Original Investigation

Sildenafil Use and Increased Risk of Incident Melanoma in US Men

A Prospective Cohort Study

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IMPORTANCE The RAS/RAF/mitogen-activated protein kinase and extracellular signal–regulated kinase (ERK) kinase/ERK cascade plays a crucial role in melanoma cell proliferation and survival. Sildenafil citrate (Viagra) is a phosphodiesterase (PDE) 5A inhibitor commonly used for erectile dysfunction. Recent studies have shown that BRAF activation down-regulates PDE5A levels, and low PDE5A expression by BRAF activation or sildenafil use increases the invasiveness of melanoma cells, which raises the possible adverse effect of sildenafil use on melanoma risk.

OBJECTIVE To evaluate the association between sildenafil use and risk of incident melanoma among men in the United States.

DESIGN, SETTING, AND PARTICIPANTS Our study is a prospective cohort study. In 2000, participants in the Health Professionals' Follow-up Study were questioned regarding sildenafil use for erectile dysfunction. Participants who reported cancers at baseline were excluded. A total of 25 848 men remained in the analysis.

MAIN OUTCOMES AND MEASURES The incidence of skin cancers, including melanoma, squamous cell carcinoma (SCC), and basal cell carcinoma (BCC), was obtained in the self-reported questionnaires biennially. The diagnosis of melanoma and SCC was pathologically confirmed.

RESULTS We identified 142 melanoma, 580 SCC, and 3030 BCC cases during follow-up (2000-2010). Recent sildenafil use at baseline was significantly associated with an increased risk of subsequent melanoma with a multivariate-adjusted hazard ratio (HR) of 1.84 (95% CI, 1.04-3.22). In contrast, we did not observe an increase in risk of SCC (HR, 0.84; 95% CI, 0.59-1.20) or BCC (1.08; 0.93-1.25) associated with sildenafil use. Moreover, erectile function itself was not associated with an altered risk of melanoma. Ever use of sildenafil was also associated with a higher risk of melanoma (HR, 1.92; 95% CI, 1.14-3.22). A secondary analysis excluding those reporting major chronic diseases at baseline did not appreciably change the findings; the HR of melanoma was 2.24 (95% CI, 1.05-4.78) for sildenafil use at baseline and 2.77 (1.32-5.85) for ever use.

CONCLUSIONS AND RELEVANCE Sildenafil use may be associated with an increased risk of developing melanoma. Although this study is insufficient to alter clinical recommendations, we support a need for continued investigation of this association.

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JAMA Intern Med. 2014;174(6):964-970. doi:10.1001/jamainternmed.2014.594
Published online April 7, 2014.

The RAS/RAF/mitogen-activated protein kinase and extracellular signal-regulated kinase (ERK) kinase (MEK)/ERK signaling pathway couples signals from cell surface receptors to transcription factors and regulates cell fate downstream of receptor tyrosine kinases, cytokines, and heterotrimetric G-protein–coupled receptors.[1] Melanoma is a major public health problem, particularly in the Western world,[2] with 76 000 estimated new cases in the United States in 2012.[3] The biological mechanism underlying melanoma development is complex, with the RAS/RAF/MEK/ERK pathway playing a key role in melanoma cell proliferation and survival.[1] Hyperactivation of ERK has been found in most human melanomas, commonly regulated through *BRAF* (OMIM *164757) or *NRAS* (OMIM *164790) somatic mutations.[1,4] Approximately 50% of melanoma tumors have *BRAF* mutations (mostly V600E mutation), leading to elevated kinase activity.[5,6] Drugs inhibiting this pathway, particularly targeting BRAF, have shown therapeutic efficacy.[6,7] The cyclic guanosine monophosphate (cGMP)–specific phosphodiesterase (PDE) 5A was recently demonstrated as a downstream target of BRAF.[8,9] Through the MEK/ERK cascade, activated BRAF down-regulates PDE5A, which lowers cGMP degradation and leads to an increase in intracellular calcium ion Ca^{2+}, triggering invasion and metastasis of melanoma cells.[8-11] In contrast, rescuing expression of PDE5A in melanoma cells decreased their invasiveness.[8] Down-regulation of PDE5A was also seen in *NRAS*-mutant cell lines, indicating that activation of mitogen-activated protein kinase signaling leads to PDE5A down-regulation in melanoma cell lines, irrespective of genetic background.[8] Phosphodiesterase 5A is the target of sildenafil citrate, commercially known as Viagra, which has been widely prescribed for erectile dysfunction (ED).[12,13] Treatment with sildenafil and other PDE5A inhibitors can promote melanoma cell invasion, particularly in the *BRAF*-mutated melanoma cell lines.[8] This indicates that PDE5A suppression by sildenafil use mimics an effect of BRAF/NRAS activation and thus may potentially function as one of the "hits" for melanomagenesis. Most recently, 2 PDE5 inhibitors were shown to promote melanin synthesis,[14] which may exacerbate melanoma development.[15] These pieces of evidence prompted our hypothesis regarding the potential link between sildenafil use and melanoma.[16]

We sought to investigate the association between sildenafil use for ED and risk of incident melanoma in the Health Professionals' Follow-up Study (HPFS). We compared the sildenafil-associated risks for melanoma and nonmelanoma skin cancers (predominantly comprising squamous cell carcinoma [SCC] and basal cell carcinoma [BCC]), the most common malignant neoplasms in humans.[17]

Methods

Study Population

The HPFS began in 1986 when 51 529 US male health professionals, aged 40 to 75 years, completed a baseline questionnaire on medical history and lifestyle practices. Health professionals are highly motivated and committed to participating in this long-term project and appreciate the accuracy of reports, given their knowledge and medical background. Biennially, participants received a questionnaire, and a response rate exceeding 90% has been achieved in the follow-up. The study was approved by the Human Research Committee at Brigham and Women's Hospital, Boston, Massachusetts. Participants' completion and return of the questionnaire was considered informed consent.

Assessment of Exposure

The primary exposure was sildenafil use for ED. In 2000, participants were queried as to whether they had undergone surgery or treatment to correct problems with erections during the past 3 months, including sildenafil, shots or penile injection, vacuum suction, alprostadil, and other treatments, and whether they had ever received any treatment for ED before, including sildenafil. However, no information on the dose or frequency of sildenafil was collected.

In 2000, participants were asked to rate their ability before 1986, in 1986 to 1989, 1990 to 1994, and 1995 to 2000, and during the past 3 months to have and maintain an erection adequate for intercourse without treatment (very poor, poor, fair, good, or very good). Men with poor or very poor ability at or before 2000 were considered to have ED in 2000 (baseline).[18,19] The high validity of a single assessment of ED has been indicated elsewhere (eMethod 1 in the Supplement).[18]

The associations between various risk factors and melanoma have been shown in other studies (eMethod 2 in the Supplement).[20-24] Information on these factors was collected in the questionnaires, including the number of moles at least 3 mm in diameter on the arms (1987); natural hair color at age 18 years (1988); and state of residence at birth and age 15 and 30 years, lifetime numbers of blistering sunburns, and adolescent tendency to sunburn (1992). According to the state of residence, the UV index at birth and age 15 and 30 years was categorized into 3 categories (≤5, 6, or ≥7). Family history of melanoma in first-degree relatives was asked about in 1990 and 1992. In 2008, sun exposure in the middle of the day during summer (10 AM to 3 PM) was inquired about for high school/college age and age 25 to 35, 36 to 59, and 60 years or older. Information on smoking, body mass index, and physical activity was collected biennially.

Assessment of Outcome

Since 1986, participants have reported diagnoses of melanoma, SCC, BCC, and other cancers on biennial surveys. When a diagnosis was reported, the participant was entered into a tracking system. Related medical records were requested with the participant's permission and reviewed by physicians masked to exposure to confirm the diagnosis. For melanoma and SCC, we excluded self-reported cases that denied the diagnosis in the further follow-up or denied the permission to review their records, and only pathologically confirmed invasive cases in the medical record review were documented as the outcome. For BCC, we did not seek to obtain medical records for all cases, but previous studies have indicated a high validity of self-reports, with more than 90% of BCCs confirmed by histopathological records.[25,26]

Statistical Analysis

Men who answered the questionnaire in 2000 served as the base population. For the primary analysis, we excluded those with missing date of birth, those with diagnosed cancers (including melanoma, SCC, BCC, and nonskin cancers) at baseline, users of other therapies but not sildenafil for ED, and nonwhite patients; 25 848 participants remained. We did not consider other relatively rare immunosuppressive conditions, such as acquired immunodeficiency syndrome.

We compared the distribution of characteristics between sildenafil users and nonusers, using t or χ^2 tests. Person-years of follow-up were calculated from the return of the 2000 questionnaire to the date of diagnosis of melanoma or nonmelanoma skin cancer, death, the last questionnaire response, or January 2010, whichever came first. Cox proportional hazards analysis was performed to calculate hazard ratios (HRs) and 95% CIs. We evaluated sildenafil use at baseline (in the past 3 months, which was reported in 2000) as the main exposure.

Multivariate models were adjusted for age; body mass index; smoking; physical activity; childhood reaction to sun; number of severe sunburns; mole count; hair color; family history of melanoma; sun exposure at high school age and age 25 to 35, 36 to 59, and 60 years or older; UV index at birth and age 15 and 30 years; and other treatments for ED (eMethod 2 [Supplement]). All models were stratified by 2-year intervals, and the main exposure and time-varying covariates were included in the analysis of each follow-up interval. Included covariates are well-defined factors associated with melanoma or sildenafil use. One factor can be a confounder because it changes the effect of the main exposure when included in the model or when included with other covariates.[27] In a sensitivity analysis, we also adjusted for history of major chronic diseases (cardiovascular disease, type 2 diabetes mellitus, or hypertension). We evaluated the age-standardized absolute risk associated with sildenafil use.

We also evaluated sildenafil use ever before (all recent and prior users). In other analyses, we excluded sildenafil users who had also used other therapeutic options for ED to eliminate the confounding of these therapies. We performed a lag analysis by excluding cases occurring in the first follow-up period (2000-2002) to clarify the temporal relationship between sildenafil use and the occurrence of outcomes.

In a secondary analysis, we also excluded those reporting cardiovascular disease, type 2 diabetes mellitus, or hypertension at baseline because the sexual intercourse and sildenafil use may have been affected by the health status, and PDE5A inhibitors have shown their efficacy in diseases other than ED, such as pulmonary hypertension and cardiac hypertrophy.[12,28-30]

To address concern about the possible confounding of erectile function, we examined whether it was associated with risk of subsequent skin cancers. We conducted an analysis excluding users of sildenafil and other treatments for ED. For this analysis, men who did not report erectile function were further excluded. To clarify the association of sildenafil use with other cancers, we evaluated the risk of incident total nonskin cancers as well as major individual cancers, adjusting for age, body mass index, smoking, physical activity, UV index at birth and age 15 and 30 years, multivitamin use, physical examination in the last 2 years, and other treatments for ED.

Analyses were performed with SAS software (version 9.2; SAS Institute). All P values were 2 tailed, with the significance level set at $P < .05$.

Results

For 25 848 participants, the mean (SD) age at baseline was 64.8 (8.8) years; 5.3% (1378 of 25 848) reported taking sildenafil for ED recently, and 6.3% (1618 of 25 848) reported ever using it (**Table 1**). Sildenafil users were more likely to be older and obese, have a history of more severe or blistering sunburns, and undergo physical examinations but had been exposed to less sunlight as adults.

From 2000 to 2010, a total of 142 melanoma, 580 SCC, and 3030 BCC cases were documented. Recent sildenafil users at baseline had a significantly elevated risk of invasive melanoma with multivariate-adjusted HR of 1.84 (95% CI, 1.04-3.22). In contrast, we did not observe a significantly altered risk of SCC or BCC associated with sildenafil use; the HR was 0.84 (95% CI, 0.59-1.20) for SCC and 1.08 (0.93-1.25) for BCC (**Table 2**). Ever use of sildenafil was also associated with a higher risk of melanoma (HR, 1.92; 95% CI, 1.14-3.22) (eTable 1 in the Supplement). In addition, controlling for the history of major chronic diseases did not change the results appreciably (data not shown).

The association between sildenafil use and melanoma remained significant after excluding the outcomes occurring in the first 2 years (HR, 2.19; 95% CI, 1.18-4.07), and excluding all users of other treatments for ED (2.18; 1.15-4.15). The age-standardized absolute risk associated with sildenafil use was 81.0 cases per 100 000 person-years (216.4/100 000 person-years in users vs 135.4/100 000 person-years in nonusers).

In the secondary analysis excluding those with major chronic diseases at baseline, 79 melanoma cases were identified among 14 912 participants. Recent sildenafil users had a significantly elevated risk of invasive melanoma (HR, 2.24; 95% CI, 1.05-4.78) (eTable 2 in the Supplement). Ever use of sildenafil was also associated with increased melanoma risk (HR. 2.77; 95% CI, 1.32-5.85).

We examined the overall erectile function and melanoma risk. Compared with those reporting very good function, we did not observe a significant change in risk among those with ED (eTable 3 in the Supplement). We further evaluated the association between sildenafil use and risk of total nonskin cancers, as well as the major individual cancers, and did not observe significant association with these cancers.

Discussion

In this prospective study, men who used sildenafil for ED had a statistically significantly elevated risk of melanoma. The association remained in the models controlling for the major host characteristics, family history of melanoma, sun exposure behavior, and UV index in the state of residence.

Table 1. Baseline Characteristics of Study Population According to Recent Use of Sildenafil Citrate for Erectile Dysfunction[a]

Characteristic	Recent Sildenafil Use[b]		*P* Value[c]
	No (n = 24 470)	Yes (n = 1378)	
Age, mean (SD), y	64.8 (8.8)	66.1 (7.7)	<.001
Body mass index, mean (SD)[d]	25.6 (5.7)	26.1 (4.8)	<.001
Physical activity, mean (SD), metabolic equivalent h/wk	34.1 (40.6)	33.7 (34.3)	.68
Current smoking	5.6	4.8	.23
Family history of melanoma	4.4	5.6	.10
Burn or blistering skin reaction to the sun	68.7	68.3	.73
UV index of residence ≥7			
At birth	27.6	28.3	.63
At age 15 y	29.2	29.6	.76
At age 30 y	34.3	36.9	.07
Natural red or blond hair	13.2	11.9	.24
≥6 moles on the arms (≥3-mm diameter)	4.8	4.7	.82
History of ≥6 severe or blistering sunburns	35.1	38.6	.01
Sun exposure ≥11 h/wk			
College/high school age	50.2	50.6	.77
Age 25-35 y	32.2	28.9	.03
Age 36-59 y	27.8	24.1	.01
Age ≥60 y	27.1	24.3	.05
Erectile dysfunction	27.1	61.5	<.001
Physical examination	85.9	91.1	<.001
Recent use of other erectile dysfunction treatment	0.0	7.6	<.001
Ever use of sildenafil	1.0	100.0	<.001
Ever use of other erectile dysfunction treatment	1.0	36.6	<.001

[a] Data from the Health Professionals' Follow-up Study at baseline (2000).

[b] Unless otherwise indicated, values represent percentages of respondents.

[c] *P* values were calculated using *t* tests (for age, body mass index, and physical activity) or χ^2 tests (for other variables).

[d] Body mass index was calculated as weight in kilograms divided by height in meters squared.

Table 2. Hazard Ratios for Incident Melanoma, Squamous Cell Carcinoma, and Basal Cell Carcinoma Associated With Use of Sildenafil Citrate[a]

Diagnosis	Person-years	Cancer Cases, No.	Hazard Ratio (95% CI)	
			Age Adjusted	Multivariate Adjusted[b]
Melanoma				
No sildenafil use	193 935	128	1 [Reference]	1 [Reference]
Sildenafil use	10 935	14	1.93 (1.11-3.37)	1.84 (1.04-3.22)
Squamous cell carcinoma				
No sildenafil use	190 716	548	1 [Reference]	1 [Reference]
Sildenafil use	10 714	32	0.90 (0.63-1.29)	0.84 (0.59-1.20)
Basal cell carcinoma				
No sildenafil use	190 716	2838	1 [Reference]	1 [Reference]
Sildenafil use	10 714	192	1.12 (0.97-1.30)	1.08 (0.93-1.25)

[a] Data from the Health Professionals' Follow-up Study (2000-2010).

[b] Adjusted for age (continuous variable), body mass index (<24.9, 25-29.9, or ≥30 [calculated as weight in kilograms divided by height in meters squared]); smoking (never, past, or current); physical activity (in quintiles, metabolic equivalent hours per week); childhood reaction to sun (tan without burn, burn, or painful burn/blisters); number of sunburns (0, 1-2, 3-5, or ≥6); mole count (0, 1-2, 3-5, or ≥6); hair color (red, blond, light brown, or dark brown/black); family history of melanoma (yes or no); sun exposure at high school age and age 25 to 35, 36 to 59, and ≥60 y (<5, 6-10, or ≥11 h/wk for each); UV index at birth and age 15 and 30 y (≤5, 6, or ≥7); and other treatment for erectile dysfunction.

Through selective regulation of cGMP, PDE5A plays an essential role in vascular smooth muscle contraction in the corpus cavernosum.[31] The PDE5A inhibitors competitively inhibit the hydrolysis of cGMP, thereby leading to smooth muscle relaxation and penile erection.[12,30] Since the approved use of sildenafil in 1998 and vardenafil hydrochloride (Levitra) and tadalafil (Cialis) in 2003, PDE5A inhibitors have remained the first-line therapy for ED.[12,28] Adverse effects are generally mild,[12] although vision-threatening ocular complications and hearing loss have been reported.[28,32]

Arozarena et al[8] recently found that PDE5A inhibition by sildenafil induces invasion of melanoma in vitro. Moreover, oncogenic *BRAF* mutation was shown to down-regulate PDE5A through the RAS/RAF/MEK/ERK signaling, and PDE5A down-regulation can stimulate a dramatic increase in melanoma cell contractility and invasion despite causing a slight decrease in

proliferation.[8,11] Among 10 *BRAF*-mutant cell lines, Arozarena et al did not find down-regulated PDE5A messenger RNA or protein expression in the 501mel cell line, in which sildenafil use induced invasion. In contrast, they did not observe increased invasion of A375 or WM266.4 cells by sildenafil, whereas both were *BRAF* mutated and had suppressed PDE5A expression.[8] These data suggest that either RAS/RAF activation or sildenafil can inhibit PDE5A activity. Sildenafil could act in the MEK/ERK downstream, acting similarly with one signal induced by RAS/RAF activation, and the effect of sildenafil on melanoma may not involve the RAS/RAF mutations/activation.[8] Whether the presence of both RAS/RAF mutations/activation and PDE5A inhibitors could trigger a synergistic or antagonistic effect remains to be investigated.

By increasing intracellular cGMP levels, sildenafil could deregulate diverse physiological functions, such as phototransduction, vascular permeability, proliferation, and apoptosis.[33] Cancer metastasis requires invasion in multiple steps and cellular adhesion to vasculature or anoikis resistance.[34] Therefore, sildenafil could induce cell invasion by fostering other cellular abilities. The *Braf*-V600E mutation has been shown to induce both melanocyte senescence and melanoma in vivo.[10] Whether PDE5A inhibition may help promote or escape melanocyte senescence in laboratory experiments is unknown, particularly in *BRAF*-driven melanomas. The finding that PDE5A down-regulation leads to increased invasion in a *BRAF*-specific manner may highlight the "oncogene addiction" that prevails in *BRAF*-mutated melanomas.[8] The lack of response of RAS-mutated melanomas to sildenafil in invasion assays may be due to the complexity of RAS signaling[8] because RAS activates other pathways except mitogen-activated protein kinase.[35] Arozarena et al[8] provided limited data on proliferation and other features of melanoma carcinogenesis, which require functional studies to clarify.

Given that PDE5A down-regulation increased invasiveness and that PDE5A expression was higher in primary tumors than in metastatic tumors, it is biologically plausible that PDE5A inhibitors may promote invasion of primary tumors. The previous study tested melanoma cell lines mostly of metastatic origin and did not test invasive potential of cells from primary tumors.[8] However, because primary tumors expressed substantially higher levels of PDE5A than did metastatic melanomas, the effect may be more marked. Melanoma is highly heterogeneous in its characteristics, unlike cell lines,[36] so even a small population of cells that respond strongly could be significant. Our study included only confirmed invasive melanomas in the radial and/or vertical growth phase, and our findings suggest an association of PDE5A inhibitors with the risk of melanoma development. The association of PDE5A inhibitors with melanoma progression, recurrence, and metastasis might be stronger, warranting further studies.

The possible differences in health status and lifestyle practices between sildenafil users and nonusers may have confounded our findings. Sildenafil use was correlated with factors that may increase melanoma diagnosis, such as more severe or blistering sunburns and more physical examinations. In contrast, users tended to have less exposure to sunlight in adulthood, which may have decreased melanoma risk. Because melanoma and nonmelanoma skin cancer share major risk factors, we sought to address the concern about residual confounding by examining the association of sildenafil use with nonmelanoma skin cancer. Sildenafil use was associated exclusively with melanoma, indicating that our findings were less likely due to sun exposure, physical examinations, or detection bias. The homogeneity of the cohort decreases the misclassification of work-related sun exposures or health awareness. Erectile function itself was not associated with melanoma either. Together, these results suggest an association between sildenafil use and melanoma, regardless of other characteristics. Even so, from findings in an observational study, we cannot rule out the possibility of residual confounding by unmeasured or imperfectly measured confounders.

We acknowledge limitations. First, sildenafil use was self-reported in 2000 and not updated during the follow-up. However, the health care–related professional background was reassuring. The misclassification of exposure would tend to affect those unexposed in 2000, leading to a conservative HR estimate. Sildenafil is usually effective within 30 to 120 minutes after administration and may be cleared rapidly, such that the PDE5A inhibition could be transient and reversible.[8,12] However, a 2-hour time window is sufficient for some drugs to produce critical transcriptional changes.[9] One study in the HPFS has indicated a sharply increased risk of ED with aging.[18] With the massive increase in sildenafil use after its introduction, among the recent users in 2000, the expected proportion of users after 2000 could be much higher than that of recent nonusers, which might lead to a chronic downstream effect of PDE5A inhibition. Nevertheless, laboratory studies are warranted to elucidate whether either temporary or long-term use of sildenafil can induce irreversible change in host features and elevated melanoma risk. For example, it remains to be examined whether a single, or repeated, dose of sildenafil can cause sufficient inhibition of PDE5A in melanocytes to promote transcriptional changes of key genes.

Second, we found a significant association of melanoma with both sildenafil recent use and ever use, wherein the HR for ever use appeared even stronger, which could partly indicate a possible cumulative effect of sildenafil use. However, we did not collect information on frequency and dosage of sildenafil use and were not able to analyze the association with cumulative sildenafil use.

Third, we did not have the information on other PDE5A inhibitors because neither vardenafil nor tadalafil had been approved by the US Food and Drug Administration in 2000. The observed association between sildenafil use and melanoma might be partly attributed to the later use of vardenafil and tadalafil among recent sildenafil users. A longer clearance time of other PDE5A inhibitors could have augmented the observed HR for sildenafil.[12] However, this would not materially jeopardize our study implications for PDE5A inhibitors.

Fourth, we assessed ED using a single assessment at baseline, which may inevitably lead to misclassification for ED during the follow-up. Participants without ED in 2000 may later experience ED owing to aging or other factors, which may affect our analysis on ED but would not affect our analysis on sildenafil use and melanoma.

Finally, our study had a modest sample size, and subgroup analyses by melanoma sites and other factors, particularly nevi,[37] were underpowered. Prior studies have shown that melanomas on the trunk more frequently harbored *BRAF* mutations than those on the head and neck.[38] *BRAF* and *NRAS* mutations also tend to occur exclusively.[4] Additional studies are required to investigate sildenafil use and melanoma risk by *BRAF/NRAS* mutations and body sites.

Conclusions

Findings in a well-established, long-term cohort study suggest a positive association between PDE5A inhibitor (sildenafil) use for ED and risk of subsequent melanoma. Our study cannot prove cause and effect. A longer follow-up and more detailed assessment of the dose and frequency of sildenafil use at multiple times in the HPFS would be necessary for future studies. We also plan to work on clinical databases to examine this association. Further studies are needed to confirm our findings in other populations, particularly in a dose-dependent manner, and to investigate underlying biological mechanisms. It would also be very important to examine the possible latency of exposure to PDE5A inhibitor (sildenafil) use and melanoma risk. Our results should be interpreted cautiously and are insufficient to alter current clinical recommendations. Nevertheless, our data provide epidemiological evidence on possible skin adverse effects of PDE5A inhibitors and support continued investigation of this relationship.

ARTICLE INFORMATION

Accepted for Publication: January 23, 2014.

Published Online: April 7, 2014. doi:10.1001/jamainternmed.2014.594.

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Author Contributions: Dr Han had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Acquisition of data: Li, Qureshi, Han.
Analysis and interpretation of data: Li, Robinson, Han.
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Statistical analysis: Li, Qureshi, Han.
Obtained funding: Han.
Administrative, technical, or material support: Qureshi, Han.
Study supervision: Li, Qureshi, Han.

Conflict of Interest Disclosures: None reported.

Funding/Support: The HPFS is partly supported by grant P01 CA055075 from the National Institutes of Health.

Role of the Sponsors: The funding source had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; and preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: David E. Fisher, MD, PhD, Massachusetts General Hospital, Boston, provided insightful comments on our revision, and Tricia Yunhui Li, MD, MS, Channing Laboratory, Brigham & Women's Hospital, Boston, assisted with data analysis. We also thank the participants and staff of the Health Professionals' Follow-up Study for their valuable contributions and the following state cancer registries for their help: Alabama, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, Florida, Georgia, Idaho, Illinois, Indiana, Iowa, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Nebraska, New Hampshire, New Jersey, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, Tennessee, Texas, Virginia, Washington, and Wyoming.

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Invited Commentary

Role of Sildenafil in Melanoma Incidence and Mortality

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In 2014, about 76 100 new melanomas will be diagnosed, and an estimated 9710 persons will die (about 6470 men and 3240 women).[1] Patients with melanoma in situ, stage 0, have a 5-year survival rate of 99% when treated with excision, whereas those with melanoma limited to the skin and with a tumor thickness of 2.01 to 4.0 mm, stage II B, have a 5-year survival rate of about 57%. Patients with metastatic melanoma, stage IV, have a 5-year survival rate of 15% to 20%. Despite newly available targeted agents, systemic therapies rarely lead to cures. These sizable survival differences illustrate the need for early detection of melanoma; early detection of primary melanomas followed by surgical excision remains critical.

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Li et al[2] performed an analysis of 25 848 men enrolled in the Health Professionals' Follow-up Study. After known risk factors were controlled for (eg, number of moles, natural hair color, lifetime number of sunburns, and family history of melanoma), sildenafil citrate (Viagra) users had an elevated risk of melanoma, with a multivariate-adjusted hazard ratio of 1.84 (95% CI, 1.04-3.22). Thus, sildenafil is proposed as a contributor to the development of melanoma. A prospective study with clearly defined inclusion and exclusion criteria and known doses of sildenafil taken is needed before a recommendation can be made to change men's use of sildenafil. Exposure to UV radiation is the only known modifiable cause of melanoma. Patients at high risk for melanoma because of fair skin, freckling, and tendency to sunburn; those who live in or visit sunny climates; and those who have a family history of melanoma can effectively reduce their risk of melanoma by routinely and thoroughly applying broad-spectrum sunscreen before going outside or by wearing sun-protective clothing.

From 1975 through 1986, the annual percentage increase in men's age-adjusted incidence rate of melanoma was 5.6%. This slowed to 2.4% per year from 1992 to 2010.[1] Sildenafil received approval for the treatment of erectile dysfunction on March 27, 1998.[3] The rate of increase in melanoma in men slowed as sildenafil came into use, which raises a cautionary note about the influence of sildenafil in the development of melanoma, but its role in the biologic behavior of melanoma in older men warrants further study.

Women consistently have a 30% survival advantage compared with men among middle-aged and older individuals, which is attributed to behavioral differences.[4] Women's survival advantage is thought to be related to their presentation for health care earlier in the disease process, owing to increased awareness of melanoma and skin self-examination; however, adjusting for stage showed that the risk of death is higher for men than for women.[5] If behavior cannot account for the sex disparity, then perhaps the biology of the tumor or of the male host accounts for the male survival disadvantage (eg, tumor type [nodular] and tumor location [scalp]). The incidence of potentially lethal thick melanomas (ie, ≥4 mm) increased significantly only in men 60 years of age or older.[4]

The findings by Li et al[2] suggest a new biologic basis for the sex survival disparity by demonstrating promotion of melanoma cell invasion with sildenafil, which targets cyclic guanosine monophosphate–specific phosphodiesterase (PDE) 5A. Arozarena et al[6] demonstrated that PDE5A was downregulated in a substantial collection of melanoma lines expressing oncogenic *BRAF*, indicating that this inherent phenotype may provide a biomarker for enhanced invasiveness and poor prognostic outcome. While PDE5A drugs could theoretically promote melanoma metastasis, sildenafil did not increase mouse lung colonization by melanoma cells.[6] Since PDE5A drugs are used as needed rather than persistently and are cleared rapidly (half-life, about 2 hours), a systemic effect would be intermittent.