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Invited Commentary

Role of Sildenafil in Melanoma Incidence and Mortality

June K. Robinson, MD

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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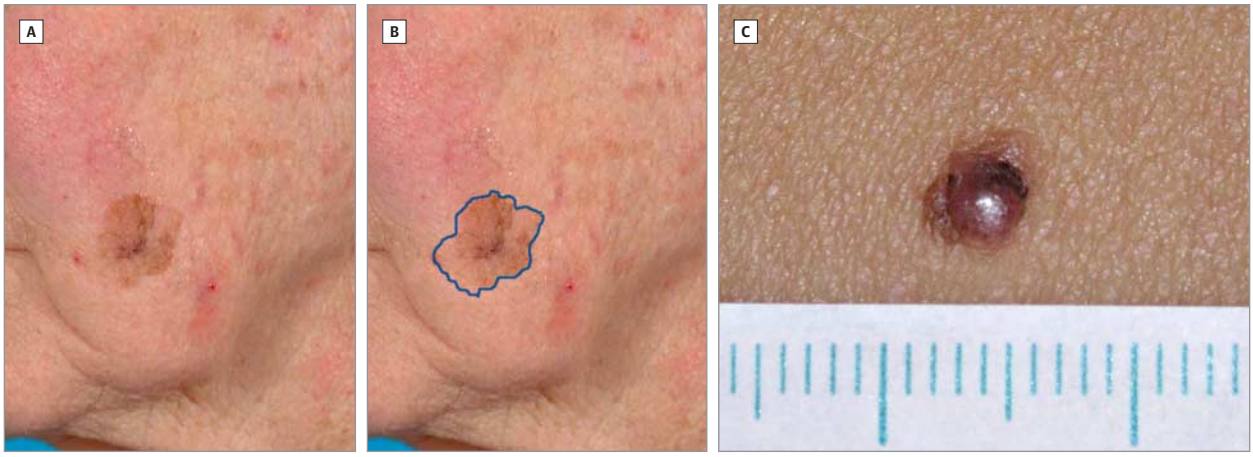
Li et al[2] performed an analysis of 25 848 men enrolled in the Health Professionals' Follow-up Study. After known risk factors were controlled for (eg, number of moles, natural hair color, lifetime number of sunburns, and family history of melanoma), sildenafil citrate (Viagra) users had an elevated 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.

Figure. Clinical Features of Melanoma



A, Macular pigmented lesion on the cheek of a man in his 80s demonstrates a diameter larger than 6 mm, a variety of tan-brown colors, and an irregular border. B, Clinically visible border traced on the image by the author demonstrates the irregular border and helps highlight the range of colors. Adapted from Guitera et al.[8] C, Clinically concerning nodular melanoma is a shiny papule with irregular borders, a hint of brown and gray at the top edge, and a 5-mm diameter. Adapted from Kalkhoran et al.[9]

The study by Li et al[2] identifies older men who use sildenafil and have a history of severe, blistering sunburns as being at risk of melanoma. Because primary care physicians are essentially the providers of care to patients older than 65 years, they are well positioned to detect early melanomas in the elderly. Melanoma screening could be performed by the physician when a sildenafil prescription is written for an older man with a history of sunburns. Some physicians will require training in screening for melanoma to improve their skills and build their confidence. Primary care physicians in Germany, after being trained for 8 hours in visual inspection of the skin, performed melanoma screening and decreased mortality from 1.9/100 000 men prior to screening (1998-1999) to 1.0/100 000 men after screening (2008-2009).[7]

With the proportion of Americans who are 65 years or older projected to increase from 12% in 2005 to 20% by 2030,[4] more patients cared for by primary care physicians will have melanomas. The mental note to screen the man requesting sildenafil could prompt the physician to check the patient's face, bald scalp, ears, and neck. It is appropriate to perform a biopsy if the physician sees a pigmented lesion with 3 of these features: a diameter of 6 mm or more, an asymmetric shape, irregular borders, and a variety of colors, ranging from tans and browns to black (**Figure**). These simple screening criteria may not help detect nodular melanomas or amelanotic melanomas, which are often smaller, lack a variety of colors, and rapidly become elevated (Figure). If a lesion is clinically concerning, the patient may return in 4 to 6 weeks to enable monitoring of the lesion for changes in the following:

- Color (multiple shades of brown, black, red, white, or blue with blending of colors)
- Size (increase of 0.5 mm in diameter within a month)
- Shape (development of irregular borders)
- Elevation (sudden appearance of a raised area within a previously flat pigmented lesion)
- Surface (spontaneous erosion, oozing, or crusting)

If changes in any of these features are identified, then a biopsy should be performed. Early detection, which may make melanoma a curable disease, may be achieved by physicians performing screening in the at-risk population for melanoma.

ARTICLE INFORMATION

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