

# Cutaneous Malignant Melanoma in Women. Phenotypic Characteristics, Sun Exposure, and Hormonal Factors: A Case–Control Study from Italy

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**PURPOSE:** We examined the role of personal host characteristics in relation to cutaneous malignant melanoma (CMM) among women, with a particular focus on hormonal and reproductive factors.

**METHODS:** A case–control study conducted in Italy between 1992 and 1994, including 316 women with incident, histologically confirmed CMM and 308 controls, admitted to the same network of hospitals as cases for acute, non-dermatological, and non-neoplastic conditions.

**RESULTS:** CMM was significantly associated with body mass index ( $\text{kg}/\text{m}^2$ ) (odds ratio [OR] = 1.96 for  $\geq 27$  compared with  $< 23$ ) and body surface area ( $\text{m}^2$ ) (OR = 1.68 for  $\geq 1.71$  compared with  $< 1.59$ ), eye color (OR = 1.74 for green/hazel compared with brown), solar lentigines (OR = 1.47), and number of melanocytic nevi (OR = 3.39 for total number of nevi  $\geq 16$  compared with  $< 5$ ). Age at first (OR = 2.69 for  $\geq 27$  compared with  $< 23$  years) and last birth (OR = 2.13 for  $\geq 31$  compared with  $< 27$  years) were associated with the risk of CMM, whereas other reproductive, menstrual, and hormonal factors, including menopause, number of live-births and abortions, use of oral contraceptives, and hormone replacement therapy were not significantly associated.

**CONCLUSIONS:** Our results confirm findings from previous studies on the role of major recognized risk factors for CMM, and add further evidence of an absence of a consistent association between hormonal and reproductive factors and CMM risk.

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**KEY WORDS:** Hormones, Menopause, Skin Pigmentation, Sunburn, Women, Melanocytic Nevi, Cutaneous Malignant Melanoma.

## INTRODUCTION

A link between the biologic behavior of melanocytes, cutaneous malignant melanoma (CMM) onset, and female hormones was suggested by animal experiments, showing

that estrogen and estrogen-progestogen preparations may cause an increase in the number of melanocytes and their melanin content (1, 2). In humans, several biological events, such as proliferation of melanocytic nevi around puberty and reported changes in number and size of nevi during pregnancy and oral contraceptives (OC) use, were also related to hormonal influence (3). Moreover, women with a history of breast cancer appear to be at higher risk of melanoma (4–6), and the slope of incidence rates of melanoma for women levels off around age 45 to 50, suggesting that menopause could play a role (7).

The evidence from epidemiological studies (8–12), including a pooled analysis of case–control studies (13) on a total of 2391 cases, shows no strong association between OC use and CMM. However, some studies (8, 14, 15), including the Nurses' Health Study (16), reported an increased risk for prolonged (i.e.,  $\geq 5$ –10 years) OC use, in particular for current users (16), and for early age at first use (8).

With reference to reproductive factors, in a cohort study from Sweden, including 4779 incident cases, a weak inverse association was reported for multiparity, and for early age at first birth (17). A case–control study from Canada on 361

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women with malignant melanoma and a similar number of matched controls, found an inverse association between risk of melanoma and number of live-births, but no association with age at first birth, menarche, or menopause (18). Two other case-control studies confirmed these latter results (12, 19). Some studies reported direct associations with late age at first birth (14) and early age at menarche (15). Several other case-control studies from North America and Europe (11, 20, 21) found no association for menopausal status, parity, and other hormonal and reproductive factors, including use of hormone replacement therapy (HRT). Hormonal and reproductive factors, however, may be a correlate of sun exposure and careful allowance for these cofactors is therefore required.

A population-based case-control study from Connecticut found no independent association between menopausal status and risk of CMM (11). Nonetheless, cases were three times more likely than controls to be obese and to report natural menopause (11). For both sexes combined, different indices of body size, including body mass index (BMI) and body surface area (BSA), were associated with the risk of CMM (22–24). A prospective study from Norway, including more than 2800 women diagnosed with CMM, found a non-significant inverse association in obese females (25). However, three other studies, two from North America (18, 26) and one from Denmark (20), reported no association between body weight and risk of CMM.

Some of these conflicting findings may be due to inadequate adjustment for potentially confounding factors, such as sun exposure history or personal pigmentary characteristics, including number and size of melanocytic nevi. Moreover, most of previous studies are from North America, Australia, and Northern Europe, where the incidence of melanoma is higher than Italy and the correlates of the disease, mainly phenotypic characteristics, sun exposure, prevalence of exogenous hormone use, and diet are different.

We examined therefore the role of major risk factors on CMM in women, with a specific focus on reproductive, menstrual, and other hormonal factors, using data from a case-control study from Italy.

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## MATERIALS AND METHODS

The present work is based on data from a multi-center case-control study on CMM, conducted within the framework of the Italian Group for Epidemiologic Research in Dermatology (GISED) between 1992 and 1994 in 16 centers from the North and 11 from the South, and whose general design has been previously described elsewhere (27).

Briefly, for the present analyses, cases included 316 women with incident, histologically confirmed CMM (International Classification of Disease for Oncology

[ICD-O] M: 8720–8780). Of these, 235 were superficial spreading (ICD-O M: 8743), 32 nodular (ICD-O M: 8721) and 24 lentigo maligna melanomas (ICD-O M: 8742), and 25 malignant melanoma not otherwise specified (ICD-O M: 8720), acral lentiginous melanoma or other specified variants (ICD-O M: 8722, 8730, 8740, 8741, 8742, 8761, 8770–8772). Approximately 1% of cases were excluded because of a previous diagnosis of a primary CMM. Controls were 308 women admitted to the same network of hospitals as cases for a wide-spectrum of acute, newly diagnosed non-dermatologic and non-neoplastic diseases. Controls with a previous diagnosis of a neoplastic disease were excluded. Twenty-four percent of controls were admitted for acute surgical conditions (mainly benign disorders of the digestive tract), 6% for gynecologic diseases (benign inflammatory disorders of the genital tract, such as salinites, and a wide spectrum of other miscellaneous conditions), 23% had acute medical disorders, 12% had traumatic or other orthopedic conditions (approximately one-third had traumatic injuries due to traffic accidents, one-third due to recreational or job activities, and one-third miscellaneous orthopedic disorders), and 35% had other illnesses, such as disorders of the ear, nose, throat, or teeth. With reference to geographic origin, 64% of cases and controls were from Northern Italy, 26% of cases and 20% of controls were from Central Italy, and 10% of cases and 16% of controls were from Southern Italy. Less than 1% of cases and controls refused to participate, and there were no relevant differences between participants and non-participants in terms of geographic origin, diagnoses, and age and gender distribution.

A structured questionnaire was administered in person by trained interviewers to collect information on socio-demographic characteristics, anthropometric measures, pigmentary characteristics, sun exposure, diet, and personal and family history of selected medical conditions, including past dermatological reports, and excision of skin lesions. Questions centered on the lifetime history of sun exposure included information on the usual pattern of reaction to first sun exposure and history of sunburns with number and severity. Sunburns were defined as episodes of intense erythema with or without blisters causing pain and discomfort for more than 2 days. Information on reproductive and hormonal factors included age at menarche, menstrual cycle pattern, type and age at menopause, number of births, spontaneous and induced abortions, age at each birth, and lifelong use of OC and HRT.

Cases and controls were also examined by trained dermatologists who counted the number of melanocytic nevi and made judgments on pigmentary traits according to standardized criteria. Nevi  $\geq 2$  mm and  $> 6$  mm in diameter were counted over the whole body surface excluding the genitalia and scalp area. A simple instrument, called a “nevometer” was used to rapidly assess the diameter

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