment: age

John et al. (2005)[92]	USA	450 PCa cases from the Greater San Francisco Bay Area Cancer Registry, which is part of SEER Cancer Registry (age 40-79) 455 cancer patients, age 40-79, recruited as controls using Waksberg method, frequency match on race and 5-year age group	State of residence location Questionnaire: self-reported sun exposure, occupational and recreational exposures Sun exposure index: difference between constitutive and facultative pigmentation, a measure of lifetime cumulative exposure	OR (95%CI) Duration of residence in low solar radiation states (year) ≥15: 1.0 1-14: 0.98 (0.66-1.46) 0 (residence in med + high solar): 0.91 (0.61-1.35) 0 (residence in high solar only): 0.95 (0.66-1.35) P trend = 0.7 Lifetime outdoor activities (h/week) <2.7: 1.0 2.7-5.6: 1.15 (0.76-1.73) 5.7-10.4: 1.09 (0.72-1.65) 10.5-19.8: 1.10 (0.73-1.67) ≥19.9: 0.95 (0.62-1.45) P trend = 0.8 Lifetime outdoor jobs (h/week) 0: 1.0 1.4: 0.96 (0.65-1.43) 1.4-5.6: 1.20 (0.81-1.77) 5.7-14.7: 0.95 (0.64-1.41) ≥14.8: 0.73 (0.48-1.11) P trend = 0.3 Sun exposure index quintiles: 1: 1.0 2: 0.87 (0.58-1.30) 3: 0.80 (0.53-1.20) 4: 0.95 (0.64-1.42) 5: 0.51 (0.33-0.80) P trend = 0.02	Diagnosis period: July 1997-December 2000 Outcome: incident advanced PCa Risk assessment: unconditional logistic regression Adjustment: age, family history, month of pigmentation measurement

Rukin et al. (2007) [94]	UK	British Northern European Caucasian men with PCa attending the University Hospital of North Staffordshire (137 with Gleason score <7 and 192 with score ≥7 -> cases or 290 with T-stage of ½ and 255 with T-stage of 3/4)	Questionnaire: UVR exposure in months/year, years of UV exposure over the 10, 20, 30 prior diagnosis, sunbathing, foreign holidays, childhood sunburn, skin type	OR (95% CI) By Gleason score: Mean cum. Sun exposure: 0.95/month (0.76-1.19) Mean exposure during 10 year prior diagnosis: 0.88 (0.68-1.14) Mean exposure during 20 year prior diagnosis: 0.95 (0.83-1.08) Mean exposure during 30 year prior diagnosis: 0.97 (0.89-1.06) By T-stage: Mean cum. Sun exposure: 0.85/month (0.70-1.02) Mean exposure during 10 year prior diagnosis: 0.69 (0.56-0.86) Mean exposure during 20 year prior diagnosis: 0.84 (0.75-0.94) Mean exposure during 30 year prior diagnosis: 0.90 (0.84-0.97)	Recruitment period: 1999-2006 Outcome: prevalent high Gleason grade or advanced T-stage PCa Risk assessment: logistic regression Adjustment: age
Rukin et al. (2007) [106]	UK	528 cases of PCa and 365 BPH controls from urology clinics in the University Hospital of North Staffordshire	Questionnaire: number of hours exposed per lifetime period, childhood sun burning, foreign holiday	OR (95% CI) Average daily sun exposure: 0.78 (0.72-0.85) Average weekday exposure: 0.85 (0.76-0.91) Average weekend exposure: 0.79 (0.73-0.86) Foreign holiday: Yes versus No: 0.58 (0.42-0.80) Childhood sunburn : Yes versus No: 0.38 (0.26-0.57) Sunbathing: Never: Reference Rarely: 0.46 (0.32-0.67) Occasionally, frequently: 0.21 (0.14-0.31)	Recruitment time: Oct. 1999 to Aug. 2002 Outcome: prevalent PCa Risk assessment: logistic regression Adjustment: age, skin type

Gilbert et al. (2009)[107]	UK	1020 PCa cases and 5044 hospital controls recruited for *ProtecT* study (men aged 50-69 at 400 general practices in 9 UK centers, tested for PSA levels)	Questionnaire: diet, health, lifestyle, skin type, sun exposure behavior. Sun exposure: hours spent outdoor in summer during childhood and adulthood Intense sun exposure: sunbathing, foreign holiday during lifetime and 2 years prior diagnosis	OR (95%CI) Time spent outside (childhood + adulthood) High 1.00 Med 0.91 (0.77-1.08) Low 0.98 (0.81-1.19) p-trend = 0.72 Time spent outside (adulthood) High 1.00 Med 0.90 (0.74-1.09) Low 0.96 (0.81-1.15) p-trend = 0.71 Acute sun exposure (childhood + adulthood) High 1.00 Med 0.94 (0.79-1.12) Low 1.14 (0.92-1.42) p-trend=0.32 Acute sun exposure (2 years prior diagnosis) High 1.00 Med 0.99 (0.84-1.18) Low 1.24 (1.03-1.50) p-trend=0.04 Time spent outside (childhood + adulthood) Outcome: low Gleason score (6 and lower) versus high Gleason score (7 and higher) High 1.00 Med 0.89 (0.6-1.23) Low 0.62 (0.4-0.91) p-trend = 0.02	Recruitment period: 2001-2008 Outcome: prevalent PCa Risk assessment: conditional logistic regression Adjustment: age, sunscreen use, pigmentation Note: Family history of PCa, smoking, physical activity and occupational social class assessed but not adjusted because results not attenuated

Chia et al. (2012) [8]	Singapore	240 PCa cases from the Singapore General Hospital. 268 hospital controls from the same hospital without history of malignant disease, and frequency matched by ethnic groups and age.	Face-to-face interview with questionnaire: hours of spending outdoor activities in the past year (not in shade between 9am and 5pm) for a list of outdoor activities.	Adjusted ORs (95% CI) <0.5 hours/week: 1.00 (reference) 0.5-10 hours/week : 1.71 (0.90-3.25) 10.1-56 hours/week: 2.03 (1.09-3.81)	Period when study conducted: April 2007-May 2009 Outcome: PCa incidence Risk assessment: unconditional logistic regression Adjustment: age, ethnicity, education, family history of any cancers, BMI, skin color

Kanaan et al. (2012) [108]	US	91 PCa cases and 91 ethnicity matched controls, all African-American men in Washington DC	Questionnaire: number of hours of sunlight exposure at age periods: 0-5, 6-11, 12-17, 18-29, 30-39 and 40 to index age, for occupational, recreational, outdoor and foreign residence exposures, then sum for cumulative number of hours of exposure per year Sunbathing score from 0 to 2, 0 being the lowest	OR (95% CI) Total sun exposure: 2.04/hour per year (0.54-7.70) Outdoor: 0.31/hour per year (0.14-0.65) Recreational: 0.77/hour per year (0.39-1.47) Professional: 0.59/hour per year (0.18-1.89) Sunbathing at ages 0-5: Low: 1.00 (ref) Medium: 0.44 (0.11-1.71) High: 0.17 (0.03-0.74) Sunbathing at other age groups: results not statistically significant	Outcome: prevalent PCa Risk assessment: conditional logistic regression Adjustment: age

Nair-Shalliker et al. (2012) [9]	Australia	1084 PCa cases of the prostate cancer care and outcome study from New South Wales Central Cancer Registry, 234 non-Hodgkin's lymphoma controls from New South Wales and Australian capital territory Electoral roll	Interview questionnaire: time spent outdoor	OR (95%CI) Ranked by cumulative hours of sun exposure in warmer months of the years when aged 30-50 ≤675: 1.00 (ref) 675.1-1025: 1.32 (0.90-1.93) 1025.1-1500: 1.51 (1.02-2.22) ≥1500.1: 2.07 (1.36-3.15) P-trend: 0.007 Ranked by hours of sun exposure on weekdays in warmer months of the years when aged 30-50 ≤250: 1.00 (ref) 250.1-500: 0.93 (0.64-1.41) 500.1-1000: 0.93 (0.65-1.37) ≥1000.1: 1.26 (0.85-1.95) p-trend: 0.46 Ranked by hours of sun exposure on weekdays in warmer months of the years when aged 30-50 ≤350: 1.00 (ref) 350.1-450: 1.28 (0.88-1.84) 450.1-600: 1.46 (1.03-2.07) ≥600.1: 5.05 (2.69-9.47) p-trend <0.0001	Case diagnosis period: October 2000-October 2002 Outcome: incident invasive PCa Risk assessment: logistic regression Adjustment: birth year, sun sensitivity

Table 3 – Cohort studies on the association of sunlight exposure and prostate cancer					
Author (year)	**Country**	**Population**	**Exposure assessment**	**Results of interest**	**Notes**
John et al. (2004)[102]	USA	3414 men from NHANES I study, 153 PCa cases Restricted to White men	Place of birth and residence Average solar radiation level assigned to each state and classified as low, medium, high according the tertile distribution	RR (95%CI) Region of residence Northeast: 1.0 Midwest: 1.05 (0.66-1.67) West: 0.94 (0.60-1.48) South: 0.68 (0.41-1.13) Solar radiation at longest residence Low: 1.0 Medium: 0.81 (0.55-1.21) High: 0.62 (0.40-0.95) Solar radiation at place of birth Low: 1.0 Medium: 0.75 (0.51-1.09) High: 0.49 (0.30-0.79)	Observation period: interviews from 1971 to 1975, follow-up: 1982-1984, 1986-1987, 1992 to 1992 Outcome: incident PCa Risk assessment: Cox proportional hazard regression Adjustment: age, family history of PCa, fat intake, calcium intake

Robsahm et al (2004) [65]	Norway (8 geographical regions)	39 583 PCa cases from Cancer Registry of Norway and exposure information from Statistics Norway	Mean annual erythemogenic UV calculated for regions II-VIII in relation to region I (Low solar exposure: regions I, II and III; medium exposure: regions IV and V; high exposure: VI, VII, VIII) Occupational exposure (mainly indoor, mixed, mainly outdoor)	RR (95%CI) Residential sunlight exposure I: 1.00 II:1.00 (0.90-1.11) III: 1.02 (0.94-1.12) IV: 0.99 (0.90-1.08) V: 1.16 (1.06-1.28) VI: 0.98 (0.90-1.07) VII : 1.10 (1.02-1.21) VIII : 0.98 (0.88-1.07) Occupational sunlight exposure Low: 1.00 Med: 1.00 (0.95-1.06) High: 0.99 (0.94-1.05) Unknown: 1.15 (1.05-1.26)	Observation period: 1964-1992 Outcome: PCa mortality Risk assessment: Cox's proportional hazard regression Adjustment: age at diagnosis, birth cohort, childbearing pattern, educational level, stage of disease at diagnosis, period of diagnosis. Adjusted for occupational exposure for analyses of residential sunlight exposure; and adjusted for residential sun exposure for analyses for occupational sunlight exposure

John et al. (2007)[93]	USA	3528 men from NHANES I study cohort 161 cases	Questionnaire: self-reported recreational and occupational exposure (never/rare, occasional, frequent)	RR (95%CI) Both never/rare or occasional: 1.00 One frequent: 0.80 (0.52-1.24) Both frequent: 1.05 (0.70-1.58)	Observation period: interviews from 1971 to 1975, follow-up: 1982-1984, 1986-1987, 1992 to 1992 Outcome: incident PCa Risk assessment: Cox proportional hazard regression Adjustment: age
Porojnicu et al. (2008) [110]	Norway	10090 deaths/46205 cases) Subjects from The National Cancer Registry of Norway	Counties grouped according to incidence rates of squamous cell carcinoma which is correlated to the accumulative UV exposure. Annual UV exposure from TOMS (1980-2000)	RR at 36 months after diagnosis (95%CI) Midwest, winter: 1 Midwest, summer: 0.8 (0.7-0.84) Southeast, winter: 1 (0.99-1.1) Southeast, summer: 0.8 (0.75-0.85)	Observation period: 1964-1992 (cohort followed for 3 years) Outcome: PCa mortality Risk assessment: Cox proportional hazards regression Adjustment: age, birth cohort, stage of disease, residential region, education level, profession
Lin et al. (2012) [70]	USA	272 796 men members of American Association of Retired Persons (AARP) recruited	Latitude and longitude of residence for UV-B dose from TOMS database	Hazard ratios (95%CI) July erythemal exposure $\leq 186.3 J/m^2$:	Observation period: 1995 – max 2006 Outcome: incident PCa Risk assessment: Cox

		for the NIH-AARP Diet and Health study [150] Excluding men other than white non-Hispanic men or without ethnicity information 21439 PCa cases		1.00 >186.3-236.8J/m^2: 0.94 (0.91-0.98) >236.8-253.7J/m^2: 0.96 (0.92-0.99) >253.7J/m^2: 0.91 (0.88-0.95)	proportional hazard regression Adjustment: baseline age, BMI, caloric intake, fruit, vegetables, red and white meat intake, alcohol consumption, smoking, education, physical activity and median household income

Appendix 2 – Collected information for the *Hobbies and Leisure Activities* section of the PROtEuS general questionnaire

I. Hobbies and Leisure Activities

1. We would like to know about your hobbies and leisure activities since you've been an adult. Could you indicate whether or not you have ever **regularly** participated in the following activities for **at least 6 months**.

Activities	yes	no	DK	Age Start	Age Stop	# of months	Frequency # of times	Frequency Per day, week or per month	Total years *(if inter-rupted*
Walking for exercise	O	O	O					O day O week O month	
Jogging or running	O	O	O					O day O week O month	
Physical conditioning	O	O	O					O day O week O month	
Golf	O	O	O					O day O week O month	
Racket sports (tennis, squash, etc.)	O	O	O					O day O week O month	
Bowling or curling	O	O	O					O day O week O month	
Swimming	O	O	O					O day O week O month	
Skiing or skating	O	O	O					O day O week O month	
Cycling	O	O	O					O day O week O month	
Dancing	O	O	O					O day O week O month	
Gardening	O	O	O					O day O week O month	
Domestic chores requiring a physical effort (shoveling, mowing the lawn, etc.)	O	O	O					O day O week O month	
Have you used pesticides?	O	O	O					O day O week O month	
Housecleaning	O	O	O					O day O week O month	
Woodworking (cutting, grinding, sanding wood)	O	O	O					O day O week O month	
Motor vehicle maintenance (ex: cars, motorcycles, 4-wheel vehicles)	O	O	O					O day O week O month	
Other physical activity Specify:	O	O	O						
1) _____				_____	_____	_____	_____	O day O week O month	_____
2) _____				_____	_____	_____	_____	O day O week O month	_____
3) _____				_____	_____	_____	_____	O day O week O month	_____
4) _____				_____	_____	_____	_____	O day O week O month	_____

Figure 1 –*Hobbies and Leisure Activities* section of the PROtEuS general questionnaire

Table 11 - List of the collected "Other physical activities" from the Hobbies and Leisure activities section of the general questionnaire

Other activities keywords	n[a]	Outdoor[b]	Number of months[c]	Number of hours[d]
aikido	1	N	0	0
alpinisme	5	Y	6	8
aquaforme	6	N	0	0
arbitre (hockey)	1	N	0	0
arbitre de football	1	Y	6	3
arbitre hockey	1	N	0	0
arts martiaux	6	N	0	0
athletisme	1	Y	6	2
auto-defense	1	N	0	0
aux fers	1	Y	6	1
aviation	1	Y	12	2
aviron	2	Y	6	2
badminton	1	N	0	0
ball hockey	1	N	0	0
balle au mur	1	N	0	0
balle donnee	1	N	6	3
balle molle	36	N	6	3
ballon balai	27	N	0	0
ballon balai crosse	1	N	0	0
baseball	82	Y	6	3
baseball (instructeur)	1	Y	6	3
basketball	25	Y	6	3
bateau	2	Y	6	2
bicyclette	9	Y	6	2
bocce petanque	1	Y	6	2
boxe	19	N	0	0
broomball	1	N	0	0
bucher du bois	2	Y	6	1
camping	2	Y	6	8
canne	1	N	0	0
canoe	2	Y	6	2
canot	12	Y	6	2
canot camping	1	Y	6	8
canot course	1	Y	6	1
canotage	3	Y	6	2
chasse	30	Y	12	4
chasse et peche	2	Y	12	4
coach soccer	1	Y	6	3
competition equestre	1	Y	6	2

conditionnement physique	3	N	0	0
conditionnement physique domicile	1	N	0	0
construction residentielle	1	Y	6	4
coupe de bois	1	Y	6	1
course traineau chien	1	Y	8	2
cricket	2	Y	6	1
criquet	2	Y	6	1
crosse	1	N	0	0
culturisme	3	N	0	0
dard	1	N	0	0
deck hockey	1	Y	6	2
diverses activites exterieures (animateur Scout - ballon et autres)	1	Y	12	6
dragon boating	1	Y	6	2
entrainement de chevaux	1	Y	12	2
entraineur (chevaux)	1	Y	12	2
entraineur baseball et hockey	1	Y	6	3
entraineur de hockey	1	N	0	0
entraineur de soccer	2	Y	6	3
entraineur et arbitre de soccer	1	Y	6	3
entretien menager	1	N	0	0
equitation	16	Y	12	2
escalade	3	Y	6	4
escrime	4	N	0	0
exploitation foret	1	Y	6	6
fastball	3	Y	6	3
fendre bois	1	Y	6	1
fer	1	Y	6	1
football	42	Y	6	3
football americain	7	Y	6	3
football, soccer	2	Y	6	3
golf	7	Y	6	5
gymnastique	1	N	0	0
halterophilie	1	N	0	0
haltérophilie	1	N	0	0
handball	7	N	0	0
hiking	4	Y	12	6
hockey	178	N	0	0
hockey a pied	1	Y	6	1
hockey bottine	1	Y	6	1
hockey cosom	2	N	0	0
hockey interieur	1	N	0	0
horse riding	1	Y	12	2

iado	1	N	0	0
instructeur de tir au fusil et pistolet/revolver	1	N	0	0
instructeur hockey	1	N	0	0
jogging	2	Y	6	1
judo	21	N	0	0
karate	27	N	0	0
karate, judo	2	N	0	0
kayak	6	Y	6	1
kendo	1	N	0	0
kiodo	1	N	0	0
kung fu	3	N	0	0
kung Fu	1	N	0	0
lawn bowling	1	Y	6	2
lutte	4	N	0	0
lutte populaire	1	N	0	0
marche	10	Y	12	1
marche montagne	1	Y	6	6
martial art	1	N	0	0
mascotte sportive	1	N	0	0
meditation	1	N	0	0
moniteur (scout)	1	Y	12	3
moniteur en readaptation (cardiologue)	1	N	0	0
moto	2	Y	12	3
motocross	1	Y	12	1
motoneige	1	Y	4	4
musculation (maison)	1	N	0	0
natation	2	N	0	0
paint-acrylic	1	N	0	0
parachute	2	Y	6	1
parachutisme	1	Y	6	1
patin	2	N	0	0
patin a roues alignees	8	Y	6	1
patinage	2	N	0	0
patins roues alignées	1	Y	6	1
peche	41	Y	6	4
peche et chasse	1	Y	12	4
pesticides	1	NA	0	0
pesticides (l’ete en floride)	1	NA	0	0
petanque	17	Y	6	2
petanque (genre)	1	Y	6	2
pilote d’avion sportive	1	Y	12	2

pilote planneur	1	Y	12	2
ping-pong	1	N	0	0
ping pong	6	N	0	0
planche a voile	11	Y	6	2
planter arbres	1	Y	6	2
plongee	1	Y	4	1
plongee en apnee	1	Y	4	1
plongee sous-marine	8	Y	4	1
poids et halteres	3	N	0	0
polo aquatique	1	N	0	0
preservation du bois	1	NA	0	0
racquetball	2	N	0	0
rainguette	1	N	0	0
randonnee dans les montagnes	2	Y	6	6
randonnee pedestre	1	Y	6	4
raquette	21	Y	4	2
raquette a neige	4	Y	4	2
roller skating	1	Y	6	1
rollerblade	4	Y	6	1
rowing (club)	1	Y	6	2
rugby	3	Y	6	3
sail board	1	Y	6	2
sailing	2	Y	6	2
saut a la perche	1	Y	6	2
sculpture marbre	1	N	0	0
shuffleboard	2	Y	6	1
ski	4	Y	4	3
ski-doo	1	Y	4	4
ski aquatique	2	Y	5	3
ski de fond	4	Y	4	3
ski nautique	9	Y	5	3
snowshoeing	1	Y	4	2
soccer	206	Y	6	3
softball	18	Y	6	3
sport de raquette	1	Y	6	2
sports de raquette	2	N	6	2
table tennis	1	N	0	0
taekwondo	5	N	0	0
tai chi	7	N	0	0
tai chi et yoga	1	N	0	0
tennis	2	Y	6	2
tennis de table	1	N	0	0
tir a carabine	1	Y	6	1

tir a l'arc	6	Y	6	2
touch football	2	Y	6	2
track & field	1	Y	6	3
trappage	1	Y	12	3
travaux domestiques	6	Y	12	1
velo stationnaire	4	N	0	0
voile	22	Y	6	2
voile deriveur	1	Y	6	2
voile regate	2	Y	6	6
voile sportive	1	Y	6	6
voilier	2	Y	6	2
volleyball	36	N	0	0
vtt	2	Y	6	2
wrestling	1	N	0	0
yoga	9	N	0	0

[a] number of participants, [b] decision whether it was considered an outdoor activity, Y = yes , N = no, NA=non-applicable. [c] number of months of possible sunlight exposure, [d] attributed number of hours generally done

Appendix 3 – Descriptive statistics

Table 12 - Distribution of the socio-demographic and clinical characteristics of the cases and controls[a] before exclusion of individuals with missing values for variables necessary for the analyses

Attributes of participants	Cases (n=1390)	Controls (n=1505)
Age (years), Mean (SD)	63.7 (6.8)	64.8 (6.9)
Ancestry, n (%)		
French	1031 (74.2)	906 (60.2)
Black	97 (7.0)	68 (4.5)
Asian	17 (1.2)	44 (2.9)
Other	235 (16.9)	473 (31.4)
Unknown	10 (0.7)	14 (0.9)
Family income group, CAD, n (%)		
<10,000	47 (3.4)	48 (3.2)
10,000-19,999	121 (8.7)	143 (9.5)
20,000-29,999	195 (14.0)	193 (12.8)
30,000-49,999	329 (23.7)	362 (24.1)
50,000-79,999	307 (22.1)	293 (19.5)
80,000-100,000	114 (8.2)	126 (8.4)
>100,000	181 (13.0)	196 (13.0)
Unknown	96 (6.9)	144 (9.6)
Education, n (%)		
Elementary or less	361 (26.0)	336 (22.3)
High school	412 (29.6)	447 (29.7)
College	203 (14.6)	267 (17.7)
Bachelor or higher	411 (29.6)	453 (30.1)
Unknown	3 (0.2)	2 (0.1)
BMI, kg/m^2, Mean (SD)	26.7 (4.0)	27.2 (4.4)
Unknown, n (%)	5 (0.4)	10 (0.7)
Ever smoker[b], n (%)	1027 (73.9)	1114 (74.0)
Ever drinker[c], n (%)	1232 (88.6)	1323 (87.9)
Physically active at work, n (%)		
Not very active	247 (17.8)	285 (18.9)
Moderately active	385 (27.7)	470 (31.2)
Very active	756 (54.4)	750 (49.8)
Unknown	2 (0.1)	0 (0.0)
Physically active during leisure time, n (%)		
Not very active	394 (28.3)	484 (32.2)
Moderately active	657 (47.3)	706 (46.9)
Very active	338 (24.3)	315 (20.9)
Unknown	1 (0.1)	0 (0.0)
Physically active at home, n (%)		
Not very active	346 (24.9)	437 (29.0)

Moderately active	681 (29.0)	770 (51.2)
Very active	361 (26.0)	298 (19.8)
Unknown	2 (0.1)	0 (0.0)
Had/have skin cancer, n (%)	42 (3.0)	41 (2.7)
First-degree relative prostate cancer, n (%)		
Yes	313 (22.2)	154 (10.2)
No	1030 (74.1)	1304 (86.6)
Unknown	47 (3.4)	47 (3.1)
Timing of last prostate cancer screening, n (%)		
Within the last 2 years	1377 (99.1)	1136 (75.5)
More than 2 years earlier	3 (0.2)	178 (11.8)
No screening	3 (0.2)	147 (9.8)
Not sure whether had screening within the previous 2 years	7 (0.5)	44 (2.9)
Gleason score, n (%)		
<6/10	12 (0.9)	
6/10	586 (42.2)	
7/10 with primary score of 3	399 (28.7)	
7/10 with primary score of 4	193 (13.9)	
7/10 with unknown primary score	7 (0.5)	
8/10-10/10	176 (12.6)	
Unknown	17 (2.6)	

[a] For all participants before excluding those with missing values for potential covariates (ancestry, education, BMI, all physical activities) [b] Ever smoker-at least 100 cigarettes in lifetime. [c] at least one alcohol beverage per month for at least one year

Appendix 4 – Correlation statistics

Table 13 - Correlation estimates for sunlight exposure and solar protection variables*

	A	B	C	D	E	F	G	H	I	J
A		0.97[a]	0.17[b]	0.17[b]	-0.07[a]	0.07[b]	0.04[b]	0.02[b]	0.58[b]	0.10[b]
B			0.24[b]	0.20[b]	-0.07[a]	0.05[b]	0.05[b]	0.01[b]	0.15[b]	0.10[b]
C				0.18[c]	0.01[b]	0.03[c]	0.08[c]	0.04[c]	0.10[c]	0.54[c]
D					0.02[b]	0.06[c]	0.07[c]	0.20[c]	0.07[c]	0.03[c]
E						0.79[b]	0.40[b]	0.25[b]	0.72[b]	0.33[b]
F							0.25[d]	0.18[c]	0.59[c]	0.23[c]
G								0.40[c]	0.24[c]	0.61[c]
H									0.07[c]	0.10[c]
I										0.16[d]
J										

* Correlation estimates on 2850 participants with complete data. [a] Spearman's ρ, [b] Square-root of R^2 of ANOVA, [c] Cramer's V, [d] kappa. A: cumulative number of events in participation in outdoor leisure activities (*CEvents*) (continuous), B: cumulative duration of participation in outdoor leisure activities (*CDuration*) (continuous), C: self-reported recreational sunlight exposure level, D: solar protection during leisure time, E: cumulative occupational sunlight exposure index (*CO*) (continuous), F: simplified occupational sunlight exposure index (*SO*), G: self-reported occupational sunlight exposure, H: solar protection at work, I: global sunlight exposure (*GSE*) index, J: global self-reported sunlight exposure index

Table 14 - Correlation estimates for independent variables other than exposure variables*

	A	B	C	D	E	F	G	H	I	J	K
A		0.07[b]	0.03[b]	0.12[b]	0.22[b]	-0.03[a]	0.11[b]	0.08[b]	0.02[b]	0.002[b]	0.04[b]
B			0.07[c]	0.06[c]	0.07[c]	0.12[b]	0.05[c]	0.14[c]	0.17[c]	0.26[c]	0.05[c]
C				0.07[c]	0.05[c]	0.03[b]	0.03[c]	0.07[c]	0.02[c]	0.06[c]	0.03[c]
D					0.05[c]	0.06[b]	0.04[c]	0.07[c]	0.04[c]	0.06[c]	0.05[c]
E						0.10[b]	0.23[c]	0.29[c]	0.14[c]	0.07[c]	0.05[c]
F							0.05[b]	0.004[b]	0.05[b]	0.004[b]	0.02[b]
G								0.15[c]	0.06[c]	0.07[c]	0.03[c]
H									0.07[c]	0.21[c]	0.05[c]
I										0.15[c]	0.001[c]
J											0.02[c]
K											

* Correlation estimates on 2850 participants with complete data. [a] Spearman's ρ, [b] Square-root of R^2 of ANOVA, [c] Cramer's V. A: age (continuous), B: ancestry, C: first-degree family history of prostate cancer, D: prostate cancer screening within 2 years prior index year, E: education, F: BMI (continuous), G: overall physical activity, H: family income, I: ever smoked at least 100 cigarettes during lifetime, J: ever drank at least one alcoholic drink per month for a year, K: ever had/have a skin cancer.

Table 15 - Correlation estimates between sunlight exposure and other independent variables*

	K	L	M	N	O	P	Q	R	S	T	U
A	0.17[a]	0.02[b]	0.0002[b]	0.05[b]	0.10[b]	-0.10[a]	0.15[b]	0.02[b]	0.03[b]	0.01[b]	0.01[b]
B	0.16[a]	0.02[b]	0.004[b]	0.03[b]	0.11[b]	-0.09[a]	0.15[b]	0.07[b]	0.03[b]	0.03[b]	0.01[b]
C	0.02[b]	0.06[c]	0.05[c]	0.06[c]	0.08[c]	0.05[b]	0.11[c]	0.11[c]	0.02[c]	0.06[c]	0.07[c]
D	0.01[b]	0.08[c]	0.05[c]	0.04[c]	0.10[c]	0.05[b]	0.08[c]	0.11[c]	0.08[c]	0.07[c]	0.06[c]
E	0.05[a]	0.04[b]	0.02[b]	0.03[b]	0.26[b]	0.05[a]	0.16[b]	0.04[b]	0.05[b]	0.02[b]	0.01[b]
F	0.07[b]	0.07[c]	0.05[c]	0.04[c]	0.23[c]	0.05[b]	0.11[c]	0.12[c]	0.07[c]	0.02[c]	0.03[c]
G	0.02[b]	0.06[c]	0.01[c]	0.03[c]	0.20[c]	0.08[b]	0.15[c]	0.10[c]	0.05[c]	0.02[c]	0.01[c]
H	0.05[b]	0.03[c]	0.02[c]	0.03[c]	0.09[c]	0.04[b]	0.09[c]	0.08[c]	0.02[c]	0.03[c]	0.01[c]
I	0.13[b]	0.04[c]	0.05[c]	0.04[c]	0.18[c]	0.06[b]	0.14[c]	0.10[c]	0.03[c]	0.02[c]	0.01[c]
J	0.02[b]	0.07[c]	0.04[c]	0.04[c]	0.16[c]	0.05[b]	0.16[c]	0.09[c]	0.04[c]	0.04[c]	0.04[c]

* Correlation estimates on 2850 participants with complete data. [a] Spearman's ρ, [b] Square-root of R^2 of ANOVA, [c] Cramer's V, [d] logistic regression coefficient. A: cumulative number of events in participations in outdoor leisure activities (*CEvents*) (continuous), B: cumulative duration of participation in outdoor leisure activities (*CDuration*) (continuous), C: self-reported recreational sunlight exposure level, D: solar protection during leisure time, E: cumulative occupational sunlight exposure index (*CO*) (continuous), F: simplified occupational sunlight exposure index (*SO*), G: self-reported occupational sunlight exposure, H: solar protection at work, I: global sunlight exposure (*GSE*) index, J: global self-reported sunlight exposure index, K: age (continuous), L: ancestry, M: first-degree family history of prostate cancer, N: prostate cancer screening within 2 years prior index year, O: education, P: BMI (continuous), Q: overall physical activity, R: family income, S: ever smoked at least 100 cigarettes during lifetime, T: ever drank at least one alcoholic drink per month for a year, U: ever had/have a skin cancer.

Appendix 5 – Logistic regression models

Table 16 –Logistic regression models for risk of prostate cancer according to the cumulative number of events in participation in outdoor leisure activities (*CEvents*), with the AIC

Model	AIC	Variables added
Model 1	3948.54	Exposure variable[a]
Model 2	3356.55	Exposure and *a priori* variables[b]
Model 3	3344.07	Education
Model 4	3350.83	Solar protection during leisure time
Model 5	3344.10	BMI
Model 6	3346.80	Physical activity
Model 7	3340.12	Education, solar protection during leisure time
Model 8	3329.24	Education, BMI
Model 9	3339.32	Education, physical activity
Model 10	3337.17	Solar protection during leisure time, BMI
Model 11	3340.36	Solar protection during leisure time, physical activity
Model 12	3333.65	BMI, physical activity
Model 13	3324.30	Education, solar protection during leisure time, BMI
Model 14	3334.07	Education, solar protection during leisure time, physical activity
Model 15	3324.80	Education, BMI, physical activity
Model 16	3326.00	Solar protection during leisure time, BMI, physical activity
Model 17	3318.58	Education, solar protection during leisure time, BMI, physical activity

[a] cumulative number of participations in outdoor leisure activities (CEvents). [b] *a* priori variables: age, first-degree family history of prostate cancer, ancestry, timing of last prostate cancer screening.

Table 17 - Logistic regression models for risk of prostate cancer according to the cumulative duration in participation in outdoor leisure activities (*CDuration*), with the AIC

Model	AIC	Variables added
Model 1	3947.25	Exposure variable[a]
Model 2	3358.12	Exposure and *a priori* variables[b]
Model 3	3344.41	Education
Model 4	3350.95	Solar protection during leisure time
Model 5	3346.71	BMI
Model 6	3347.17	Physical activity
Model 7	3339.29	Education, solar protection during leisure time
Model 8	3330.55	Education, BMI
Model 9	3338.51	Education, physical activity
Model 10	3338.17	Solar protection during leisure time, BMI
Model 11	3339.20	Solar protection during leisure time, physical activity
Model 12	3335.36	BMI, physical activity
Model 13	3324.26	Education, solar protection during leisure time, BMI
Model 14	3332.16	Education, solar protection during leisure time, physical activity
Model 15	3325.05	Education, BMI, physical activity
Model 16	3325.92	Solar protection during leisure time, BMI, physical activity
Model 17	3317.51	Education, solar protection during leisure time, BMI, physical activity

[a] cumulative duration of participation in outdoor leisure activities (CDuration). [b] *a* priori variables: age, first-degree family history of prostate cancer, ancestry, timing of last prostate cancer screening

Table 18 - Logistic regression models according to the cumulative occupational sunlight exposure index (*CO*), with the AIC

Models	AIC	Variables
Model 1	3952.0	Exposure index[a]
Model 2	3345.3	Exposure index, *a priori* included variables[b]
Model 3	3345.7	Solar protection work
Model 4	3353.4	Leisure exposure (i)
Model 5	3347.2	Leisure exposure (c)
Model 6	3353.7	Solar protection work, leisure exposure (i)
Model 7	3347.6	Solar protection work, leisure exposure (c)
Model 8	3348.3	Leisure exposure (i), solar protection leisure
Model 9	3342.0	Leisure exposure (c), solar protection leisure
Model 10	3349.6	Leisure exposure (i), solar protection work and leisure
Model 11	3343.4	Leisure exposure (c), solar protection work and leisure

[a] Univariate logistic regression model with only the exposure variable, [b] Multivariate logistic regression model with the obligatory variables: occupational sunlight exposure variable, age, ancestry, first-degree family history of prostate cancer, education, prostate cancer screening. All the following models include these variables. (i) designates an interaction variable between the exposure index and the indicated factor, (c) designates the indicated factor as a confounder variable.

Table 19 - Logistic regression models according to the simplified occupational sunlight exposure index (*SO*), with the AIC

Model	AIC	Variables
Model 1	3951.5	Exposure index[a]
Model 2	3344.9	Exposure index, *a priori* included variables[b]
Model 3	3345.1	Solar protection work
Model 4	3353.8	Leisure exposure (i)
Model 5	3346.8	Leisure exposure (c)
Model 6	3354.1	Solar protection work, leisure exposure (i)
Model 7	3347.0	Solar protection work, leisure exposure (c)
Model 8	3348.7	Leisure exposure (i), solar protection leisure
Model 9	3341.6	Leisure exposure (c), solar protection leisure
Model 10	3350.0	Leisure exposure (i), solar protection work and leisure
Model 11	3342.9	Leisure exposure (c), solar protection work and leisure

[a] Univariate logistic regression model with only the exposure variable, [b] Multivariate logistic regression model with the obligatory variables: occupational sunlight exposure variable, age, ancestry, first-degree family history of prostate cancer, education, prostate cancer screening. All the following models include these variables. (i) designates an interaction variable between the exposure index and the indicated factor, (c) designates the indicated factor as a confounder variable.

Table 20 - Logistic regression models according to the global sunlight exposure (*GSE*) index, with the AIC

Model	AIC	Variables
Model 1	3950.26	Exposure index[a]
Model 2	3345.32	Exposure index, *a priori* included variables[b]
Model 3	3345.77	Solar protection at work
Model 4	3339.76	Solar protection during leisure time
Model 5	3332.09	BMI
Model 6	3341.84	Physical activity
Model 7	3341.15	Solar protection at work and during leisure time
Model 8	3332.71	Solar protection at work, BMI
Model 9	3342.07	Solar protection at work, physical activity
Model 10	3325.09	Solar protection during leisure time, BMI
Model 11	3334.62	Solar protection during leisure time, physical activity
Model 12	3329.14	BMI, physical activity
Model 13	3326.58	Solar protection at work and during leisure time, BMI
Model 14	3336.07	Solar protection at work and during leisure time, physical activity
Model 15	3329.57	Solar protection at work, BMI, physical activity
Model 16	3320.55	Solar protection during leisure time, BMI, physical activity
Model 17	3322.13	Solar protection at work and during leisure time, BMI, physical activity

[a] Univariate logistic regression model with only the exposure variable, [b] Multivariate logistic regression model with the obligatory variables: global sunlight exposure variable, age, ancestry, first-degree family history of prostate cancer, education, prostate cancer screening. All the following models include these variables.

Appendix 6 – List of participating hospitals

Notre-Dame Hospital

St-Luc Hospital

Hôtel-Dieu de Montréal Hospital

Maisonneuve-Rosemont Hospital

Jean-Talon Hospital

Charles-Lemoyne Hospital

Centre hospitalier Fleury

Appendix 7 – Authorization from the coauthors for the inclusion of the manuscript in the thesis