

Supplementary Online Content

Li WQ, Qureshi AA, Robinson KC, Han J. Sildenafil use and increased risk of incident melanoma in US men: a prospective cohort study. *JAMA Internal Medicine*. Published online April 7, 2014. doi:10.1001/jamainternmed.2014.594.

eMethod 1. Assessment of Erectile Dysfunction (ED)

eMethod 2. Melanoma-Associated Factors

eReferences for eMethods 1 and 2

eTable 1. The Hazard Ratio (HR) of Incident Melanoma, Squamous Cell Carcinoma (SCC), and Basal Cell Carcinoma (BCC) Associated With Ever Use of Sildenafil in the Past, HPFS 2000-2010

eTable 2. The HR of Incident Melanoma, SCC, and BCC Associated With Use of Sildenafil, HPFS 2000-2010, Excluding Subjects With Major Chronic Diseases at Baseline

eTable 3. The HR of Incident Melanoma Associated With Ability to Have and Maintain an Erection, HPFS 2000-2010

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethod 1. Assessment of Erectile Dysfunction (ED)

In 2000, the participants were also asked to rate their ability before 1986, 1986-1989, 1990-1994, 1995-2000, and during the past 3 months, without treatment, to have and maintain an erection adequate for intercourse. Response options included very poor, poor, fair, good and very good. Men with poor or very poor ability at or before 2000 were considered to have ED. The accuracy of a single assessment for ED has been reported extensively. A pilot study among 2072 healthy HPFS participants found that scores on the UCLA Prostate Cancer Index sexual function scale were highly correlated with the single question from that scale assessing erectile function (Pearson and Spearman $r = 0.90$).¹⁻² In addition, in a validation study of 137 men aged 55-85 years in Massachusetts Male Aging Study, ED measured by a self-reported single question, which is very similar to our question, was closely correlated with the results of an independent urologic examination (Spearman $r = 0.80$), which was composed of four major components (a physical examination, detailed sexual history, medical history, and psychosocial history). Receiver operating curve analysis showed that the self-reported ED can accurately predict the clinician-diagnosed ED (area under the curve = 0.89)³.

eMethod 2. Melanoma-Associated Factors

The positive associations of melanoma risk with older age, male sex, family history of melanoma, higher number of moles, history of severe sunburn, childhood burn reaction to sun, light hair color, higher sun exposure, and higher UV index of residence have been indicated consistently in previous studies⁴⁻⁶. Smoking was associated with a decreased risk of melanoma in the HPFS and in a meta-analysis⁷. Body mass index was found to be inversely associated with non-melanoma skin cancer in the HPFS and no association was found for melanoma⁸. However, a recent meta-analysis found a significantly increased risk of melanoma associated with overweight and obese in males⁹. In one recent study in the HPFS, physical activity was associated with a statistically significantly increased risk of both SCC and BCC, and a non-significantly increased risk of melanoma⁸.

In the prospective analysis for the association between sildenafil use and risk of melanoma, multivariate Cox-regression models were adjusted for age (continuous variable), body mass index (<24.9, 25-29.9, or ≥ 30 kg/m²), smoking (never, past, or current), physical activity (in quintiles, metabolic equivalent hours/wk), childhood reaction to sun (tan without burn, burn, or painful burn/blisters), times of sunburns (0, 1-2, 3-5, or ≥ 6), mole count (0, 1-2, 3-5, or ≥ 6), hair color (red, blonde, light brown, or dark brown/black), family history of melanoma (yes or no), sun exposures at high school, age 25-35, age 36-59, and age ≥ 60 (<5, 6-10, or ≥ 11 hours for each), UV index at birth, age 15, and age 30 (≤ 5 , 6, or ≥ 7), as well as other treatment for erectile function problems. An indicator variable was created for the missing category of each covariate. Comparing the age-adjusted HR and the multivariate-adjusted HR, adjusting for covariates only led to a slightly decrease in the effect estimates, but no material change of the associations.

eReferences for eMethods 1 and 2

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eTable 1. The Hazard Ratio (HR) of Incident Melanoma, Squamous Cell Carcinoma (SCC), and Basal Cell Carcinoma (BCC) Associated With Ever Use of Sildenafil in the Past, HPFS 2000-2010

	Person-Years	Cases	Age-adjusted HR (95% CI)	Multivariate-adjusted HR (95% CI) ^a
Melanoma				
No-use	192 053	125	1.00	1.00
Use	12 817	17	2.04 (1.22-3.40)	1.92 (1.14-3.22)
SCC				
No-use	188 863	544	1.00	1.00
Use	12 567	36	0.85 (0.61-1.19)	0.77 (0.55-1.09)
BCC				
No-use	188 863	2806	1.00	1.00
Use	12 567	224	1.11 (0.97-1.28)	1.06 (0.93-1.22)

^aAdjusted for age (continuous variable), body mass index (<24.9, 25-29.9, or ≥30 kg/m²), smoking (never, past, or current), physical activity (in quintiles, metabolic equivalent hours/wk), childhood reaction to sun (tan without burn, burn, or painful burn/blisters), times of sunburns (0, 1-2, 3-5, or ≥6), mole count (0, 1-2, 3-5, or ≥6), hair color (red, blonde, light brown, or dark brown/black), family history of melanoma (yes or no), sun exposures at high school, age 25-35, age 36-59, and age ≥60 (<5, 6-10, or ≥11 hours for each), UV index at birth, age 15, and age 30 (≤5, 6, or ≥7), as well as other treatment for erectile function problems.

eTable 2. The Hazard Ratio (HR) of Incident Melanoma, SCC, and BCC Associated With Use of Sildenafil, HPFS 2000-2010, Excluding Subjects With Major Chronic Diseases at Baseline

	Person-Years	Cases	Age-adjusted HR (95% CI)	Multivariate-adjusted HR ^a (95% CI)
Melanoma				
No-use	113 515	70	1.00	1.00
Use	5774	9	2.37 (1.17-4.77)	2.24 (1.05-4.78)
SCC				
No-use	111 692	291	1.00	1.00
Use	5676	14	0.80 (0.47-1.37)	0.80 (0.46-1.37)
BCC				
No-use	111 692	1631	1.00	1.00
Use	5676	89	1.00 (0.80-1.24)	1.05 (0.84-1.30)

^a Adjusted for age (continuous variable), body mass index (<24.9, 25-29.9, or ≥30 kg/m²), smoking (never, past, or current), physical activity (in quintiles, metabolic equivalent hours/wk), childhood reaction to sun (tan without burn, burn, or painful burn/blisters), times of sunburns (0, 1-2, 3-5, or ≥6), mole count (0, 1-2, 3-5, or ≥6), hair color (red, blonde, light brown, or dark brown/black), family history of melanoma (yes or no), sun exposures at high school, age 25-35, age 36-59, and age ≥60 (<5, 6-10, or ≥11 hours for each), UV index at birth, age 15, and age 30 (≤5, 6, or ≥7), as well as other treatment for erectile function problems.

eTable 3. The Hazard Ratio (HR) of Incident Melanoma Associated With Ability to Have and Maintain an Erection, HPFS 2000-2010^a

	Person-Years	Cases	Age-adjusted HR (95% CI)	Multivariate-adjusted HR (95% CI) ^b
Very good	56 196	39	1.00	1.00
Good	39 399	22	0.79 (0.46-1.33)	0.76 (0.45-1.30)
Fair	23 649	15	0.85 (0.46-1.58)	0.86 (0.46-1.61)
Erectile dysfunction	36 706	29	1.02 (0.58-1.80)	1.03 (0.57-1.85)

^a Users of sildenafil and other treatments for erectile function problems were excluded.

^b Adjusted for age (continuous variable), body mass index (<24.9, 25-29.9, or ≥30 kg/m²), smoking (never, past, or current), physical activity (in quintiles, metabolic equivalent hours/wk), childhood reaction to sun (tan without burn, burn, or painful burn/blisters), times of sunburns (0, 1-2, 3-5, or ≥6), mole count (0, 1-2, 3-5, or ≥6), hair color (red, blonde, light brown, or dark brown/black), family history of melanoma (yes or no), sun exposures at high school, age 25-35, age 36-59, and age ≥60 (<5, 6-10, or ≥11 hours for each), UV index at birth, age 15, and age 30 (≤5, 6, or ≥7).