# Phosphodiesterase-5 Inhibitors and the Risk of Melanoma Skin Cancer

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# Abstract

**Background:** There is controversy regarding the association between phosphodiesterase-5 (PDE5) inhibitors, drugs used in the treatment of erectile dysfunction (ED), and melanoma skin cancer. I assessed this association in a large, population-based cohort study.

**Methods:** Using the United Kingdom Clinical Practice Research Datalink, I assembled a cohort of men newly-diagnosed with ED between 1998 and 2014, and followed until 2015. PDE5 inhibitor use was treated as a time-varying variable, and lagged by one year for latency purposes. Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) of incident melanoma associated with PDE5 inhibitor use overall, and by number of prescriptions and pills received. Identical analyses were conducted for basal and squamous cell carcinoma, two cancers for which PDE5-related pathways are not thought to be involved.

**Results:** The cohort included 142,983 patients, of whom 440 patients were newly-diagnosed with melanoma skin cancer (incidence rate: 63.0 per 100,000 person-years). Compared with non-use, PDE5 inhibitor use was not associated with an overall increased risk of melanoma (incidence rates: 66.7 versus 54.1 per 100,000 person-years; HR: 1.18, 95% CI: 0.95-1.47). The risk was significantly increased among those who had received ≥7 prescriptions and ≥25 pills (HR: 1.30, 95% CI: 1.01-1.69 and HR: 1.34, 95% CI: 1.04-1.72, respectively). In contrast, there was no overall association with basal and squamous cell carcinoma, and with no clear duration-response relationship.

**Conclusions:** The use of PDE5 inhibitors was not associated with an overall increased risk of melanoma skin cancer.

# Résumé

**Contexte :** Il existe une controverse au sujet de l'association entre les inhibiteurs de la phosphodiestérase-5 (PDE5), les médicaments utilisés dans le traitement de la dysfonction érectile (ED), et le mélanome de la peau. Nous avons évalué cette association dans une grande étude de cohorte basée sur la population.

**Méthodes :** En utilisant le *United Kingdom Clinical Practice Research Datalink*, nous avons réuni une cohorte d'hommes nouvellement diagnostiqués avec ED entre 1998 et 2014, et suivis jusqu'en 2015. L'utilisation de l'inhibiteur de la PDE5 a été traitée comme une variable variant dans le temps, et décalée d'une année aux fins de la latence. Les modèles Cox à risques proportionnels ont été utilisés pour estimer les risques relatifs (RR, ici le risque instantané de décès) ajustés avec des intervalles de confiance(IC) à 95% du mélanome incident lié à l'utilisation globale d'inhibiteurs de la PDE5, et par le nombre de prescriptions et de pilules reçues. Des analyses identiques ont été réalisées pour le carcinome basocellulaire et le carcinome épidermoïde, deux cancers pour lesquels PDE5 ne sont pas considérés comme étant impliqués.

**Résultats :** La cohorte comprenait 142,983 patients, dont 440 qui ont été nouvellement diagnostiqués avec le cancer de la peau de mélanome (taux d'incidence : 63,0 pour 100.000 personnes-années). Par rapport à la non-utilisation, l'utilisation d'inhibiteur de la PDE5 n'a pas été associée à un risque augmenté globalement significatif de mélanome (taux : 66,7 contre 54,1 pour 100.000 années-personnes ; RR : 1,18, IC à 95% : 0,95 à 1,47). Le risque a été significativement augmenté chez ceux qui avaient reçu ≥ 7 prescriptions et ≥ 25 pilules

(RR : 1,30, IC 95% : 1.01-1.69 et HR : 1,34, IC 95% : 1,04 à 1,72, respectivement). En revanche, il n'y avait pas d'association globale avec le carcinome basocellulaire et le carcinome épidermoïde, et sans relation durée-réponse claire.

**Conclusions :** L'utilisation d'inhibiteurs de la PDE5 n'a pas été associée à un risque augmenté de cancer de la peau de mélanome.

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# Preface & Contribution of Authors

The thesis is based on my Master's project "Phosphodiesterase-5 Inhibitors and the Risk of Melanoma Skin Cancer." The results of the study have recently been published in European Urology (2015 impact factor: 14.976) (1), and has been the subject of an editorial (2). The authors and their contributions are listed below.

| **Collaborators of the Study** | **Contribution** |
|---|---|
| Yi Lian BSc | Study concept and design<br>Statistical analysis<br>Drafting of the manuscript<br>Critical revision of the manuscript for important intellectual content |
| Hui Yin MSc | Statistical analysis<br>Critical revision of the manuscript for important intellectual content |
| Michael Pollak MD | Critical revision of the manuscript for important intellectual content |
| Serge Carrier MD | Critical revision of the manuscript for important intellectual content |
| Robert Platt PhD | Study concept and design<br>Critical revision of the manuscript for important intellectual content |
| Samy Suissa PhD | Study concept and design<br>Critical revision of the manuscript for important intellectual content<br>Thesis supervision |
| Laurent Azoulay PhD | Study concept and design<br>Critical revision of the manuscript for important intellectual content<br>Thesis supervision |

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# Abbreviations

| | |
|---|---|
| cGMP | Cyclic guanosine monophosphate |
| CI | Confidence interval |
| CPRD | Clinical Practice Research Datalink |
| HR | Hazard Ratio |
| NAION | Non-arteritic anterior ischaemic optic neuropathy |
| PDE5 | Phosphodiesterase-5 |
| SD | Standard deviation |
| UK | United Kingdom |

# Chapter 1: Introduction

Phosphodiesterase-5 (PDE5) inhibitors, which include sildenafil, tadalafil, and vardenafil, are effective treatments for erectile dysfunction (3-5). The first PDE5 inhibitor (sildenafil) was approved and entered the market in 1998 and soon gained popularity. Overall, these drugs have been deemed to be relatively safe in a number of pre-marketing clinical trials and post-marketing surveillance studies (6-10).

However, in 2014 an observational study associated the use of PDE5 inhibitors with an 84% increased risk of melanoma skin cancer (11). The biological rationale for this association involved PDE5 inhibitors interrupting various signaling pathways in melanoma skin cancer cells, thereby increasing the risk of cancer (12-14). However, in a subsequent study (15), the effect was limited to patients who only received one prescription, a finding that is consistent with a non-causal association. That study also reported a modest association with basal cell carcinoma, a non-melanoma skin cancer that is not thought to involve the PDE5 pathways (15). Both of the aforementioned studies had a number of methodological shortcomings that limit their interpretation (discussed in detail in Section 2.4 below).

Given the widespread use of PDE5 inhibitors and the need to assess their safety, I conducted a large, population-based cohort study to determine whether the use of PDE5 inhibitors is associated with an increased risk of melanoma and non-melanoma skin cancer in patients with erectile dysfunction.

# Chapter 2: Literature Review

This chapter is divided into four sections. The first section provides an overview of erectile dysfunction and its risk factors and treatments. The second section is a detailed description of PDE5 inhibitors, which is the most common treatment for erectile dysfunction. The third section describes melanoma and non-melanoma skin cancers (basal cell carcinoma and squamous cell carcinoma), which includes their epidemiology, risk factors and treatment. The final section is a review of the two aforementioned observational studies that investigated the association between PDE5 inhibitors and melanoma skin cancer (11, 15). As this study was performed using a database from the United Kingdom (UK), some of the information presented in this chapter is specific to the UK.

## 2.1 Erectile dysfunction

Erectile dysfunction, or impotence, is defined as the general and prolonged inability of a man to obtain or sustain a penile erection that is hard or strong enough to provide for successful sexual intercourse. Erectile dysfunction can be an ongoing and repetitive condition that requires treatment. Causes and treatments are varied, which will be discussed below in greater details (16, 17).

### 2.1.1 Epidemiology of erectile dysfunction

Erectile dysfunction is a common condition among men worldwide. According to the 1994 Massachusetts Male Aging Study, one of the largest ever conducted in males, the

overall prevalence of erectile dysfunction was 52% among men aged 40 to 70 years (17). In a Canadian study published in 2006, the prevalence of erectile dysfunction among a sample of men aged 40 to 88 years was 49.4% (18). A recent systematic review indicated that the prevalence of erectile dysfunction is similar in North America, Europe and Australia (19). A limited number of studies and reviews indicated that countries in Asia and South America exhibit similar erectile dysfunction statistics (20, 21).

Many of the aforementioned studies reported age-specific data, which include incidence rates and prevalence. A common pattern in these studies is that both incidence rates and prevalence increases significantly with age. Table 1 summarizes the incidence rates and prevalence of erectile dysfunction in different age groups reported in the Massachusetts Male Aging Study, as an example (17, 22). In summary, erectile dysfunction is a condition that affects millions of men worldwide.

**Table 1: Incidence rates and prevalence of moderate/severe erectile dysfunction in different age groups in the Massachusetts Male Aging Study**

| Age Groups | 40-49 | | 50-59 | | 60-69 | |
|---|---|---|---|---|---|---|
| | 40-44 | 45-49 | 50-54 | 55-59 | 60-64 | 65-69 |
| Incidence Rates* | 12.4 | | 29.8 | | 46.4 | |
| Prevalence (%) | 22 | 28 | 30 | 35 | 41 | 49 |
| * cases per 1000 man-years | | | | | | |

### 2.1.2 Risk factors

Erection is a reaction of men to sexual arousal that requires the normal functioning of a series of systems of the human body (23). As a result, there is a wide range of causes of

erectile dysfunction, many of which are results, or signs of more serious health conditions. This section summarized the main causes and risk factors of erectile dysfunction.

Firstly, a certain level of sexual desire (libido) is necessary for a man to be sexually aroused. This requires the mental well-being of men. Conditions such as depression and anxiety may cause reduced libido and are therefore risk factors for erectile dysfunction (24-26).

Secondly, a functioning nervous system plays a vital role. When a man becomes aroused, his brain will send a signal through the peripheral nervous system to the nerves in his penis (27). Therefore, neurologic conditions in either the central or the peripheral nervous system may cause erectile dysfunction (19, 28-30). Such conditions include stroke, head injuries, spinal cord injuries or disorders, multiple sclerosis, Parkinson's disease, and injuries or surgeries in penis, pelvis or surrounding areas (19, 28-30).

Thirdly, adequate blood circulation is important. After the nerves in the penis receives the signal, it will increase the blood flow to the penis. As a result, cardiovascular conditions that affect the blood flow of patients may lead to erectile dysfunction. Thompson et al. (31) showed that cardiovascular diseases (including congestive heart failure, myocardial infarction, angina, transient ischemic attack, and arrhythmia) and erectile dysfunction share similar risk factors and that they are significantly associated. They concluded that erectile dysfunction is a harbinger of cardiovascular events in some men (31). Some established risk factors include smoking, hypertension and diabetes (22, 32). Subsequent diabetic neuropathy (nerve damage) in some diabetic patients could lead to

erectile dysfunction in the way that is described in the previous paragraph (33). In addition, the fact that sexual intercourse is inadvisable for male patients with certain cardiovascular conditions adds another layer of complexity to the correlation between erectile dysfunction and cardiovascular disease (34).

Fourthly, anatomical conditions of the penis can lead to erectile dysfunction. Peyronie's disease, which is a connective tissue disorder of the penis can cause erectile dysfunction (35). Furthermore, some studies suggested a potential association between prolonged cycling and erectile dysfunction (36). Logically, cycling could have an effect on penile nerves, blood flow and the anatomy of the penis. However, the association has not been well-established and the mechanism behind it is not clear. (36, 37)

Finally, there is a hormonal aspect of erectile dysfunction. Testosterone, the male sex hormone plays a key role in the male reproductive system. (38) It has been shown in some studies that hypogonadism (a condition characterized by low testosterone levels) is associated with erectile dysfunction (39). Nonetheless, this is not widely recognized (40). The level of thyroid hormone has also been shown to be associated with male sexual symptoms. Indeed, both hyperthyroidism and hypothyroidism have been shown to be associated with increased risk of erectile dysfunction (41).

In summary, a wide range of conditions may cause erectile dysfunction, and are thus potential risk factors for this condition. This includes pharmaceutical agents such as antipsychotics, antihypertensives, anti-androgens, as well as indicators of unhealthy lifestyle such as use of illegal drugs, smoking and excessive alcohol consumptions (42-47).

All of the aforementioned conditions, medications and lifestyle factors need to be considered in the diagnosis and treatment of erectile dysfunction.

### 2.1.3 Diagnosis

In Canada, most erectile dysfunction cases are diagnosed and treated by primary care physicians (48). According to the 2015 Canadian Urological Association practice guidelines for erectile dysfunction, patients may seek medical attention if the problem with erection (defined in Section 2.1) has lasted at least 3 months (49). In the UK, the National Health Service suggests that men should see their general practitioner if the problem with erection has lasted for a few weeks. When consulting a primary care physician or a general practitioner, patients may be asked a variety of questions, according to the number of risk factors summarized in the previous section. The Canadian guidelines and the British Society for Sexual Medicine Guidelines on the Management of Erectile Dysfunction provide detailed information (49, 50).

First, it needs to be determined whether the condition is physiological or psychological. Generally, failure to erect that happens only when a patient is attempting to have sex may indicate a psychological cause (21). On the other hand, erectile dysfunction that happens all the time (e.g. absence of morning awakening erections, spontaneous erections or masturbatory erections) may suggest a physiological cause (49, 50).

Similar to the diagnosis of any disease, physicians usually ask patients about their symptoms including severity and duration, as well as lifestyle such as smoking and drinking status. Patients may also be asked about their relationship status, history of sexual

partners and relationships, as well as sexual orientation and gender identity. In addition, general practitioners will consider patients' mental health status and may refer patients to more detailed psychological assessment if erectile dysfunction is thought to be psychological (49, 50).

Underlying physical causes will always be investigated. As described in the previous section, many causes and risk factors for erectile dysfunction are injuries and diseases that can be identified in the patients' medical history. Also, both Canadian and UK guidelines suggest that all patients have a focused physical examination. One of such examinations is a genital examination for anatomical conditions. Other examinations include blood tests for hormone levels and/or blood glucose and lipids, blood pressure, heart rate, waist circumference and weight, some of which are basic tests for cardiovascular health and diabetes. In the diagnosis of erectile dysfunction, cardiovascular conditions are given the highest attention. Both guidelines require that all men with unexplained erectile dysfunction have a thorough evaluation for underlying cardiovascular diseases (49, 50). Further specialized investigations are not necessary for most patients unless specifically indicated, for example, healthy young patients who are at low risk of erectile dysfunction (49, 50).

### 2.1.4 Treatment

The primary goal of management of erectile dysfunction is to enable the individual or couple to enjoy a satisfactory sexual experience (49, 50). This involves identifying and treating any curable causes of erectile dysfunction, initiating lifestyle changes, risk factor

modification, and providing education and counselling to patients and their partners (50). These are described in detail below.

Firstly, underlying health conditions such as cardiovascular diseases and diabetes may need to be treated before treating erectile dysfunction. Men that are shown to be at low risk of cardiovascular diseases can be treated within the primary care setting (49, 50). For those men at intermediate or high risk, treatment for erectile dysfunction must be deferred until the cardiovascular conditions are established and/or stabilized, as is recommended in the UK (50). However, the Canadian guidelines do not emphasize the treatment of co-existing cardiovascular diseases (49). Nonetheless, both guidelines suggest that treating these underlying conditions are generally beneficial for the management of erectile dysfunction (49, 50).

Secondly, treatment for erectile dysfunction often target reversible causes, including hormonal conditions, the use of medications, as well as psychological causes. erectile dysfunction patients with hypogonadism may be treated with testosterone replacement therapy (49, 50). In case of potential drug-related erectile dysfunction, the UK National Health Services requires patients never to stop taking a prescribed medication as an attempt to resolve erectile dysfunction. Patients are advised to always consult their general practitioner and a possible solution is finding an alternative. However, the Canadian guideline does not have a similar statement (49). In the case of psychological causes, psychosexual counselling and therapy are advised (49-51).

Furthermore, lifestyle changes can be beneficial. A healthy lifestyle can lead to better health conditions, and thus minimize the risk of erectile dysfunction. This includes losing weight if overweight or obese, giving up smoking, cutting back alcohol consumption, giving up illegal drugs, and exercising regularly (50).

Finally, there are direct treatments for erectile dysfunction (50). First-line treatments include PDE5 inhibitors (Section 2.2) and vacuum erection devices. A vacuum erection device works by creating a pressure thus draw blood in to the penis. Second-line treatments include intracavernous injection therapy (self-injection of alprostadil into the penis), intraurethral alprostadil (a suppository applied to the urethra), and topical alprostadil (a cream applied topically to the penis). Third-line treatment is penile prosthesis, which is the surgical implantation in the penis of either a malleable or inflatable device.

## 2.2 Phosphodiesterase-5 inhibitors

### 2.2.1 Indications

The primary indication of PDE5 inhibitors is treatment of erectile dysfunction. Other indications include the treatment of pulmonary arterial hypertension and benign prostate hyperplasia (52-54).

### 2.2.2 Mechanism

As mentioned in Section 2.1.2, the brain sends a signal to the nerves in the penis when a man is sexually aroused. The response is that nerves and endothelial cells release nitric oxide directly into the penis (55). Cyclic guanosine monophosphate (cGMP) is then produced and triggers the relaxation of smooth muscle cells lining the blood vessels supplying the penis, leading to arterial dilation and venous constriction, thus erection (55). PDE5 enzyme is the catalyst in the degradation of cGMP, thus inhibiting the PDE5 enzyme will maintain a high concentration of cGMP (55, 56). Briefly, PDE5 inhibitors cause vasodilation by inhibiting the degradation of cGMP by the PDE5 enzyme, thereby increasing the blood flow to the penis in the presence of sexual stimulation.

### 2.2.3 PDE5 inhibitor drugs

Four major types of PDE5 inhibitors are approved for the treatment of erectile dysfunction: sildenafil (Viagra®), tadalafil (Levitra®), vardenafil (Cialis®) and avanafil (Stendra®). Sildenafil was first approved by the United States Food and Drug Administration in 1998 and both tadalafil and vardenafil were approved in 2003. Avanafil

was approved and released to the United States market in 2012. Sildenafil and tadalafil are also indicated in the treatment of pulmonary artery hypertension, while vardenafil is also indicated in the treatment of benign prostatic hyperplasia (52-54). All four types of PDE5 inhibitors were approved in Canada and the UK. Furthermore, due to the late development of avanafil, it was not included in the study.

### 2.2.4 Directions of use

This section is restricted to the oral administration of these PDE5 inhibitors in the treatment of erectile dysfunction. While there are other routes of administration, such as transdermal patches and injections, these are generally applied when the first-line oral treatment yields unsatisfactory results (Section 2.1.4).

Compared to tadalafil, sildenafil and vardenafil are short-acting drugs, with a half-life of 4-5 hours, while tadalafil is relatively long-acting, with a half-life of approximately 17.5 hours (52-54, 57). Given the short half-life of sildenafil, this drug usually starts to work within 30-60 minutes of ingestion with an effect lasting up to 4 hours (54). Similarly, manufacturers of vardenafil suggests that patients take the drug 1 hour prior to sexual activity (52). Due to the long-acting nature of tadalafil, the manufacturer provides two options for tadalafil (53). Firstly, it starts working in as little as 30 minutes, and thus can also be taken as needed, with a single dose lasting for up to 36 hours. Secondly, the drug can be used on a daily basis, which allows men to be able to attempt sex anytime between doses. The table below is a summary of the pharmacological properties of these drugs and their directions of use.

**Table 2: Half-life and direction of use of sildenafil, vardenafil, tadalafil and avanafil**

| Drug | Sildenafil | Vardenafil | Tadalafil | Avanafil |
|---|---|---|---|---|
| Half-life | 4-5 hours | 4-5 hours | 17.5 hours | 5 hours |
| As-needed use | Yes | Yes | Yes | Yes |
| Onset of action | 30-60 minutes | 60 minutes | 30 minutes | 30-45 minutes |
| Daily use | No | No | Yes | No |

### 2.2.5 Contraindications and warnings

The product monographs of sildenafil, vardenafil and tadalafil are highly consistent with minor differences in terms of contraindications and warnings (52-54). Two common contraindications are co-administration with any types of nitrate-containing medication and previous episode of non-arteritic anterior ischaemic optic neuropathy (NAION) (52-54). In addition, various cardiovascular conditions, even though not contraindicated for these drugs, are important warnings that are emphasized in all three monographs (52-54).

It has been shown that PDE5 inhibitors potentiate the blood pressure-lowering effect of nitrates and could lead to life-threatening hypotension (58, 59). Therefore, the co-administration of PDE5 inhibitors and nitrates is absolutely contraindicated. In some erectile dysfunction patients, where nitrate administration is deemed medically necessary, a certain time period has to be elapsed after the last dose of PDE5 inhibitors before nitrate administration. According to manufacturer's pharmacokinetic profile of sildenafil, plasma concentration in healthy volunteers 24 hours after a single 100 mg oral dose is approximately 2 ng/mL, which is much lower than peak concentration of 440 ng/mL (54). Nevertheless, it is still unknown whether nitrates can be safely administered at this time point (54). Furthermore, this does not take into account the possibility that patients with

conditions such as renal or hepatic impairment may have a slower drug metabolism and excretion rate (and thus a higher post-dose plasma concentration of sildenafil) (54). On the other hand, the product monographs of vardenafil and tadalafil suggest a 24-hour and 48-hour time period, respectively, after the last dose and before nitrate administration. However, they both require that nitrates be administered under close medical supervision with appropriate hemodynamic monitoring (52, 53).

Another common contraindication of all three drugs is NAION. Patients with a previous episode of NAION should not be prescribed any PDE5 inhibitors (52-54). Post-marketing case reports of vision loss due to NAION, although very rare, led to the decision made by the United States Food and Drug Administration, that the manufacturers should add NAION as a contraindication in the label of all three PDE5 inhibitor classes (60). Nonetheless, studies suggest that the association between PDE5 inhibitor use and NAION requires more conclusive evidence (61).

General warning messages in the product monographs mentioned cardiovascular conditions including myocardial infarction, stroke, angina, cardiac failure, and severe or uncontrolled arrhythmia, hypotension (<90/50 mmHg) and hypertension (>170/110 mmHg) (52-54). In patients with these conditions, sexual activity potentially increases the risk of cardiac events, and is thus not recommended (52-54).

### 2.2.6 Side effect profile

All three drugs (sildenafil, vardenafil and tadalafil) went through pre-marketing clinical trials and are under certain post-marketing surveillance (3-5, 52-54). Adverse

effects reported during randomized controlled trials are generally transient and mild in nature, which include headache, dizziness, flushing, dyspepsia, nausea and nasal congestion (52-54). Serious adverse effects such as serious cardiovascular events, sudden loss of hearing, visual impairment, seizure, prolonged erection, etc. have been reported in post-marketing surveillance. However, these adverse effects are generally rare and with no clear mechanism of action (52-54). In many cases, it is difficult or impossible to determine whether these events are related to the use of the drugs even though they are temporally associated (52-54). Furthermore, in cases with known mechanism, it is often hard to distinguish whether the adverse effect is caused by the drug or pre-existing health conditions (e.g. serious cardiac events in patients with a history of cardiovascular diseases during or after sexual activity) (52-54).

Even though the drug monographs are constantly updated according to post-marketing surveillance, its ability to report long term adverse effects such as cancer is limited. Skin cancer, as one of the most common cancers, is described in the next section (Section 2.3).

## 2.3 Skin cancer

Skin cancer, including melanoma and non-melanoma skin cancer, is the outcome of interest of the thesis. This section is an overview of skin cancer, in terms of the epidemiology, risk factors, diagnosis and treatment.

Skin cancers are cancers that arise from the skin due to the abnormal cell development, which allows them to invade or spread to other parts of the human body. The three most common malignant skin cancers are melanoma, basal cell carcinoma and squamous cell carcinoma. They are each named after the type of skin cells that it arises from, (i.e. melanocyte, basal cell and squamous cell, respectively). basal cell carcinoma and squamous cell carcinoma, along with a few other less common skin cancers, are collectively known as non-melanoma skin cancers.

### 2.3.1 Epidemiology of skin cancer

Skin cancer, mostly non-melanoma skin cancer, is the most common type of cancer in the Caucasian populations, and is thus in a number of countries including Canada, UK, US, Australia, New Zealand, and others (62-64). In Canada, an estimated 78,300 new cases of non-melanoma skin cancer cases were expected to be diagnosed in 2015, with melanoma skin cancer the seventh most common cancer in both men and women (62). Statistics from the UK showed that there were around 72,100 new cases of non-melanoma, and 14,509 malignant melanoma skin cancer cases (with about 75% being basal cell carcinoma and 20% being squamous cell carcinoma) diagnosed in 2013 (63). Malignant melanoma is the fifth most common cancer in the UK and its incidence rates have more

than quadrupled (345% increase), increasing faster than any other top ten most common cancers in the UK over the last several decades (63). Australia and New Zealand exhibit the highest rate of skin cancer in the world due to the effect of its local stratospheric ozone depletion (65).

Although the incidence rates of skin cancers are quite high, their mortality rates are rather low (66, 67). Moreover, most non-melanoma skin cancer cases are not lethal (66). Only around 638 individuals died from non-melanoma skin cancer in 2012 in England while tens of thousands of new cases of non-melanoma skin cancer are diagnosed each year (63). For malignant melanoma skin cancer, approximately 90% of the patients survive for over ten years in the UK. Women have slightly better survival than men. UK statistics showed that 97% of men survive for at least one year and it falls to 88% for 5 years, while the numbers are 98% and 92% for women, respectively (63).

### 2.3.2 Risk factors

The primary cause of all three major types of skin cancer is ultraviolet radiation, from the sun or tanning beds (68). Excessive exposure to sunlight could cause sunburns and patches of rough, dry skin called solar keratosis, which can lead to several times higher risk of melanoma and non-melanoma skin cancer (69, 70). Other risk factors of skin cancer include both congenital and postnatal traits, which are described in detail below.

In the perspective of congenital causes, studies have shown that individuals who have fair skin with blond or red hair and freckles that usually get burned in the sun are at higher risk of developing skin cancer (71). People with darker skin, on the other hand, have

a stronger natural protection against skin cancer (71). The presence of moles is another risk factor for developing skin cancers. The more moles one has on his/her body, especially those with asymmetrical shape and irregular borders, the higher his/her risk for skin cancers is (69, 71). Some inherited genetic syndromes and skin conditions, such as xeroderma pigmentosum and Gorlin syndrome, or particular types of birthmark, such as large congenital melanocytic naevi, also lead to a higher risk of cancerous cell development (69, 72, 73). People are also at higher risk when they have close relatives with melanoma, which could be possibly explained by genetic reasons (69, 71, 74).

In terms of postnatal causes, the location of birth plays a role in determining the risk factor for skin cancer. People born in a country with hot climate, such as Australia, tend to have a higher risk of skin cancer compared to individuals with similar skin color but lives in a colder climate (69). Tobacco smoking has been shown to be associated with increased risk of skin cancer in some studies, while recent observational studies reported a protective effect on melanoma (75-77). In addition, immunodeficiency is a well-established risk factor for skin cancer. Individuals with compromised immunities resulting from immunosuppressive medication, HIV/AIDS infection or organ transplant are more likely to develop melanoma and non-melanoma skin cancer (78-82). Besides, studies showed that melanoma risk is increased, especially among men with Parkinson's disease (83-86). Obesity is another risk factor for both malignant melanoma and non-melanoma skin cancers. Malignant melanoma risk has been shown to be 31% higher in overweight and obese men, but the risk was not elevated in overweight and obese women (87). In other studies on non-melanoma skin cancer, the risk of basal cell carcinoma and squamous cell

carcinoma was shown to be roughly 20-40% higher in those with body mass index (BMI) lower than 25 compared to the others. It is worth mentioning that, the authors concluded that obesity is most likely to be a surrogate for lack of chronic sun exposure, especially in women (88, 89).

### 2.3.3 Diagnosis

The skin has two main layers, epidermis and dermis. Melanoma is a cancer of melanocytes, which are the pigment (melanin) producing cells between the basal cells found in the epidermis of skin, hair and eyes. Melanoma could be various in color, ranging from pink, red to brown or black. It usually has an asymmetrical shape and irregular border. Basal cells lie in the innermost layer of the epidermis. basal cell carcinoma usually appears as a raised, fleshy, smooth and pearly shaped bump on the skin being exposed to sunlight (90). Squamous cells are the main part of the epidermis that sit above the basal cells and the melanocytes. squamous cell carcinoma usually has a red, crusted, or scaly patch looking on the skin (90). The UK National Health Services suggests that patients see their general practitioner whenever an abnormal area has appeared on the skin, such as a new mole, a change in an existing mole, and a lump or discolored patch that does not heal. The diagnosis of all three types of skin cancer is by biopsy (90).

### 2.3.4 Treatment

The UK National Institute for Health and Care Excellence has provided healthcare guidelines for the treatment of skin cancer (90). The guidelines suggests that the treatment depends on the the type and stage of the cancer. The stage of a cancer contains critical

information on how deeply the cancerous cells have gone into the skin and how far they have spread. The staging of skin cancer ranges from 0 to 4, with 0 being the earliest diagnosed and 4 being the latest. Overall, the main treatment for all three types of skin cancer is surgery.

For early stage melanoma (i.e. stage 0 and stage 1 where melanoma is on the surface of the skin and is 1-2cm thick), a surgical excision that removes the melanoma and a small area of skin around it is enough (90, 91). For advanced stages (stage 2 where melanoma is thicker than 2cm, ulcerated and stage 3 where melanoma has spread to nearby lymph nodes), treatment is the same as for early stage melanoma, with the addition of follow-up monitoring for recurrence (90, 91). For late stage melanoma (stage 4 where melanoma has spread to other part of the body or comes back at a different location), surgery may not be able to cure melanoma thus treatment will be focusing on slowing cancer progressing, reducing symptoms and extending life expectancy (90, 91). Patients with late stage melanoma may receive radiotherapy and chemotherapy (90, 91).

Due to the relatively low malignancy, invasiveness and probability of recurrence of non-melanoma skin cancer, surgical excision is enough to cure the cancer in many cases (90). Non-melanoma skin cancers, especially basal-cell carcinomas, are unlikely to develop metastasis or lead to deaths of the patients (66). Over 90% of patients with basal cell carcinoma could be cured by surgery without recurrence (66). Other treatments for non-melanoma skin cancer include curettage, cryotherapy, radiotherapy and chemotherapy, which may be applied depend on the individual circumstances. Finally, imiquimod, a

prescription drug, is indicated for the treatment of basal cell carcinoma, by activating immune responses of the body to attack cancer cells.

## 2.4 Observational studies

To date, two observational studies have assessed the association between PDE5 inhibitors and skin cancer (11, 15). The authors of the two previous studies proposed a potential rationale behind the association and conducted population-based studies to investigate the association. The biological rationale for this association involved PDE5 inhibitors interrupting various signaling pathways in melanoma skin cancer cells, thereby increasing the risk of cancer (12-14). This section summarizes their main findings and methodological limitations.

### 2.4.1 Li et al. 2014

In 2014, Li et al. (11) investigated the association between the use of sildenafil and the risk of melanoma in a prospective cohort analysis based on the United States Health Professionals' Follow-up Study. A cohort of 25,848 men were assembled in 2000 and followed until 2010. Exposure to sildenafil was based on a questionnaire, in which patients were asked to report any surgery or treatment in the three-month period before cohort entry. Their finding suggests that sildenafil is associated with an 84% increased risk of melanoma skin cancer. The study has a number of limitations. First, the time span of this study was 2000 to 2010, but exposure was only measured during a three-month period before 2000. Considering the fact that the first sildenafil became available in 1998 (over a year before 2000) and that the drug was a blockbuster during the first decade since its introduction, individuals who had taken the drug before the three-month period or those who initiated the drug during the ten-year follow-up were considered as misclassified as

non-users. Secondly, some information used in the study were collected by questionnaires based on patients' memory (e.g. sun exposure at high school/college age and history of sunburns), thus recall bias may be present. Finally, the study did not adjust for some important risk factors for skin cancer and erectile dysfunction, such as compromised immunity and cardiovascular comorbidities, which are potential confounders of the association. (See Section 2.1.2 and 2.3.2 for reference.)

### 2.4.2 Loeb et al. 2015

In the 2015 study, Loeb et al. (15) reported a nested case-control study performed within the Swedish Prescribed Drug Register. A total of 4,065 melanoma skin cancer cases diagnosed between 2006 and 2012 were identified and were compared with 20,325 cancer-free controls (15). The study reported a 21% increased risk of melanoma associated with the use of PDE5 inhibitors (sildenafil, vardenafil and tadalafil) (15) but the association was limited to those patients who had filled a single prescription. In addition, they also reported a modest association with basal cell carcinoma (15), a cancer that is not thought to involve the pathophysiological pathway (92-94). According to the authors, these unusual findings suggested that the association may not be causal. However, these findings are likely due to important methodological limitations. First, the register used in the study started in 2005, which was over 6 years after the first PDE5 inhibitor entered the market. As a result, some of the new users in the register could actually be prevalent users. Inclusion of these individuals (cases or controls) could lead to exposure misclassification thus biasing the results (95). Furthermore, the authors did not lag the exposure in the primary analysis. Lagging the exposure for latency purposes is necessary for observational

studies that investigate non-acute outcomes such as cancer. (See Section 4.4 for more details.) The authors were aware of this and conducted a sensitivity analysis where they applied a one-year lag period. The finding was not significant, thus not consistent with their primary analysis (OR:1.11 [0.94-1.31]).

### 2.4.3 Main limitations

As discussed in Section 2.4.1 and 2.4.2, there are a number of methodological limitations in the two previous studies (Li et al. 2014 and Loeb et al. 2015; Summarized in Table 3). In summary, the first study is subjected to exposure misclassification due to a single exposure measurement at baseline and recall bias due to the use of questionnaires. The second study was limited by exposure misclassification caused by the inclusion of prevalent users.

Given the limitations of the previous studies, and continued uncertainties related to the safety of PDE5 inhibitors, additional well-conducted studies are needed to investigate this possible association.

**Table 3: Two previous observational studies on the association between PDE5 inhibitors and skin cancer outcomes**

| Study | Li et al. 2014 | Loeb et al. 2015 |
|---|---|---|
| Study Design | Prospective cohort study | Nested case-control study |
| Exposure of interest | Sildenafil | Sildenafil, tadalafil and vardenafil |
| Outcome of interest | | |
| Melanoma | HR: 1.84 (1.04-3.22) | OR: 1.21 (1.08-1.36) |
| Basal cell carcinoma | HR: 1.08 (0.93-1.25) | OR: 1.19 (1.14-1.25) |
| Squamous cell carcinoma | HR: 0.84 (0.59-1.20) | OR: NA |
| Main limitations | Exposure misclassification<br>Recall bias | Exposure misclassification<br>Prevalent user bias |

# Chapter 3: Objectives and hypothesis

## 3.1 Objectives

The objective of this study is to determine whether the use of PDE5 inhibitors is associated with an increased the risk of melanoma and non-melanoma skin cancer, separately.

### 3.1.1 Primary aims

1. To determine whether the use of PDE5 inhibitors (sildenafil, tadalafil and vardenafil) is associated with an increased risk of melanoma skin cancer.

2. To determine whether the use of PDE5 inhibitors (sildenafil, tadalafil and vardenafil) is associated with an increased risk of non-melanoma skin cancer (basal and squamous cell carcinoma).

### 3.1.2 Secondary aims

1. To investigate whether there is duration-response relationship between the use of PDE5 inhibitors and the risk of melanoma skin cancer.

2. To assess the association with each of the three available PDE5 inhibitors (sildenafil, tadalafil and vardenafil) and the risk of melanoma skin cancer.

3. To assess the association with each of the three available PDE5 inhibitors (sildenafil, tadalafil and vardenafil) and the risk of each skin cancer type, separately (melanoma, basal and squamous cell carcinoma).

## 3.2 Hypotheses

### 3.2.1 Hypotheses of the primary aims

1. The use of PDE5 inhibitors is not associated with increased risk of melanoma skin cancer.

2. The use of PDE5 inhibitors is not associated with increased risk of non-melanoma skin cancer.

### 3.2.2 Hypotheses of the secondary aims

1. There is no duration-response relationship.

2. The association with melanoma does not vary across PDE5 inhibitor classes.

3. The association with non-melanoma does not vary across PDE5 inhibitor classes.

### 3.2.3 Rationale for the hypotheses

1. The mechanism proposed in previous studies has not been confirmed.

2. All three PDE5 inhibitors are short-acting drugs and are generally not used regularly.

# Chapter 4: Methods

## 4.1 Data source

The study was conducted using the UK Clinical Practice Research Datalink (CPRD). The CPRD, known as the General Practice Research Database (GPRD) before 2012, has data from as early as 1987. In the UK, general practitioner is the most important component of primary care (96). Over 98% of the UK population are registered with a primary care general practitioner, who are the first persons that the patients see for any non-emergency medical needs (96). Therefore, the CPRD is a rich source of longitudinal medical data that contains the medical records of more than 14 million patients (96) that have been shown be representative of the UK population in terms of age, sex and ethnicity (97). Patients are either treated under the primary care settings by their general practitioners or referred to secondary care (e.g. specialists). At each visit, general practice staff record patients' demographics, diagnoses, symptoms, signs, prescriptions, immunisations, behavioural factors, tests, and referrals to and feedbacks from secondary care. Diagnoses recorded in the CPRD have been shown to have high validity, with a median positive predictive value of 89% (97, 98). Prescriptions written by the general practitioners are automatically recorded, along with the dosage instructions and quantity, leaving no room for error (96). In summary, the CPRD is an ideal source for pharmacoepidemiology research.

The study protocol was approved by the Independent Scientific Advisory Committee of the CPRD (protocol number: 15_118A) (Section 8.1), and the Research Ethics Board of the Jewish General Hospital, Montreal, Canada.

## 4.2 Study population

I conducted a cohort study among all males newly-diagnosed with erectile dysfunction between January 1, 1998 (the year the first PDE5 inhibitor, sildenafil, entered the UK market) and June 30, 2014. Cohort entry was defined by the date of the first-ever erectile dysfunction diagnosis. Erectile dysfunction patients were determined by Read codes that are related to erectile dysfunction, impotence, referral to erectile dysfunction specialists, referral to psychological counselling for erectile dysfunction and other non-PDE5 inhibitor treatments for erectile dysfunction. (Appendix Table 1) The rationale behind assembling an incident cohort of patients with erectile dysfunction was to minimize potential confounding due to possible differences in various aspects between men with and without erectile dysfunction. To be included in the cohort, patients were required to be at least 40 years of age, have at least one year of baseline medical history, and have never been prescribed PDE5 inhibitors at any time before cohort entry (to minimize the inclusion of prevalent users). I also excluded patients diagnosed with any type of skin cancer (melanoma skin cancer and non-melanoma skin cancer, including basal cell carcinoma, squamous cell carcinoma, and other non-melanoma skin cancers; identified on the basis of Read codes [Appendix Table 2]) at any time before cohort entry. Finally, all patients were required to have at least one year of follow-up after cohort entry, which was necessary for latency purposes. These features were designed to overcome the limitations of previous studies discussed in Section 2.4 and details can be found in the following sections.

### 4.3 Follow-up of the incident erectile dysfunction cohort

Thus, patients meeting the study inclusion criteria were followed starting one year after cohort entry until an incident diagnosis of skin cancer (melanoma or non-melanoma skin cancer; the first to occur during follow-up), or censored upon death from any cause, end of registration with the general practice, or end of the study period (June 30, 2015), whichever occurred first. Patients with an incident diagnosis of skin cancer during the lag period were also excluded. However, I did not make the exclusion at this stage for programming reasons. Because I had sensitivity analyses investigating the effect of different lag periods, the exclusion of patients with an incident diagnosis of skin cancer was done at the beginning of each analysis, depending on the lag period applied.

### 4.4 Exposure definition

The use of PDE5 inhibitors (sildenafil, tadalafil, and vardenafil, Appendix Table 3) was treated as a time-varying variable in the models. Unlike most prescription drugs that have dosage instructions, PDE5 inhibitors are mostly used on an as-needed basis. This leads to difficulty capturing the exact duration of use, especially for those who had only one prescription. Therefore, I decided to use the following primary exposure definition that is simple and easy to interpret. Patients were considered unexposed until the year after the first PDE5 inhibitor prescription (i.e. after applying a one-year lag period) and considered exposed thereafter until the end of follow-up. Lagging the exposure was performed for latency purposes (by imposing a minimum etiological time window between treatment initiation and diagnosis of skin cancer), and to minimize detection bias (a situation where

the initiation of a drug is associated with more frequent physician visits and thus a greater probability of diagnosing cancer). The lag period was set to one year arbitrarily, meaning that any skin cancer events diagnosed within one year after the first PDE5 inhibitor prescription were not thought to be causally associated with the outcome. These events were therefore classified as unexposed events. I tested the robustness of my time-dependent analyses to varying lag period in the sensitivity analyses (Section 4.7.3).

I also considered two secondary time-dependent exposure definitions. In the first, I cumulated the total number of prescriptions received until the time of the event. In the second, I cumulated the total number of pills received up until the time of the event by summing the specified number of pills per prescription through all prescriptions. These measures were able to provide some information on the duration of PDE5 inhibitor use and were used in the one of the two previous observational studies on the topic (15). The reference category for all analyses was non-use of PDE5 inhibitors up until the time of the event.

## 4.5 Outcome definition

Within the erectile dysfunction cohort, I identified all patients with a first-ever diagnosis of melanoma and non-melanoma skin cancer (Appendix Table 2, B32* and some BBE* for melanoma and B33* for non-melanoma skin cancer, based on Read codes). If a patient was diagnosed with both skin cancer types during follow-up, the first cancer type was used for the analysis. If a patient was diagnosed with both skin cancer types on the same day, he was considered as a melanoma event.

For non-melanoma skin cancer diagnosis codes (B33*) that were unspecific (not basal cell carcinoma, squamous cell carcinoma, or other specific skin cancers), I looked back and forward up to 6 months for morphology medical codes (BB*) and/or excision procedure codes (7G*). If such codes were present and specific (basal cell carcinoma, squamous cell carcinoma, and other specific skin cancers), and all of such codes match the diagnosis code, the case was classified as the type of skin cancer in these codes (i.e. basal cell carcinoma, squamous cell carcinoma, and other specific skin cancers). The event date was defined by the date of the earliest of these codes (including the diagnosis code). If such codes were absent or still unspecific, the case was classified as unknown non-melanoma skin cancer. If more than one type (any combinations of basal cell carcinoma, squamous cell carcinoma and other specific skin cancer) of codes were found within the one-year range, or any of these codes did not match the diagnosis code, the skin cancer type of these patients could not be determined. Therefore, they were also considered as unknown non-melanoma skin cancer cases.

Only melanoma, basal cell carcinoma and squamous cell carcinoma outcomes were analysed. Other specific non-melanoma skin cancer or unknown non-melanoma skin cancer were not part of my research question. Therefore, patients that belonged to these two categories were also followed censored at the time of diagnosis but their skin cancer events were not analyzed as outcomes. The purpose of this algorithm was to improve the accuracy of skin cancer diagnoses and the time of these diagnoses.

### 4.6 Potential confounders

I adjusted the model for the following potential confounders measured at cohort entry: age, year of cohort entry, alcohol-related disorders, smoking status, BMI, Charlson Comorbidity Index, along with number of different drug classes and number of physician visits in the year before cohort entry. All of these variables are indicators of patients' general health status and are commonly adjusted for in many observational studies. The models also included known skin cancer risk factors, including presence of naevi, precancerous skin lesions, use of antiparkinsonian drugs, and immunosuppression (this variable included medical conditions that require immunosuppressants [rheumatoid arthritis, inflammatory bowel disease, psoriasis, lupus, vasculitis and previous organ transplant] and use of immunosuppressive and immunomodulatory drugs), all measured at any time before cohort entry. Finally, Brookhart et al. (99) showed, in a study on statin, that patients who are adherent to long-term therapies are more likely to seek out preventive health services, such as screening tests and vaccinations. Failure to account for these facts may lead to healthy user bias (a situation where healthy or health-conscious patients are more likely to be exposed) and surveillance bias (a situation where more preventive health services may increase the chance of the detection of any disease). PDE5 inhibitor is similar to statin in the sense that they are both used chronically to improve the quality of life. Therefore, users of PDE5 inhibitors may have different health-seeking behaviors than non-users, which may introduce healthy user bias and surveillance bias, I adjusted the models for the following indicators of health-seeking behavior: influenza vaccination, referral to

colonoscopy, prostate-specific antigen (PSA) testing, all measured in the year before cohort entry.

## 4.7 Statistical analysis

### 4.7.1 Primary analyses

I used descriptive statistics to summarize the characteristics of the entire cohort, and for those exposed and unexposed to PDE5 inhibitors at cohort entry. I also calculated crude incidence rates of melanoma and non-melanoma skin cancer with 95% confidence intervals (CIs) based on the Poisson distribution.

Time-dependent Cox proportional hazards models were used to estimate hazard ratios (HRs) with 95% CIs of incident melanoma skin cancer, comparing the use of PDE5 inhibitors with non-use. For comparison purposes, I conducted identical analyses for basal cell carcinoma and squamous cell carcinoma, two non-melanoma skin cancers which are not thought to involve PDE5 pathways (92-94, 100). All models were adjusted for the potential confounders listed above (Section 4.6).

### 4.7.2 Secondary analyses

I conducted three secondary analyses. The first and second assessed whether there was an association in terms of total number of prescriptions and pills received (Section 4.4). These variables were entered in tertile categories in the models, based on the distribution of use in the cohort. Finally, the third analysis assessed whether the risk varied by type of PDE5 inhibitor. Thus, for this analysis, the use of PDE5 inhibitors was further

categorized into the following four mutually-exclusive time-varying exposure categories: sildenafil only, tadalafil only, vardenafil only, and use of more than one type.

### 4.7.3 Sensitivity analyses

I conducted seven sensitivity analyses to assess the robustness of my findings. First, given uncertainties related to the latency time window between treatment initiation and development of melanoma skin cancer, I repeated the analyses by varying the exposure lag period to 0 months (no lag), 6 months, and 2 years. Second, users of PDE5 inhibitors tend to be of higher socioeconomic status (15), a variable that has been associated with both health-seeking behaviors (101) and a higher incidence of skin cancer (102). Thus, I repeated the analyses after restricting the cohort to patients with at least one health-seeking behavior (influenza vaccination, referral to colonoscopy and PSA testing) in the year before cohort entry. Third, to account for the fact that non-users may be more likely to be those with contraindications to PDE5 inhibitors, I repeated the analyses after excluding at baseline and censoring upon follow-up patients with cardiovascular contraindications (myocardial infarction, stroke, congestive heart failure, coronary artery disease, hypertension, hypotension, angina, use of antihypertensive drugs, and use of nitrates). Fourth, given the possible association between prostate cancer and melanoma skin cancer (103), I repeated the analyses by excluding and censoring upon a diagnosis of prostate cancer. Fifth, I repeated the analyses after considering competing risks due to deaths from any cause using the subdistribution hazards model proposed by Fine and Gray (104). Sixth, I used multiple imputation methods for smoking status and body mass index, two variables with missing information (105). Finally, because of the relatively long follow-up and

potential time-dependent confounding, I repeated the analysis with marginal structural models using inverse probability of treatment and censoring weighting (106). The exposure status, as well as all the potential confounders (Section 4.6), were updated every 30-day time intervals starting from cohort entry. Pooled logistic regression was used to estimate the probability of being exposed, conditional on the covariates measured in the preceding time interval. For each patient, the (unstabilized) IPTW was equal to the cumulative product of the inverse probabilities up to each time interval. Upon investigating the distribution of the unstabilized weights, stabilized weights were used (unstabilized weights multiplied by the predicted probability of receiving the observed treatment conditional on the covariates measured at cohort entry). The stabilized IPCW was estimated in a similar fashion. A pseudo-population was constructed, weighted by the product of the IPTWs and IPCWs. Finally, a Cox proportional hazards model was used to estimate the HR of melanoma skin cancer within this pseudo-population, with CIs estimated using robust variance estimators (107). All analyses were conducted with SAS version 9.4 (SAS Institute, Cary, NC).

# Chapter 5: Results

## 5.1 Characteristics of the study population

The cohort included 142,983 patients with erectile dysfunction (Figure 1), where the mean (standard deviation [SD]) age at cohort entry was 59.0 (10.2) years and the mean (SD) follow-up was 4.9 (3.8) years. Overall, users and non-users of PDE5 inhibitors were similar on most characteristics, with the exception of PDE5 inhibitor users having a lower comorbidity score, and fewer physician visits, but being more likely of having an influenza vaccination and a PSA test in the year before cohort entry (Table 4).

**Figure 1: Study flow diagram describing the assembly of the erectile dysfunction cohort using the UK Clinical Practice Research Datalink**

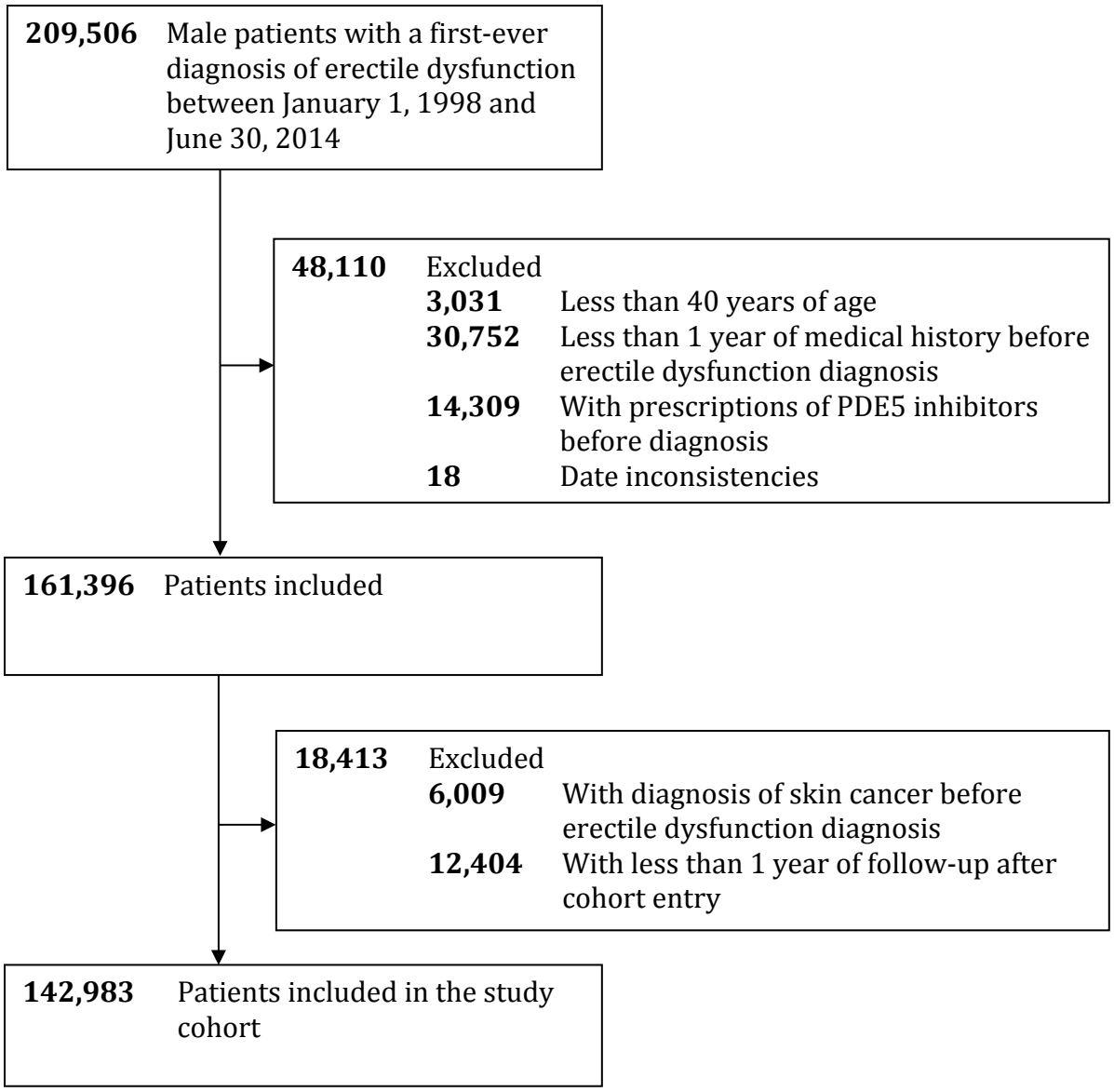


**Table 4: Baseline characteristics of the cohort overall, and according to use of phosphodiesterase 5 inhibitors at cohort entry**

| Characteristic | | PDE5 inhibitors† | |
|---|---|---|---|
| | Entire cohort | Use | No use |
| Number | 142,983 | 58,732 | 84,611 |
| Age, years (mean, SD) | 59.0 (10.2) | 58.8 (9.8) | 59.2 (10.4) |
| Alcohol-related disorders, n (%) | 18,978 (13.3) | 7,220 (12.4) | 11,758 (13.9) |
| Smoking status, n (%) | | | |
| Current | 30,007 (21.0) | 12,248 (21.0) | 17,759 (21.0) |
| Past | 49,650 (34.7) | 20,216 (34.6) | 29,434 (34.8) |
| Unknown | 4,270 (3.0) | 1,485 (2.6) | 2,785 (3.3) |
| Body mass index, n (%) | | | |
| < 25.0 kg/m$^2$ | 31,738 (22.2) | 13,596 (23.3) | 18,142 (21.4) |
| 25-29.9 kg/m$^2$ | 56,121 (39.3) | 23,314 (39.9) | 32,807 (38.8) |
| ≥ 30.0 kg/m$^2$ | 38,750 (27.1) | 14,751 (25.3) | 23,999 (28.4) |
| Unknown | 16,374 (11.5) | 6,711 (11.5) | 9,663 (11.4) |
| Precancerous skin lesions, n (%) | 19,633 (13.7) | 8,203 (14.1) | 11,430 (13.5) |
| Presence of naevi, n (%) | 7,621 (5.3) | 3,272 (5.6) | 4,349 (5.1) |
| Immunosuppression, n (%) | 14,959 (10.5) | 6,335 (10.9) | 8,624 (10.2) |
| Antiparkinsonian drugs, n (%) | 2,215 (1.6) | 734 (1.3) | 1,481 (1.8) |
| Charlson comorbidity score, n (%) | | | |
| 0 | 72,424 (50.7) | 30,035 (51.5) | 42,389 (50.1) |
| 1-2 | 53,199 (37.2) | 23,083 (39.5) | 30,116 (35.6) |
| ≥ 3 | 17,360 (12.1) | 5,254 (9.0) | 12,106 (14.3) |
| No. of different drug classes, mean (SD)* | 5.6 (5.2) | 5.3 (4.8) | 5.7 (5.5) |
| No. of physician visits, (mean, SD) | 4.5 (6.8) | 4.3 (6.4) | 4.6 (7.1) |
| | | | |
| Health-seeking related variables* | | | |
| Influenza vaccination, n (%) | 43,838 (30.7) | 20,396 (34.9) | 23,442 (27.7) |
| Referral to colonoscopy, n (%) | 1,447 (1.0) | 604 (1.0) | 843 (1.0) |
| Prostate-specific antigen testing, n (%) | 17,797 (12.5) | 8,271 (14.2) | 9,526 (11.3) |

* Measured in the year before cohort entry.
† Among patients who received a prescription on the same day as cohort entry (i.e. first-ever diagnosis of erectile dysfunction.

The cohort generated 698,479 person-years of follow-up, during which time 440 patients were newly-diagnosed with melanoma skin cancer, generating a crude incidence rate (95% CI) of 63.0 (57.2-69.2) per 100,000 person-years. A total of 3253 and 332 patients were diagnosed with basal cell carcinoma and squamous cell carcinoma, generating crude incidence rates (95% CI) of 465.7 (449.9-482.0) and of 47.5 (42.6-52.9) per 100,000 person-years, respectively.

### 5.2 Melanoma skin cancer

Overall, the use of PDE5 inhibitors was not associated with a statistically significant increased risk of melanoma skin cancer (66.7 versus 54.1 per 100,000 person-years; adjusted HR: 1.18, 95% CI: 0.95-1.47; Table 5). In secondary analyses, a duration-response relationship was observed with receiving ≥7 prescriptions associated with a 30% increased risk of melanoma skin cancer (adjusted HR: 1.30, 95% CI: 1.01-1.69). The median (interquartile range) number of prescriptions among those who received ≥7 prescriptions was 20 (28). Similarly, receiving ≥25 pills was associated with 34% increased risk of melanoma skin cancer (adjusted HR: 1.34, 95% CI: 1.04-1.72, respectively). No single drug was statistically associated with an increased risk of melanoma skin cancer due to the fewer events in each exposure category, although the HR for sildenafil was elevated (HR: 1.22, 95% CI: 0.97-1.54; Figure 2).

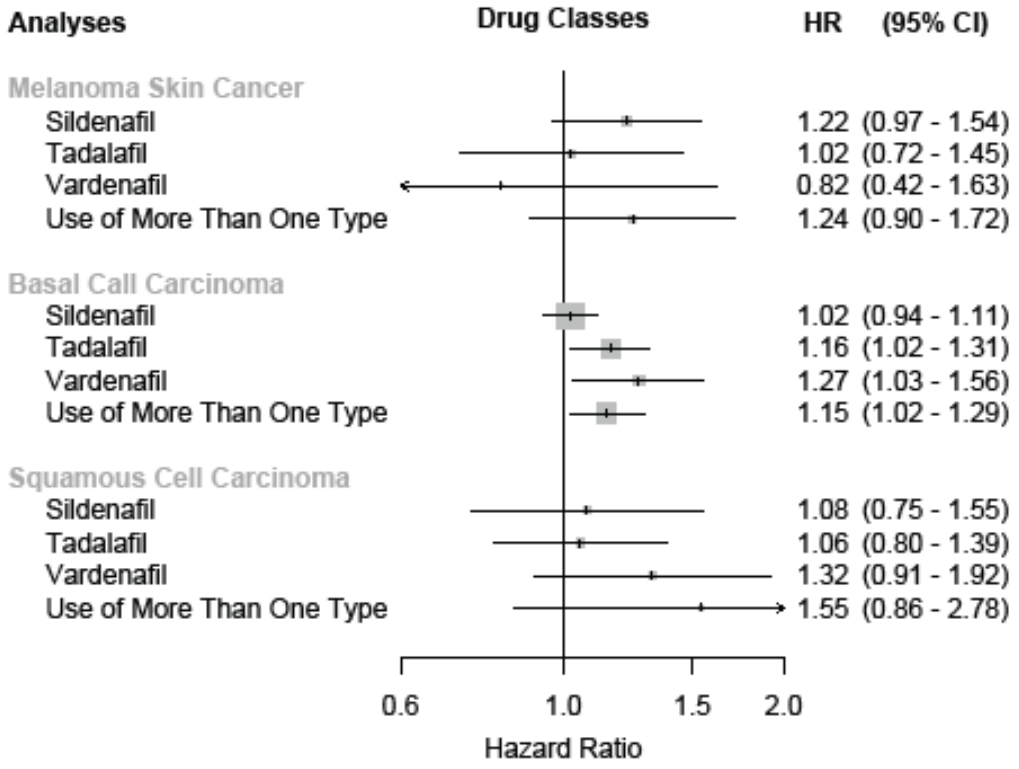
**Table 5: Crude and adjusted hazard ratios for the primary and secondary analyses assessing the association between phosphodiesterase 5 inhibitors and the risk of melanoma skin cancer in a cohort of patients with erectile dysfunction**

| Phosphodiesterase 5 inhibitor use | Events | Person-years | Incidence rate (95% CI)* | Crude HR | Adjusted HR (95% CI)† |
|---|---|---|---|---|---|
| Primary analysis | | | | | |
| No use | 112 | 207,001 | 54.1 (44.6-65.1) | 1.00 | 1.00 [Reference] |
| Use | 328 | 491,478 | 66.7 (59.7-74.4) | 1.19 | 1.18 (0.95-1.47) |
| | | | | | |
| No. of prescriptions | | | | | |
| 1 | 102 | 156,051 | 65.4 (53.3-79.3) | 1.20 | 1.15 (0.88-1.51) |
| 2-6 | 97 | 159,915 | 60.7 (49.2-74.0) | 1.09 | 1.07 (0.82-1.41) |
| ≥ 7 | 129 | 175,512 | 73.5 (61.4-87.3) | 1.28 | 1.30 (1.01-1.69) |
| | | | | | |
| No. of pills | | | | | |
| 1-4 | 90 | 135,337 | 66.5 (53.5-81.7) | 1.21 | 1.17 (0.88-1.55) |
| 5-24 | 89 | 157,383 | 56.5 (45.4-69.6) | 1.02 | 1.00 (0.75-1.32) |
| ≥ 25 | 149 | 198,758 | 75.0 (63.4-88.0) | 1.31 | 1.34 (1.04-1.72) |

* Per 100 000 person-years.

† Adjusted for age, year of cohort entry, alcohol-related disorders, smoking status, body mass index, precancerous skin lesions, presence of naevi, immunosuppression, use of antiparkinsonian drugs, Charlson comorbidity score, number of different drug classes used, and number of physician visits in the year before cohort entry, and health-seeking–related variables (influenza vaccination, referral to colonoscopy, and prostate-specific antigen testing, all measured in the year before cohort entry).

**Figure 2: Adjusted Hazard Ratios for the secondary analyses assessing the association between different PDE5 inhibitor drugs and the risk of melanoma skin cancer, basal cell carcinoma, and squamous cell carcinoma**



### 5.3 Non-melanoma skin cancer

Compared with non-use, the use of PDE5 inhibitors was not associated with increased risk of basal cell carcinoma or squamous cell carcinoma (HR: 1.07, 95% CI: 0.99-1.16 and HR: 1.12, 95% CI: 0.87-1.44, respectively; Table 6-7). In secondary analyses, there was no clear duration-response relationship in terms of number of prescriptions and pills received (Table 6-7). The use of tadalafil, vardenafil, and use of more than one type of drug were all associated with an increased risk of basal cell carcinoma. These associations were not observed with squamous cell carcinoma (Figure 2).

**Table 6: Crude and adjusted hazard ratios for the primary and secondary analyses assessing the association between phosphodiesterase 5 inhibitors and the risk of basal cell carcinoma in a cohort of patients with erectile dysfunction**

| Phosphodiesterase 5 inhibitor use | Events | Person-years | Incidence rate (95% CI)* | Crude HR | Adjusted HR (95% CI)† |
|---|---|---|---|---|---|
| Primary analysis | | | | | |
| No use | 900 | 207,001 | 434.8 (406.8-464.1) | 1.00 | 1.00 [Reference] |
| Use | 2,353 | 491,478 | 478.8 (459.6-498.5) | 1.05 | 1.07 (0.99-1.16) |
| No. of prescriptions | | | | | |
| 1 | 697 | 156,051 | 446.6 (414.1-481.1) | 1.02 | 1.01 (0.91-1.11) |
| 2-6 | 818 | 159,915 | 511.5 (477.1-547.8) | 1.14 | 1.15 (1.04-1.26) |
| ≥ 7 | 838 | 175,512 | 477.5 (445.7-510.9) | 1.01 | 1.06 (0.97-1.17) |
| No. of pills | | | | | |
| 1-4 | 612 | 135,337 | 452.2 (417.1-489.5) | 1.03 | 1.01 (0.91-1.12) |
| 5-24 | 781 | 157,383 | 496.2 (462.0-532.3) | 1.11 | 1.11 (1.01-1.22) |
| ≥ 25 | 960 | 198,758 | 483.0 (452.9-514.5) | 1.03 | 1.09 (0.99-1.20) |

* Per 100 000 person-years.

† Adjusted for age, year of cohort entry, alcohol-related disorders, smoking status, body mass index, precancerous skin lesions, presence of naevi, immunosuppression, use of antiparkinsonian drugs, Charlson comorbidity score, number of different drug classes used, and number of physician visits in the year before cohort entry, and health-seeking–related variables (influenza vaccination, referral to colonoscopy, and prostate-specific antigen testing, all measured in the year before cohort entry).

**Table 7: Crude and adjusted hazard ratios for the primary and secondary analyses assessing the association between phosphodiesterase 5 inhibitors and the risk of squamous cell carcinoma in a cohort of patients with erectile dysfunction**

| Phosphodiesterase 5 inhibitor use | Events | Person-years | Incidence rate (95% CI)* | Crude HR | Adjusted HR (95% CI)† |
|---|---|---|---|---|---|
| Primary analysis | | | | | |
| No use | 84 | 207,001 | 40.6 (32.4-50.2) | 1.00 | 1.00 [Reference] |
| Use | 248 | 491,478 | 50.5 (44.4-57.1) | 1.12 | 1.12 (0.87-1.44) |
| No. of prescriptions | | | | | |
| 1 | 77 | 156,051 | 49.3 (38.9-61.7) | 1.22 | 1.12 (0.82-1.54) |
| 2-6 | 82 | 159,915 | 51.3 (40.8-63.6) | 1.17 | 1.17 (0.86-1.59) |
| ≥ 7 | 89 | 175,512 | 50.7 (40.7-62.4) | 1.00 | 1.07 (0.79-1.46) |
| No. of pills | | | | | |
| 1-4 | 71 | 135,337 | 52.5 (41.0-66.2) | 1.30 | 1.18 (0.86-1.63) |
| 5-24 | 81 | 157,383 | 51.5 (40.9-64.0) | 1.18 | 1.16 (0.85-1.58) |
| ≥ 25 | 96 | 198,758 | 48.3 (39.1-59.0) | 0.97 | 1.04 (0.77-1.41) |

* Per 100 000 person-years.

† Adjusted for age, year of cohort entry, alcohol-related disorders, smoking status, body mass index, precancerous skin lesions, presence of naevi, immunosuppression, use of antiparkinsonian drugs, Charlson comorbidity score, number of different drug classes used, and number of physician visits in the year before cohort entry, and health-seeking–related variables (influenza vaccination, referral to colonoscopy, and prostate-specific antigen testing, all measured in the year before cohort entry).

## 5.4 Sensitivity analyses

Overall, the results of the sensitivity analyses yielded consistent findings, with the exception of two sensitivity analyses (Tables 8-14). Figure 3, at the end of this section, is a summary of the sensitivity analyses with patterns in terms of total number of prescriptions and pills received.

Firstly, my time-dependent exposure definition and analyses were robust to varying lag periods. As shown in Table 8-10, the overall use of PDE5 inhibitors is not associated with an increased risk of melanoma in the three analyses with different lag periods (0 month, HR: 1.18, 95% CI: 0.96-1.44; 6 months, HR: 1.19,95% CI: 0.97-1.47; 2 years, HR: 1.23,95% CI: 0.97-1.56) However, receiving ≥7 prescriptions and ≥25 pills was associated with increased risk of melanoma (Figure 3, Table 8-10). These findings were consistent with the primary analyses.

**Table 8: Crude and adjusted hazard ratios for the sensitivity analysis (with no lag period) assessing the association between phosphodiesterase 5 inhibitors and the risk of melanoma skin cancer in a cohort of patients with erectile dysfunction**

| Phosphodiesterase 5 inhibitor use | Events | Person-years | Incidence rate (95% CI)* | Crude HR | Adjusted HR (95% CI)† |
|---|---|---|---|---|---|
| Primary analysis | | | | | |
| No use | 134 | 253,076 | 52.9 (44.4-62.7) | 1 | 1.00 [Reference] |
| Use | 381 | 594,959 | 64.0 (57.8-70.8) | 1.17 | 1.18 (0.96-1.44) |
| No. of prescriptions | | | | | |
| 1 | 141 | 214,693 | 65.7 (55.3-77.5) | 1.24 | 1.22 (0.96-1.55) |
| 2-6 | 110 | 198,087 | 55.5 (45.6-66.9) | 1.03 | 1.03 (0.80-1.33) |
| ≥ 7 | 130 | 182,178 | 71.4 (59.6-84.7) | 1.24 | 1.28 (1.00-1.65) |
| No. of pills | | | | | |
| 1-4 | 127 | 185,031 | 68.6 (57.2-81.7) | 1.29 | 1.27 (1.00-1.63) |
| 5-24 | 102 | 199,551 | 51.1 (41.7-62.0) | 0.95 | 0.95 (0.73-1.23) |
| ≥ 25 | 152 | 210,377 | 72.3 (61.2-84.7) | 1.27 | 1.32 (1.03-1.68) |

* Per 100 000 person-years.

† Adjusted for age, year of cohort entry, alcohol-related disorders, smoking status, body mass index, precancerous skin lesions, presence of naevi, immunosuppression, use of antiparkinsonian drugs, Charlson comorbidity score, number of different drug classes used, and number of physician visits in the year before cohort entry, and health-seeking–related variables (influenza vaccination, referral to colonoscopy, and prostate-specific antigen testing, all measured in the year before cohort entry).

**Table 9: Crude and adjusted hazard ratios for the sensitivity analysis (6-month lag period) assessing the association between phosphodiesterase 5 inhibitors and the risk of melanoma skin cancer in a cohort of patients with erectile dysfunction**

| Phosphodiesterase 5 inhibitor use | Events | Person-years | Incidence rate (95% CI)* | Crude HR | Adjusted HR (95% CI)† |
|---|---|---|---|---|---|
| Primary analysis | | | | | |
| No use | 120 | 229,903 | 56.1 (46.8-66.7) | 1.00 | 1.00 [Reference] |
| Use | 352 | 542,800 | 64.8 (58.3-72.0) | 1.19 | 1.19 (0.97-1.47) |
| No. of prescriptions | | | | | |
| 1 | 120 | 180,370 | 66.5 (55.2-79.6) | 1.26 | 1.24 (0.96-1.60) |
| 2-6 | 102 | 180,819 | 56.4 (46.0-68.5) | 1.05 | 1.05 (0.80-1.36) |
| ≥ 7 | 130 | 181,611 | 71.6 (59.8-85.0) | 1.26 | 1.30 (1.00-1.67) |
| No. of pills | | | | | |
| 1-4 | 108 | 156,154 | 69.2 (56.7-83.5) | 1.31 | 1.28 (0.99-1.67) |
| 5-24 | 92 | 178,439 | 51.6 (41.6-63.2) | 0.96 | 0.95 (0.72-1.25) |
| ≥ 25 | 152 | 208,207 | 73.0 (61.9-85.6) | 1.29 | 1.33 (1.04-1.71) |

* Per 100 000 person-years.

† Adjusted for age, year of cohort entry, alcohol-related disorders, smoking status, body mass index, precancerous skin lesions, presence of naevi, immunosuppression, use of antiparkinsonian drugs, Charlson comorbidity score, number of different drug classes used, and number of physician visits in the year before cohort entry, and health-seeking–related variables (influenza vaccination, referral to colonoscopy, and prostate-specific antigen testing, all measured in the year before cohort entry).

**Table 10: Crude and adjusted hazard ratios for the sensitivity analysis (2-year lag period) assessing the association between phosphodiesterase 5 inhibitors and the risk of melanoma skin cancer in a cohort of patients with erectile dysfunction**

| Phosphodiesterase 5 inhibitor use | Events | Person-years | Incidence rate (95% CI)* | Crude HR | Adjusted HR (95% CI)† |
|---|---|---|---|---|---|
| Primary analysis | | | | | |
| No use | 91 | 168,290 | 54.1 (43.5-66.4) | 1.00 | 1.00 [Reference] |
| Use | 280 | 399,874 | 70.0 (62.1-78.7) | 1.27 | 1.23 (0.97-1.56) |
| No. of prescriptions | | | | | |
| 1 | 91 | 118,566 | 76.8 (61.8-94.2) | 1.41 | 1.33 (0.99-1.78) |
| 2-6 | 75 | 126,891 | 59.1 (46.5-74.1) | 1.08 | 1.03 (0.76-1.40) |
| ≥ 7 | 114 | 154,417 | 73.8 (60.9-88.7) | 1.32 | 1.31 (0.99-1.74) |
| No. of pills | | | | | |
| 1-4 | 80 | 102,948 | 77.7 (61.6-96.7) | 1.43 | 1.34 (0.99-1.82) |
| 5-24 | 72 | 124,530 | 57.8 (45.2-72.8) | 1.05 | 1.00 (0.74-1.37) |
| ≥ 25 | 128 | 172,397 | 74.2 (61.9-88.3) | 1.33 | 1.32 (1.01-1.74) |

* Per 100 000 person-years.

† Adjusted for age, year of cohort entry, alcohol-related disorders, smoking status, body mass index, precancerous skin lesions, presence of naevi, immunosuppression, use of antiparkinsonian drugs, Charlson comorbidity score, number of different drug classes used, and number of physician visits in the year before cohort entry, and health-seeking–related variables (influenza vaccination, referral to colonoscopy, and prostate-specific antigen testing, all measured in the year before cohort entry).

Table 11 presents the results of the sensitivity analyses where I restricted to patients with at least one health seeking behavior in the year prior to cohort entry. This sub-cohort represents a group of patients that were more health-conscious thus were more likely to be diagnosed should they had developed skin cancer. The findings did not agree with the primary analysis. Specifically, the overall use of PDE5 inhibitors was associated with an increased risk of melanoma skin cancer (HR: 1.46, 95% CI: 1.05-2.04). Similar to the primary analysis, there is evidence of a duration-response relationship (≥7 prescriptions, HR: 1.64, 95% CI: 1.12-2.40 and ≥25 pills, HR: 1.69, 95% CI: 1.16-2.45; Table 11).

**Table 11: Crude and adjusted hazard ratios for the sensitivity analysis assessing the association between phosphodiesterase 5 inhibitors and the risk of melanoma skin cancer in a cohort restricted to patients with health-seeking behaviors**

| Phosphodiesterase 5 inhibitor use | Events | Person-years | Incidence rate (95% CI)* | Crude HR | Adjusted HR (95% CI)† |
|---|---|---|---|---|---|
| Primary analysis | | | | | |
| No use | 45 | 78,550 | 57.3 (41.8-76.7) | 1.00 | 1.00 [Reference] |
| Use | 169 | 195,566 | 86.4 (73.9-100.5) | 1.44 | 1.46 (1.05-2.04) |
| No. of prescriptions | | | | | |
| 1 | 49 | 58,476 | 83.8 (62.0-110.8) | 1.45 | 1.36 (0.90-2.04) |
| 2-6 | 50 | 61,268 | 81.6 (60.6-107.6) | 1.38 | 1.37 (0.91-2.06) |
| ≥ 7 | 70 | 75,822 | 92.3 (72.0-116.6) | 1.48 | 1.64 (1.12-2.40) |
| No. of pills | | | | | |
| 1-4 | 46 | 50,942 | 90.3 (66.1-120.4) | 1.56 | 1.46 (0.96-2.21) |
| 5-24 | 43 | 60,567 | 71.0 (51.4-95.6) | 1.20 | 1.18 (0.78-1.80) |
| ≥ 25 | 80 | 84,057 | 95.2 (75.5-118.5) | 1.54 | 1.69 (1.16-2.45) |

* Per 100 000 person-years.

† Adjusted for age, year of cohort entry, alcohol-related disorders, smoking status, body mass index, precancerous skin lesions, presence of naevi, immunosuppression, use of antiparkinsonian drugs, Charlson comorbidity score, number of different drug classes used, and number of physician visits in the year before cohort entry, and health-seeking–related variables (influenza vaccination, referral to colonoscopy, and prostate-specific antigen testing, all measured in the year before cohort entry).

Similarly, excluding and censoring patients with cardiovascular contraindications led to a higher overall HR for melanoma skin cancer (Table 12, HR: 1.47, 95% CI: 0.90-2.40). The finding was not statistically significant due to limited number of events but the estimated HR was elevated. In addition, this analysis exhibited clear evidence of a duration-response relationship (≥7 prescriptions, HR: 1.85, 95% CI: 1.05-3.26 and ≥25 pills, HR: 1.84, 95% CI: 1.06-3.18; Figure 3 and Table 12). The rationale of this analysis was to mimic a randomized controlled trial where patients with cardiovascular contraindications and warnings of the drug were excluded.

However, the next sensitivity analysis where I excluded and censored patients with prostate cancer yielded consistent findings to the primary analysis (Table 13), in terms of both overall use (HR: 1.21, 95% CI: 0.97-1.51) and duration-response relationship (≥7 prescriptions, HR: 1.35, 95% CI:1.04-1.76; ≥25 pills, HR: 1.39, 95% CI:1.07-1.79).

**Table 12: Crude and adjusted hazard ratios for the sensitivity analysis assessing the association between phosphodiesterase 5 inhibitors and the risk of melanoma skin cancer in a cohort excluding at baseline and censoring upon follow-up patients with cardiovascular contraindications**

| Phosphodiesterase 5 inhibitor use | Events | Person-years | Incidence rate (95% CI)* | Crude HR | Adjusted HR (95% CI) † |
|---|---|---|---|---|---|
| Primary analysis | | | | | |
| No use | 20 | 58,077 | 34.4 (21.0-53.2) | 1.00 | 1.00 [Reference] |
| Use | 90 | 155,719 | 57.8 (46.5-71.0) | 1.64 | 1.47 (0.90-2.40) |
| No. of prescriptions | | | | | |
| 1 | 27 | 56,035 | 48.2 (31.8-70.1) | 1.37 | 1.24 (0.69-2.22) |
| 2-6 | 30 | 53,999 | 55.6 (37.5-79.3) | 1.58 | 1.41 (0.80-2.49) |
| ≥ 7 | 33 | 45,685 | 72.2 (49.7-101.4) | 2.06 | 1.85 (1.05-3.26) |
| No. of pills | | | | | |
| 1-4 | 23 | 48,307 | 47.6 (30.2-71.4) | 1.35 | 1.23 (0.67-2.24) |
| 5-24 | 28 | 53,119 | 52.7 (35.0-76.2) | 1.50 | 1.34 (0.75-2.38) |
| ≥ 25 | 39 | 54,293 | 71.8 (51.1-98.2) | 2.05 | 1.84 (1.06-3.18) |

* Per 100 000 person-years.

† Adjusted for age, year of cohort entry, alcohol-related disorders, smoking status, body mass index, precancerous skin lesions, presence of naevi, immunosuppression, use of antiparkinsonian drugs, Charlson comorbidity score, number of different drug classes used, and number of physician visits in the year before cohort entry, and health-seeking–related variables (influenza vaccination, referral to colonoscopy, and prostate-specific antigen testing, all measured in the year before cohort entry).

**Table 13: Crude and adjusted hazard ratios for the sensitivity analysis assessing the association between phosphodiesterase 5 inhibitors and the risk of melanoma skin cancer in a cohort excluding at baseline and censoring upon follow-up patients with prostate cancer**

| Phosphodiesterase 5 inhibitor use | Events | Person-years | Incidence rate (95% CI)* | Crude HR | Adjusted HR (95% CI) † |
|---|---|---|---|---|---|
| Primary analysis | | | | | |
| No use | 108 | 201,234 | 53.7 (44.0-64.8) | 1.00 | 1.00 [Reference] |
| Use | 316 | 469,126 | 67.4 (60.1-75.2) | 1.22 | 1.21 (0.97-1.51) |
| No. of prescriptions | | | | | |
| 1 | 99 | 150,803 | 65.6 (53.4-79.9) | 1.21 | 1.17 (0.89-1.55) |
| 2-6 | 93 | 152,450 | 61.0 (49.2-74.7) | 1.11 | 1.10 (0.83-1.45) |
| ≥ 7 | 124 | 165,873 | 74.8 (62.2-89.1) | 1.32 | 1.35 (1.04-1.76) |
| No. of pills | | | | | |
| 1-4 | 87 | 131,073 | 66.4 (53.2-81.9) | 1.23 | 1.18 (0.89-1.57) |
| 5-24 | 86 | 150,294 | 57.2 (45.8-70.7) | 1.04 | 1.03 (0.77-1.36) |
| ≥ 25 | 143 | 187,760 | 76.2 (64.2-89.7) | 1.35 | 1.39 (1.07-1.79) |

* Per 100 000 person-years.

† Adjusted for age, year of cohort entry, alcohol-related disorders, smoking status, body mass index, precancerous skin lesions, presence of naevi, immunosuppression, use of antiparkinsonian drugs, Charlson comorbidity score, number of different drug classes used, and number of physician visits in the year before cohort entry, and health-seeking–related variables (influenza vaccination, referral to colonoscopy, and prostate-specific antigen testing, all measured in the year before cohort entry).

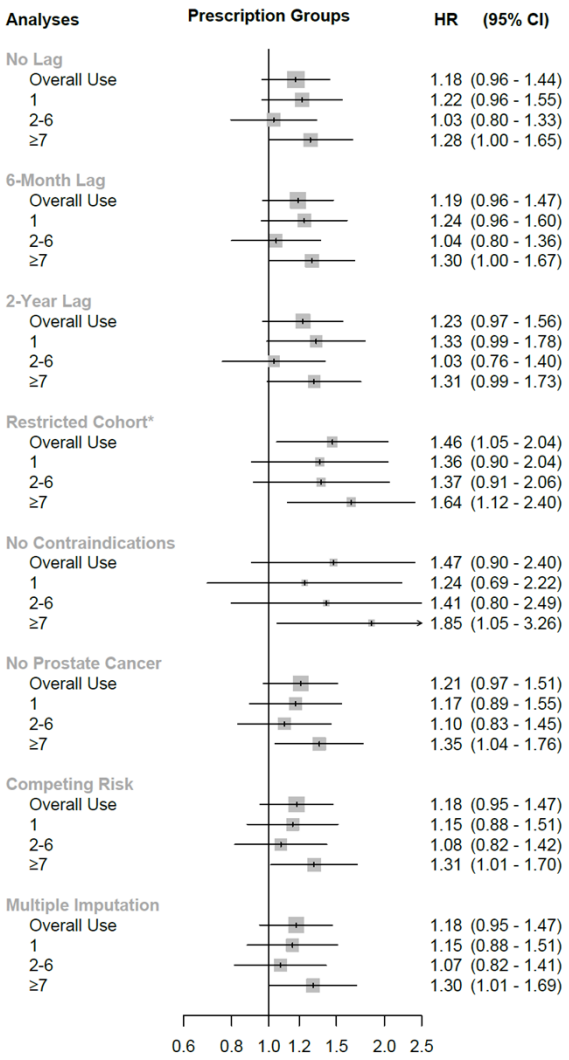
The remaining three sensitivity analyses accounted for competing risk due to death from any cause, missing data in smoking status and BMI, and potential time-dependent confounding and informative censoring. They all generated consistent results to the primary analyses. First, the subdistribution hazards model did not report an increased risk (HR: 1.18, 95% CI: 0.95-1.47, Table 14). Next, the imputed dataset showed no increased risk either (HR: 1.18, 95% CI: 0.95-1.47). Finally, the marginal structural model yielded consistent results (marginal HR: 1.11, 95% CI: 0.83-1.47).

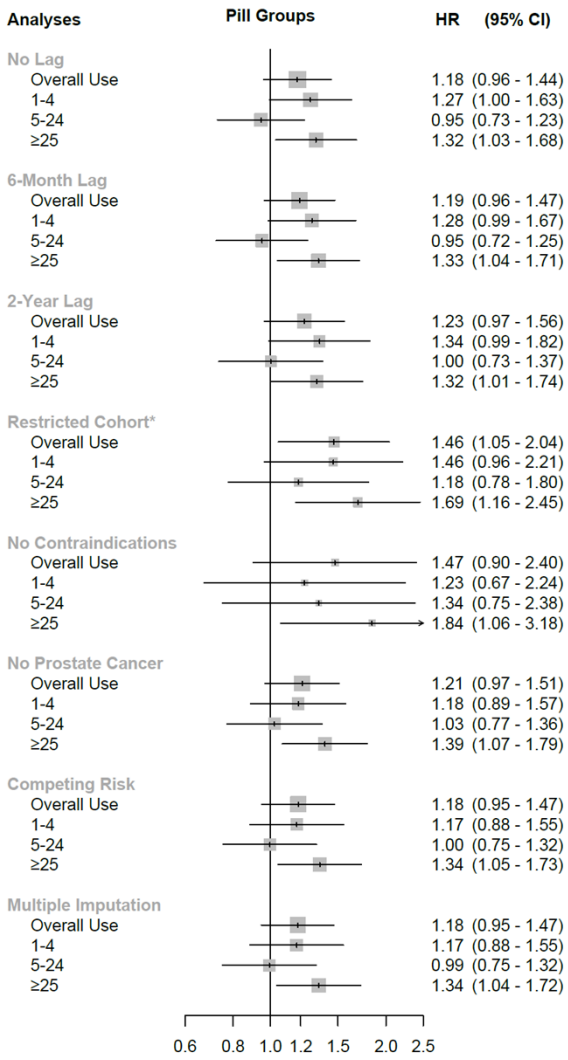
**Table 14: Crude and adjusted hazard ratios for the sensitivity analysis assessing the association between phosphodiesterase 5 inhibitors and the risk of melanoma skin cancer in a cohort restricted to patients with erectile dysfunction, considering competing risks due to death from any cause**

| Phosphodiesterase 5 inhibitor use | Events | Person-years | Incidence rate (95% CI)* | Crude HR | Adjusted HR (95% CI)† |
|---|---|---|---|---|---|
| Primary analysis | | | | | |
| No use | 112 | 207,001 | 54.1 (44.6-65.1) | 1.00 | 1.00 [Reference] |
| Use | 328 | 491,478 | 66.7 (59.7-74.4) | 1.20 | 1.18 (0.95-1.47) |
| No. of prescriptions | | | | | |
| 1 | 102 | 156,051 | 65.4 (53.3-79.3) | 1.20 | 1.15 (0.88-1.51) |
| 2-6 | 97 | 159,915 | 60.7 (49.2-74.0) | 1.10 | 1.08 (0.82-1.42) |
| ≥ 7 | 129 | 175,512 | 73.5 (61.4-87.3) | 1.29 | 1.31 (1.01-1.70) |
| No. of pills | | | | | |
| 1-4 | 90 | 135,337 | 66.5 (53.5-81.7) | 1.22 | 1.17 (0.88-1.55) |
| 5-24 | 89 | 157,383 | 56.5 (45.4-69.6) | 1.02 | 1.00 (0.75-1.32) |
| ≥ 25 | 149 | 198,758 | 75.0 (63.4-88.0) | 1.32 | 1.35 (1.05-1.73 ) |

* Per 100 000 person-years.

† Adjusted for age, year of cohort entry, alcohol-related disorders, smoking status, body mass index, precancerous skin lesions, presence of naevi, immunosuppression, use of antiparkinsonian drugs, Charlson comorbidity score, number of different drug classes used, and number of physician visits in the year before cohort entry, and health-seeking–related variables (influenza vaccination, referral to colonoscopy, and prostate-specific antigen testing, all measured in the year before cohort entry).




* Cohort restricted to patients with at least one health-seeking behavior (influenza vaccination, referral to colonoscopy and PSA testing) in the year before cohort entry.

**Figure 3: Forest plots summarizing the sensitivity analyses for melanoma skin cancer**

# Chapter 6: Discussion

## 6.1 General findings

The findings of this large, population-based study, indicate that the use of PDE5 inhibitors is not associated with an overall increased risk of melanoma skin cancer, but with the risk increasing with number of prescriptions and pills received (30% and 34% increased risk, respectively). These findings remained consistent in several sensitivity analyses. In contrast, the use of PDE5 inhibitors was not associated with an increased risk of basal cell carcinoma and squamous cell carcinoma.

## 6.2 Comparison with previous literature

To my knowledge, two observational studies have been conducted on this subject (11, 15). In the first study using the Health Professionals' Follow-up Study, the use of sildenafil was associated with an 84% increased risk of melanoma skin cancer (HR: 1.84, 95% CI: 1.04-3.22), while no association was observed with basal cell carcinoma and squamous cell carcinoma (11). However, exposure was assessed using a questionnaire that was administered at a single time point (in 2000). In the second study using a nested case-control approach within the Swedish registries, the use of PDE5 inhibitors was associated with an overall increased risk of melanoma (odds ratio [OR]: 1.21, 95% CI: 1.08-1.36), but this association was limited to patients who had filled a single prescription (OR: 1.32, 95% CI: 1.10-1.59) (15). The authors also reported an association with basal cell carcinoma (HR:

1.19, 95% CI 1.14-1.25), for which there is no clear biological mechanism for a possible association with PDE5 inhibitor use (15).

In contrast to the previous studies (11, 15), my cohort was restricted to patients with erectile dysfunction primarily for two reasons. First, comparing PDE5 inhibitor users to males from the general population may introduce surveillance bias, as the former have been shown to be more health-conscious individuals (15). This might explain the association with basal cell carcinoma in one of the studies (15). Second, erectile dysfunction has been shown to be associated with obesity, diabetes, and cardiovascular diseases (31, 43, 108), some of which may be directly or indirectly associated with melanoma skin cancer (109). Thus, comparing PDE5 inhibitor users to non-users from the general population may introduce confounding by indication.

### 6.3 Biological plausibility

The association between the use of PDE5 inhibitors and melanoma skin cancer is biologically plausible. First, PDE5 is widely expressed in many tissues, including melanocytes (12, 110). Second, it is well established that activating mutations of the oncogene *Braf* are common in melanoma skin cancer (111). Although some preclinical studies have raised the possibility that PDE5 inhibition might have therapeutic value in cancer treatment (112, 113), Arozarena et al. (12) showed that one consequence of *Braf* activation is suppression of expression of PDE5A – the gene that encodes PDE5, and that this leads to increased invasiveness. Thus, pharmacologic inhibition of PDE5A could simulate the effect of *Braf* activation on this target gene. This action of PDE5A inhibitors

might have little consequence for melanoma cases that already have their target silenced by *Braf* activation, but nevertheless could have a measurable effect based on actions early in melanogenesis and/or on the subset of melanomas that do not have *Braf* mutations. Finally, the absence of an association with basal cell carcinoma and squamous cell carcinoma is consistent with the hypothesis that PDE5 is not involved in the pathophysiological pathways of these cancers (92-94, 100).

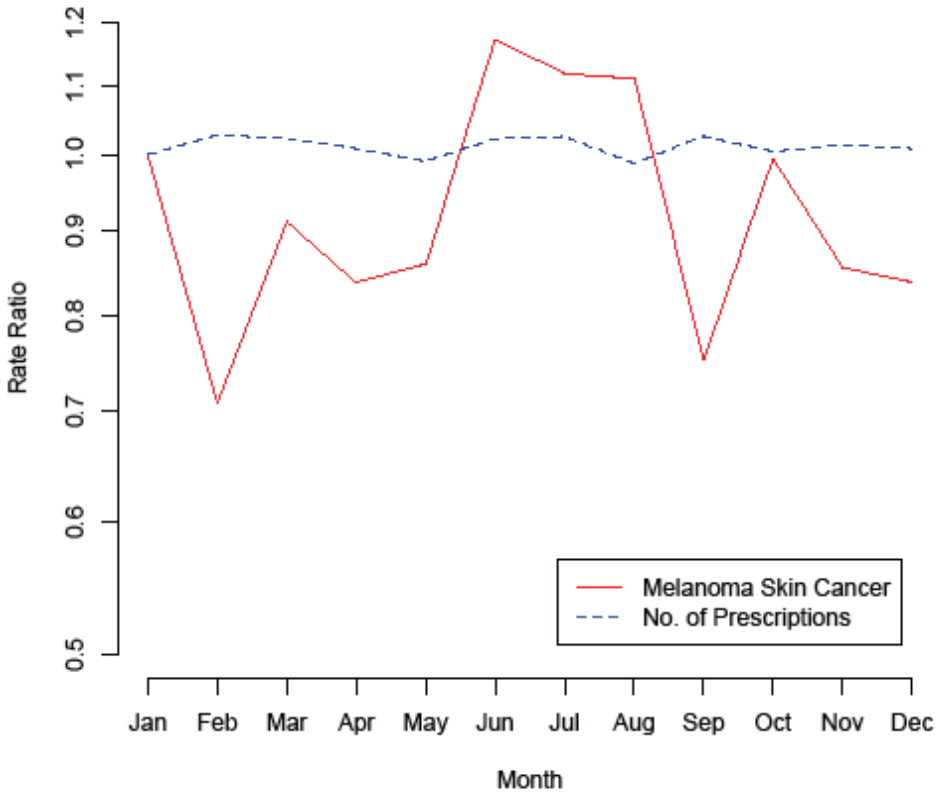
### 6.4 Strengths and limitations

My study has a number of strengths. First, restricting the cohort to patients with erectile dysfunction minimized surveillance bias and possible confounding by indication. Second, the use of PDE5 inhibitors was treated as time-dependent variable in the model, which eliminated immortal time bias (a bias resulting from misclassifying unexposed person-time as exposed person-time) (114). Third, I considered exposure lag periods, which were to account for minimum latencies and to minimize detection bias. Finally, I performed a number of sensitivity analyses that produced generally consistent results.

My study has some limitations. First, the CPRD records prescription written by general practitioners and not specialists, and thus exposure misclassification is possible. However, such misclassification would lead to an underestimation of the association. Second, while melanoma skin cancer has been shown to be well recorded in the CPRD compared with the UK National Cancer Data Repository (115), it was not possible to assess the association with tumor grade and stage. Finally, it was not possible to adjust the models for ultraviolet radiation, the most important risk factor for melanoma and non-melanoma

skin cancer (69, 116). However, confounding would be introduced only if PDE5 inhibitor users are more likely to be exposed to ultraviolet radiation than non-users. To mitigate this issue, I adjusted the models for health-seeking behaviors, and performed sensitivity analyses restricting the cohort to such patients, as well as excluding patients with cardiovascular contraindications (the latter being a sicker group less likely to engage in recreational exposure to ultraviolet radiation). I note that the HRs were further elevated in these sensitivity analyses, with clear duration-response relationships. Furthermore, while my data are consistent with other observational studies reporting a seasonal variation in the diagnosis of melanoma skin cancer (with peaks in the summer months) (117), the prescribing rate of PDE5 inhibitors in my cohort did not follow a seasonal pattern (Figure 4). This argues against the hypothesis that the observed association is confounded by some seasonal variation in the prescribing rate of these drugs and the diagnostic rate of melanoma skin cancer.

**Figure 4: Rate ratios for seasonal variations in melanoma skin cancer and PDE5 inhibitor prescriptions**




* Rate ratios were generated using Poisson regression with offsets equal to log of person-time, and adjusted for age and calendar year. The reference category was set to January.

## 6.5 Take home message

The findings of this large, population-based study indicate that the use of PDE5 inhibitors is associated with a modest increased risk of melanoma skin cancer that varies in a duration-dependent fashion. Given the morbidity and mortality associated with this cancer, additional studies are needed to replicate my findings.

# Chapter 7: Reference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# Chapter 8: Appendix

## 8.1 Ethics approval

**ISAC EVALUATION OF PROTOCOLS FOR RESEARCH INVOLVING CPRD DATA**

**FEEDBACK TO APPLICANTS**

| | | | |
|---|---|---|---|
| **CONFIDENTIAL** | | ***by e-mail*** | |
| **PROTOCOL NO:** | | **15_118A2** | |
| **PROTOCOL TITLE:** | | Phosphodiesterase-5 Inhibitors and the Risk of Non-Melanoma and Melanoma Skin Cancer | |
| **APPLICANT:** | | Samy Suissa, Director, Centre for Clinical Epidemiology, Jewish General Hospital. | |
| **APPROVED** ☒ | **APPROVED WITH COMMENTS (resubmission not required)** ☐ | **REVISION/ RESUBMISSION REQUESTED** ☐ | **REJECTED** ☐ |
| **INSTRUCTIONS:**<br>***Please include your response/s to the Reviewer's feedback below <u>only</u> if you are required to Revise/ Resubmit your protocol.***<br>***Protocols with an outcome of 'Approved' or 'Approved with comments' <u>do not</u> require resubmission to the ISAC.***<br>**REVIEWER COMMENTS:**<br><br>The proposed amendment to 15_118A is approved. | | | |
| **DATE OF ISAC FEEDBACK:** | | 10/09/2015 | |
| **DATE OF APPLICANT FEEDBACK:** | | | |

***For protocols approved from 01 April 2014 onwards, applicants are required to include the ISAC protocol in their journal submission with a statement in the manuscript indicating that it had been approved by the ISAC (with the reference number) and made available to the journal reviewers. If the protocol was subject to any amendments, the last amended version should be the one submitted.***

***** Please refer to the ISAC advice about protocol amendments provided below*****

**Amendments to protocols approved by ISAC** Version June 2015

During the course of some studies, it may become necessary to deviate from a protocol which has been approved by ISAC. Any deviation to an ISAC approved protocol should be clearly documented by the applicant but not all such amendments need be submitted for ISAC review and approval. The general principles to be applied in regard to the need for submission are as follows:

- Major amendments should be submitted
- Minor amendments need not be submitted (but must still be documented by the applicant and should normally be mentioned at the publication stage)

In cases of uncertainty, the applicant should contact the ISAC secretariat for advice quoting the original reference number and providing a brief explanation of the nature of the amendment(s) and underlying reason(s).

**Major Amendments**

We consider an amendment as major if it substantially changes the study design or analysis plan of the proposed research. An amendment should be considered major if it involves the following (although this is not necessarily an exhaustive list):

- A change to the primary hypothesis being tested in the research
- A change to the design of the study
- Additional outcomes or exposures unrelated to the main focus of the approved study*
- Non-trivial changes to the analysis strategy
- Not performing a primary outcome analysis
- Omissions from the analysis plan which may impact on important validity issues such as confounding
- Change of Chief Investigator
- Use of additional linkages to other databases
- Any new proposal involving contact with health professionals or patient or change in regard to such matters

* N.B. extensive changes in this respect will require a new protocol rather than an amendment - if in doubt please consult the Secretariat

**Minor Amendments**

Examples of amendments which can generally be considered minor include the following:

- Change of personnel other than the Chief Investigator (these should be notified to the Secretariat)
- A change to the definition of the study population, providing the change is mentioned and justified in the paper/output [NB previously major]
- Extension of the time period in relation to defining the study population
- Changes to the definitions of outcomes or exposures of interest, providing the change is mentioned and justified in the paper/output [NB previously major]
- Not using linked data which are part of the approved protocol, unless the linked data are considered critical in defining exposures or outcomes (in which case this would be a major amendment)
- Limited additional analysis suggested by unexpected findings, provided these are clearly presented as post-hoc
- Additional methods to further control for confounding or sensitivity analysis provided these are to be reported as secondary to the main findings
- Validation and data quality work provided additional information from GPs is not required

To submit an amendment of protocol to the ISAC, please submit the following documents to the ISAC mailbox (isac@cprd.com)

1. A covering letter providing justification for the request

2. A completed and, if necessary, updated application form with all changes highlighted; if new linkages are required the current version of the ISAC application form must be completed. Otherwise, the original form may be amended as necessary

3. **The updated protocol document containing the heading 'Amendment' at the end of it.** Please include all amendments to the protocol under this heading. No other changes should be made to the already approved document.

## 8.2 Appendix Table 1

| Erectile Dysfunction | | | |
|---|---|---|---|
| **Med Code** | **Clinical Events** | **Read Code** | **Read Term** |
| 102274 | 54349 | 1D1B.00 | C/O erectile dysfunction |
| 106360 | 191 | K27y700 | Erectile dysfunction due to diabetes mellitus |
| 12867 | 2161 | 7C25E00 | Treatment of erectile dysfunction NEC |
| 102490 | 35277 | 66Av.00 | Diabetic assessment of erectile dysfunction |
| 102434 | 12260 | 66Au.00 | Diabetic erectile dysfunction review |
| 81439 | 178 | 7C25F00 | Operations on penis for erectile dysfunction NEC |
| 3838 | 356425 | E227311 | Erectile dysfunction |
| 12790 | 1381 | 8HTj.00 | Referral to erectile dysfunction clinic |
| 17894 | 1837 | K27y100 | Impotence of organic origin |
| 710 | 166967 | E227300 | Impotence |
| 10648 | 9214 | 67IA.00 | Advice about impotence |
| 41382 | 43 | 7A6G500 | Ligation of penile veins for impotence |
| 92310 | 4 | Z9E9.00 | Provision of device for impotence |
| 17639 | 1050 | Eu52213 | [X]Psychogenic impotence |
| 37391 | 28 | 7A6G000 | Revascularisation for impotence |
| 40725 | 14 | ZG43600 | Advice on technique for impotence |

## 8.3 Appendix Table 2

| Melanoma Skin Cancer | | |
|---|---|---|
| **Med Code** | **Read Code** | **Read Term** |
| 54685 | B326100 | Malignant melanoma of upper arm |
| 42153 | B32y.00 | Malignant melanoma of other specified skin site |
| 73744 | B322z00 | Malignant melanoma of ear and external auricular canal NOS |
| 46255 | B327.00 | Malignant melanoma of lower limb and hip |
| 28556 | B32z.00 | Malignant melanoma of skin NOS |
| 54305 | B327200 | Malignant melanoma of knee |
| 95629 | B325500 | Malignant melanoma of perineum |
| 53369 | B327900 | Malignant melanoma of great toe |
| 57260 | B322.00 | Malignant melanoma of ear and external auricular canal |
| 65625 | B324.00 | Malignant melanoma of scalp and neck |
| 65164 | B326.00 | Malignant melanoma of upper limb and shoulder |
| 50505 | B326000 | Malignant melanoma of shoulder |
| 53629 | B325200 | Malignant melanoma of buttock |
| 54632 | B321.00 | Malignant melanoma of eyelid including canthus |
| 70637 | B320.00 | Malignant melanoma of lip |
| 99257 | B324z00 | Malignant melanoma of scalp and neck NOS |
| 47252 | B323.00 | Malignant melanoma of other and unspecified parts of face |
| 38689 | B325.00 | Malignant melanoma of trunk (excluding scrotum) |
| 37872 | B327400 | Malignant melanoma of lower leg |
| 34259 | B325300 | Malignant melanoma of groin |
| 64327 | B327z00 | Malignant melanoma of lower limb or hip NOS |
| 63997 | B326500 | Malignant melanoma of thumb |
| 43463 | B325700 | Malignant melanoma of back |
| 41278 | B323000 | Malignant melanoma of external surface of cheek |
| 49814 | B325000 | Malignant melanoma of axilla |
| 67806 | B323z00 | Malignant melanoma of face NOS |
| 39878 | B327300 | Malignant melanoma of popliteal fossa area |
| 71136 | B323100 | Malignant melanoma of chin |
| 96585 | B32y000 | Overlapping malignant melanoma of skin |
| 43715 | B325600 | Malignant melanoma of umbilicus |
| 61246 | B327600 | Malignant melanoma of heel |
| 32768 | B325100 | Malignant melanoma of breast |
| 45139 | B323400 | Malignant melanoma of external surface of nose |
| 865 | B32..00 | Malignant melanoma of skin |

| | | |
|---|---|---|
| 102145 | B322100 | Malignant melanoma of external auditory meatus |
| 62475 | B326300 | Malignant melanoma of hand |
| 25602 | B326400 | Malignant melanoma of finger |
| 45306 | B324100 | Malignant melanoma of neck |
| 45760 | B325z00 | Malignant melanoma of trunk, excluding scrotum, NOS |
| 47094 | B323200 | Malignant melanoma of eyebrow |
| 73536 | B327000 | Malignant melanoma of hip |
| 41490 | B327700 | Malignant melanoma of foot |
| 58958 | B323500 | Malignant melanoma of temple |
| 59061 | B322000 | Malignant melanoma of auricle (ear) |
| 45755 | B326200 | Malignant melanoma of fore-arm |
| 55292 | B326z00 | Malignant melanoma of upper limb or shoulder NOS |
| 55881 | B324000 | Malignant melanoma of scalp |
| 51209 | B325800 | Malignant melanoma of chest wall |
| 68133 | B323300 | Malignant melanoma of forehead |
| 51873 | B327100 | Malignant melanoma of thigh |
| 109002 | B325400 | Malignant melanoma of perianal skin |
| 36899 | B327800 | Malignant melanoma of toe |
| 42714 | B327500 | Malignant melanoma of ankle |
| 39059 | BBEX.00 | [M]Melanoma in situ |
| 63574 | BBEC.00 | [M]Malignant melanoma in junctional naevus |
| 92293 | BBES.00 | [M]Spindle cell melanoma, type B |
| 40303 | BBET.00 | [M]Mixed epithelioid and spindle melanoma |
| 51353 | BBE1000 | [M]Malignant melanoma, regressing |
| 73251 | BBEM.00 | [M]Malignant melanoma in giant pigmented naevus |
| 7483 | BBE1.12 | [M]Melanoma NOS |
| 17232 | BBEA.00 | [M]Amelanotic melanoma |
| 20982 | BBE2.00 | [M]Nodular melanoma |
| 24208 | BBEH.00 | [M]Superficial spreading melanoma |
| 62088 | BBEG.00 | [M]Malignant melanoma in Hutchinson's melanotic freckle |
| 22692 | BBEG000 | [M]Acral lentiginous melanoma, malignant |
| 579 | BBE1.00 | [M]Malignant melanoma NOS |
| 58835 | BBE1100 | [M]Desmoplastic melanoma, malignant |
| 23085 | BBEP.00 | [M]Epithelioid cell melanoma |
| 11922 | BBEG.11 | [M]Lentigo maligna melanoma |
| 7693 | BBE..00 | [M]Naevi and melanomas |
| 33734 | BBEz.00 | [M]Naevi or melanoma NOS |
| 44061 | BBEQ.00 | [M]Spindle cell melanoma NOS |
| 68889 | BBE4.00 | [M]Balloon cell melanoma |

| | | |
|---|---|---|
| 24551 | BBE1.11 | [M]Melanocarcinoma |
| 44157 | BBE1.13 | [M]Melanosarcoma NOS |
| 20709 | BBEF.00 | [M]Hutchinson's melanotic freckle |
| 2705 | BBEF.11 | [M]Lentigo maligna |
| 8640 | 7G03J00 | Excision of melanoma |
| **Non-Melanoma Skin Cancer** | | |
| **Med Code** | **Read Code** | **Read Term** |
| 70380 | B335000 | Malignant neoplasm of skin of axillary fold |
| 23480 | B335900 | Malignant neoplasm of perianal skin |
| 61194 | B337z00 | Malignant neoplasm of skin of lower limb or hip NOS |
| 15868 | B335z00 | Malignant neoplasm of skin of trunk, excluding scrotum, NOS |
| 42429 | B33X.00 | Malignant neoplasm overlapping lesion of skin |
| 5034 | B33..12 | Epithelioma |
| 4632 | B33..00 | Other malignant neoplasm of skin |
| 30577 | B336200 | Malignant neoplasm of skin of fore-arm |
| 53515 | B332.00 | Malignant neoplasm skin of ear and external auricular canal |
| 62080 | B332100 | Malignant neoplasm of skin of external auditory meatus |
| 56954 | B337200 | Malignant neoplasm of skin of knee |
| 45077 | B335700 | Malignant neoplasm of skin of back |
| 18245 | B330.00 | Malignant neoplasm of skin of lip |
| 30747 | B336.00 | Malignant neoplasm of skin of upper limb and shoulder |
| 54234 | B334.00 | Malignant neoplasm of scalp and skin of neck |
| 46008 | B333z00 | Malignant neoplasm skin other and unspec part of face NOS |
| 49403 | B333100 | Malignant neoplasm of skin of chin |
| 54352 | B336300 | Malignant neoplasm of skin of hand |
| 93490 | B33z.11 | Squamous cell carcinoma of skin NOS |
| 60526 | B336z00 | Malignant neoplasm of skin of upper limb or shoulder NOS |
| 46458 | B335600 | Malignant neoplasm of skin of perineum |
| 43122 | B336000 | Malignant neoplasm of skin of shoulder |
| 30645 | B333000 | Malignant neoplasm of skin of cheek, external |
| 62305 | B335800 | Malignant neoplasm of skin of buttock |
| 64270 | B337500 | Malignant neoplasm of skin of ankle |
| 41958 | B331200 | Malignant neoplasm of lower eyelid |
| 66319 | B335500 | Malignant neoplasm of skin of groin |
| 67914 | B337900 | Malignant neoplasm of skin of great toe |
| 2492 | B33z.00 | Malignant neoplasm of skin NOS |
| 66447 | B335A00 | Malignant neoplasm of skin of scapular region |
| 1940 | B33..13 | Rodent ulcer |
| 37016 | B33..14 | Malignant neoplasm of sebaceous gland |

| | | |
|---|---|---|
| 40443 | B33..15 | Malignant neoplasm of sweat gland |
| 3445 | B33..16 | Epithelioma basal cell |
| 876 | B33..11 | Basal cell carcinoma |
| 18354 | B33y.00 | Malignant neoplasm of other specified skin sites |
| 33682 | B337400 | Malignant neoplasm of skin of lower leg |
| 55550 | B331100 | Malignant neoplasm of upper eyelid |
| 18618 | B335300 | Malignant neoplasm of skin of abdominal wall |
| 65782 | B337800 | Malignant neoplasm of skin of toe |
| 67748 | B335400 | Malignant neoplasm of skin of umbilicus |
| 58601 | B337100 | Malignant neoplasm of skin of thigh |
| 21327 | B333500 | Malignant neoplasm of skin of temple |
| 37165 | B334000 | Malignant neoplasm of scalp |
| 33271 | B332200 | Malignant neoplasm of pinna NEC |
| 62399 | B332z00 | Malig neop skin of ear and external auricular canal NOS |
| 70587 | B337700 | Malignant neoplasm of skin of foot |
| 36731 | B331000 | Malignant neoplasm of canthus |
| 30543 | B335200 | Malignant neoplasm of skin of breast |
| 30576 | B333300 | Malignant neoplasm of skin of forehead |
| 70988 | B337000 | Malignant neoplasm of skin of hip |
| 24375 | B339.00 | Dermatofibrosarcoma protuberans |
| 16202 | B333400 | Malignant neoplasm of skin of nose (external) |
| 43619 | B334100 | Malignant neoplasm of skin of neck |
| 25245 | B336400 | Malignant neoplasm of skin of finger |
| 104025 | B337600 | Malignant neoplasm of skin of heel |
| 37969 | B335100 | Malignant neoplasm of skin of chest, excluding breast |
| 55670 | B333200 | Malignant neoplasm of skin of eyebrow |
| 68197 | B337300 | Malignant neoplasm of skin of popliteal fossa area |
| 27370 | B333.00 | Malignant neoplasm skin of other and unspecified parts face |
| 42707 | B336100 | Malignant neoplasm of skin of upper arm |
| 73760 | B334z00 | Malignant neoplasm of scalp or skin of neck NOS |
| 64406 | B336500 | Malignant neoplasm of skin of thumb |
| 43087 | B331.00 | Malignant neoplasm of eyelid including canthus |
| 57442 | B337.00 | Malignant neoplasm of skin of lower limb and hip |
| 57446 | B335.00 | Malignant neoplasm of skin of trunk, excluding scrotum |
| 93352 | B338.00 | Squamous cell carcinoma of skin |
| 33997 | B332000 | Malignant neoplasm of skin of auricle (ear) |
| 34395 | BB24.00 | [M]Verrucous carcinoma NOS |
| 45510 | BB2M.00 | [M]Lymphoepithelial carcinoma |
| 56600 | BB2A.11 | [M]Epidermoid carcinoma NOS |

| | | |
|---|---|---|
| 41481 | BB2K.00 | [M]Queyrat's erythroplasia |
| 29787 | BB2C.00 | [M]Squamous cell carcinoma, keratinising type NOS |
| 45458 | BB2F.00 | [M]Squamous cell carcinoma, spindle cell type |
| 33497 | BB2J.00 | [M]Squamous cell carcinoma, microinvasive |
| 24293 | BB2B.00 | [M]Squamous cell carcinoma, metastatic NOS |
| 8917 | BB2L.00 | [M]Bowen's disease |
| 57513 | BB2C.11 | [M]Epidermoid carcinoma, keratinising type |
| 61928 | BB2H.00 | [M]Squamous cell ca-in-situ, questionable stromal invasion |
| 43717 | BB24.11 | [M]Verrucous epidermoid carcinoma |
| 4852 | BB24.12 | [M]Verrucous squamous cell carcinoma |
| 19041 | BB29.12 | [M]Intraepidermal carcinoma NOS |
| 48182 | BB29.11 | [M]Epidermoid carcinoma in situ |
| 41816 | BB2E.00 | [M]Squamous cell carcinoma, small cell, non-keratinising |
| 94873 | BB2A.13 | [M]Squamous cell carcinoma of skin NOS |
| 57680 | BB2A.12 | [M]Spinous cell carcinoma |
| 31004 | BB2G.00 | [M]Adenoid squamous cell carcinoma |
| 19678 | BB29.13 | [M]Intraepithelial squamous cell carcinoma |
| 59143 | BB2D.00 | [M]Squamous cell carcinoma, large cell, non-keratinising |
| 1624 | BB2A.00 | [M]Squamous cell carcinoma NOS |
| 10134 | BB29.00 | [M]Squamous cell carcinoma in situ NOS |
| 49765 | BB38.12 | [M]Epithelioma adenoides cyst |
| 59919 | BB32.00 | [M]Multicentric basal cell carcinoma |
| 102417 | BB3C.00 | [M]Superficial basal cell carcinoma |
| 103178 | BB3F.00 | [M]Basal cell carcinoma, infiltrative |
| 29282 | BB30.00 | [M]Basal cell tumour |
| 13574 | BB36.00 | [M]Metatypical carcinoma |
| 29524 | BB34.00 | [M]Basal cell carcinoma, fibroepithelial type |
| 102547 | BB3D.00 | [M]Basal cell carcinoma, nodular |
| 35457 | BB35.00 | [M]Basosquamous carcinoma |
| 9885 | BB33.00 | [M]Basal cell carcinoma, morphoea type |
| 3028 | BB31.00 | [M]Basal cell carcinoma NOS |
| 103066 | BB3G.00 | [M]Pigmented basal cell carcinoma |
| 103440 | BB3E.00 | [M]Basal cell carcinoma, micronodular |
| 67966 | BBE1.14 | [M]Naevocarcinoma |
| 68447 | BBEV.00 | [M]Blue naevus, malignant |
| 18270 | 7G03K00 | Excision malignant skin tumour |
| 93402 | 7G05D00 | Excision biopsy of basal cell carcinoma |
| 11834 | 7G05600 | Excision biopsy of rodent ulcer |

## 8.4 Appendix Table 3

| Phosphodiesterase-5 Inhibitors | | | |
|---|---|---|---|
| **Product Code** | **Therapy Events** | **Drug Substance Name** | **Substance Strength** |
| 1456 | 88701 | Sildenafil citrate | 50mg |
| 1452 | 17560 | Sildenafil citrate | 25mg |
| 1732 | 109358 | Sildenafil citrate | 100mg |
| 704 | 105057 | Sildenafil citrate | 25mg |
| 554 | 709098 | Sildenafil citrate | 50mg |
| 1257 | 1021224 | Sildenafil citrate | 100mg |
| 61184 | 0 | Sildenafil citrate | 100mg |
| 6809 | 92436 | Vardenafil hydrochloride trihydrate | 20mg |
| 45844 | 619 | Vardenafil hydrochloride trihydrate | 10mg |
| 52369 | 1 | Vardenafil hydrochloride trihydrate | 10mg |
| 6214 | 56036 | Vardenafil hydrochloride trihydrate | 10mg |
| 14860 | 3855 | Vardenafil hydrochloride trihydrate | 5mg |
| 6203 | 10426 | Vardenafil hydrochloride trihydrate | 5mg |
| 6777 | 31949 | Vardenafil hydrochloride trihydrate | 20mg |
| 45776 | 602 | Vardenafil Hydrochloride | 10mg |
| 6457 | 19440 | Vardenafil hydrochloride trihydrate | 10mg |
| 50233 | 6 | Tadalafil | 10mg |
| 794 | 163334 | Tadalafil | 10mg |
| 39243 | 3093 | Tadalafil | 2.5mg |
| 39096 | 28100 | Tadalafil | 5mg |
| 39285 | 17738 | Tadalafil | 5mg |
| 48764 | 1 | Tadalafil | 20mg |
| 6015 | 71792 | Tadalafil | 10mg |
| 49347 | 2 | Tadalafil | 20mg |
| 39289 | 4678 | Tadalafil | 2.5mg |
| 6148 | 181280 | Tadalafil | 20mg |
| 49411 | 66 | Sildenafil citrate | 2mg/1ml |
| 35192 | 455 | Sildenafil Citrate | 10mg/5ml |
| 6207 | 335590 | Tadalafil | 20mg |