Abstract. Long-term smoking appears to be inversely correlated with development of melanoma. Chronic ultraviolet (UV) irradiance also reduces and/or delays the development of melanoma. Thus, a common process is indicated. To examine the link between smoking and melanoma, articles reporting the relation between incidence of lung cancer and melanoma for individuals were sought. A very strong inverse correlation (r = -0.96) was found between the standardized incidence ratios for lung cancer and melanoma, passing through the value of 1 for each with a slope of -0.74. Smoking increases skin aging or elastosis in a manner similar to that of UV irradiance. Development of elastosis seems to explain why long-term smoking and chronic UV irradiance reduce the risk of melanoma. Further work is required to elucidate the mechanism whereby elastosis retards and reduces the development of melanoma.

The connection between smoking and risk of melanoma is intriguing. Most studies have reported that measures of smoking were inversely correlated with melanoma incidence (Table I). No suggestions have been made for what mechanism might explain these observations. The situation for melanoma contrasts with that for basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), for which smoking is a risk factor (3, 6-13).

In addition, body sites subject to chronic solar ultraviolet (UV) irradiance develop melanoma later in life than do sites subject to sporadic solar UV irradiance, as shown in a study of melanoma incidence with respect to body site, age, and period. In 1960-1964, a site with intermittent irradiance, the trunk, had the highest incidence rates for men aged 30-49 years, whereas sites with continuous irradiance, the head and neck, had the highest rates for men and women older than 50 years (14). Similar results were reported in a study of melanoma incidence in British Columbia (15). These studies suggest that processes associated with chronic UV irradiance decrease the risk of melanoma. This conclusion is not, however, to suggest that UV is not a significant risk factor for melanoma. Several studies have reported that UVA (320-400 nm) is an important risk factor for melanoma (16-20), and a recent review summarized the evidence for sunlight as an important risk factor for melanoma (21). However, the studies of incidence of melanoma by site and age indicate that there may be a similar mechanism explaining why smoking and chronic UV irradiance reduce the risk of melanoma. The goal of this work is to propose and evaluate a mechanism that could explain why smoking reduces the risk of melanoma.

Patients and Methods

To find studies that assessed the effects of long-term smoking along with the risk of melanoma, one must use a suitable index for smoking. A convenient one is the incidence of lung cancer by the individual or in the cohort. Lung cancer death rates are a good index of smoke exposure for approximating non-lung cancer death rates in black men (22). Lung cancer mortality rates have been used in several ecological studies of risk factors for cancer, resulting in excellent agreement with what is known about the risk of smoking for other types of cancer (23-25). It is reasonable to assume that lung cancer incidence is also a useful index of long-term smoking. In the United States, about 85%-90% of lung cancer results from smoking, with other contributions from secondhand smoke (26), air pollution (27) and occupational exposures including asbestos (28). It is expected that the nonsmoking risk factors will be similar for groups studied and that many of the nonsmoking risk factors for lung cancer will have an effect on melanoma risk similar to that of smoking. This assumption would not apply to asbestos, but asbestos probably currently accounts for few lung cancer cases.

A literature search was carried out using the National Library of Medicine’s PubMed database for reports in which risk of melanoma and lung cancer incidence rates were determined either for individuals or defined cohorts. The search was extensive but may not be exhaustive.

The reports of correlations between melanoma and lung cancer incidence are given in Table II. All these studies were observational.
Although correlations with mortality rates are also listed, they are not used in the analysis because they are also affected by the health care system of the place and time and, thus, are not entirely related to risk factors for incidence.

The data were used in a linear and quadratic regression analysis performed using SPSS 13.0 (SPSS, Chicago, IL, USA).

**Results**

The regression result is shown in Figure 1. For a linear regression of 13 values, the following expression was found:

\[ MI = 1.76 - 0.74 \times LCI, r = 0.96, \]
where MI is melanoma incidence standardized incidence ratio, LCI is lung cancer standardized incidence ratio, and r is the correlation coefficient. The regression line passes near where lung cancer and melanoma incidence equal 1.

For a second-order regression, the following expression was found:

\[ MI = 1.93 - 1.17 \text{LCI} + 0.19 \text{LCI}^2, r = 0.97 \]

Thus, this analysis indicates that long-term smoking, as evidenced by development of lung cancer, is inversely correlated with risk of developing melanoma.

**Discussion**

These results support the role of long-term smoking with risk of melanoma. With that established, it is useful to seek the mechanisms related to this finding.

Smoking generates free radicals and oxidative stress (40) and reduces the body’s antioxidant defenses (41, 42). Free radicals seem to play an important role in the etiology of BCC and SCC (43). Thus, free radical generation and reduced antioxidant defense seem to explain the association between smoking and risk of nonmelanoma skin cancer (44). Although free radicals are also involved in the etiology of melanoma (45), some other mechanism seems to override the direct effect of free radical production in the etiology of melanoma.

A second effect of smoking is increased skin aging, including elastosis (46-49). Elastosis is defined as nodular aggregations of fibrous to amorphous material in the papillary dermis (50). This effect is similar to that arising from UV irradiance (50). One article reported that smoking and sun exposure independently and synergistically contributed significantly to facial wrinkle formation (47). The mechanism underlying this effect seemed to be increased expression of matrix metalloproteinase-1 (MMP-1) (47).

"*In vitro* studies indicate that tobacco smoke extract impairs the production of collagen and increases the production of tropoelastin and matrix metalloproteinases (MMP), which degrade matrix proteins, and also causes an abnormal production of elastosis material. Smoking increases MMP levels, which leads to the degradation of collagen, elastic fibers, and proteoglycans, suggesting an imbalance between biosynthesis and degradation in dermal connective tissue metabolism. Reactive oxygen species are also involved in tobacco smoke-induced premature skin aging." (45)

However, photodamaged skin displays various levels of epidermal thickness, dermal elastosis, reduced fragmented collagen, increased MMP, inflammatory infiltrates and vessel ectasia (50). These physical changes are also likely to be generated by smoking. Thus, although elastosis is the proposed effect of skin aging that reduces the risk of melanoma, the other effects just described could also affect the risk of melanoma.

A comparison of the features of skin aging caused by UV irradiance and smoking is presented in Table III.

**Effect of skin aging on risk of melanoma.** One of the important measures of high-level sun exposure is elastosis, a condition marked by loss of elasticity of the skin due to degeneration of the connective tissue (54).

A study in Korea found that solar elastosis was present in 62.1% of the tumors on the head and neck, compared with 8.3% in those of the trunk and limbs (\( p < 0.001 \)) (55). In a study in Australia, melanomas of the head and neck were significantly more likely to have dermal elastosis (adjusted odds ratio, 9.3; 95% confidence interval, 3.5-25) than those on the back (56). The head and neck area receives much more UV irradiance than does the back in the adult period (57, 58).
Related to these observations are those indicating that melanoma develops at different ages for various anatomical sites. Melanoma is more likely to develop later in life for sites on the head and neck (14, 58-62). Some studies reported that melanoma is more likely to develop early in life for sites on the trunk (14, 58, 60, 62).

Prognosis for melanoma of the back is worse than that for the head and neck (63,64). Thus, increased elastosis is associated with better prognosis. This result probably helps explain the finding that measures of increased sun exposure were linked to increased survival rates for those diagnosed with melanoma in Connecticut (65).

**Vitamin D.** Vitamin D has been proposed as a risk reduction factor for melanoma (66). A case–control study found that oral intake of more than 158 IU of vitamin D per day per 1,000 kCal compared with less than 58 IU/day/1000 kCal was correlated with a melanoma incidence–adjusted odds ratio of 0.61 (95% confidence interval, 0.40-0.95), and the trend was significant ($p=0.03$) (67). Melanoma risk is increasingly linked to solar UVA doses (16-20, 68) and use of sunscreen that blocks UVB well but not UVA (16, 19).

In Europe, mortality rates for melanoma increase with increasing latitude, in contrast to those for nonmelanoma skin cancer, which decrease with increasing latitude in Western Europe (18, 69). Changes in skin pigmentation with latitude may explain some of the latitudinal dependence of melanoma in Europe [see (70) for a discussion of the role of skin pigmentation in regulating the penetration of UV]. Melanoma mortality inversely correlated with nonmelanoma skin cancer in Spain for women but not for men (25). Melanoma incidence rates correlated with all solid tumors except skin and lip in sunny countries, in contrast to BCC and SCC, which were correlated with reduced incidence of solid tumors (7). These findings were interpreted as showing that UVB is an important risk factor for BCC and SCC but not for melanoma (8). Thus, vitamin D probably plays a role in reducing melanoma incidence and mortality rates as well.

A study in the UK found that those with BCC who had less skin aging than their peers without BCC (71). BCC is similar to melanoma in that it occurs deeper in the epidermis than SCC. Thus, elastosis may also play a role in the etiology of BCC.

**Conclusion**

These results strongly support a beneficial role of elastosis in reducing the risk of melanoma incidence for those who smoke. These results also support a role of elastosis in reducing or delaying the development of melanoma by chronic UV irradiance. Further work is required to elucidate the mechanism whereby elastosis delays and otherwise reduces the incidence of melanoma.

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**References**


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