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Correlations Between Cutaneous Malignant Melanoma and Other Cancers: An Ecological Study in Forty European Countries

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ABSTRACT

Background: The presence of noncutaneous neoplasms does not seem to increase the risk of cutaneous malignant melanoma; however, it seems to be associated with the development of other hematological, brain, breast, uterine, and prostatic neoplasms. An ecological transversal study was conducted to study the geographic association between cutaneous malignant melanoma and 24 localizations of cancer in forty European countries.

Methods: Cancer incidence rates were extracted from GLOBOCAN database of the International Agency for Research on Cancer. We analyzed the age-adjusted and gender-stratified incidence rates for different localizations of cancer in forty European countries and calculated their correlation using Pearson's correlation test.

Results: In males, significant correlations were found between cutaneous malignant melanoma with testicular cancer ($r = 0.83$ [95% confidence interval (CI): 0.68–0.89]), myeloma ($r = 0.68$ [95% CI: 0.46–0.81]), prostatic carcinoma ($r = 0.66$ [95% CI: 0.43–0.80]), and non-Hodgkin lymphoma (NHL) ($r = 0.63$ [95% CI: 0.39–0.78]). In females, significant correlations were found between cutaneous malignant melanoma with breast cancer ($r = 0.80$ [95% CI: 0.64–0.88]), colorectal cancer ($r = 0.72$ [95% CI: 0.52–0.83]), and NHL ($r = 0.71$ [95% CI: 0.50–0.83]).

Conclusions: These correlations call to conduct new studies about the epidemiology of cancer in general and cutaneous malignant melanoma risk factors in particular.

Keywords: Cancer, ecological, epidemiology, incidence, melanoma

INTRODUCTION

Worldwide, incidence rates of cutaneous malignant melanoma are rising in the last decades and only are exceeded by female pulmonary cancer.[1,2]

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The most evident risk factors for cutaneous malignant melanoma are environmental and lifestyles (exposure to ultraviolet [UV] radiation and geographic localization) together with individual factors (number of nevus, dysplastic nevus, family history of melanoma, immunosuppression, inability to get a tan, hypersensitivity to sunlight, clear eyes, bland, and red hair).[3] Regarding general population, the presence of

two risk factors increases the risk of cutaneous malignant melanoma 2–4 times and the presence of three or more risk factors increases the risk 20 times. Recognized risk factors do not justify more than 40% of attributable risk in the population.[1-5]

This calls to conduct further epidemiological studies and search for other risk factors such as hormones, lifestyles, alimentation, and occupation.

A classic strategy in search for new risk factors is to initiate investigation with ecological observational studies. Increased risk related to family history, genetic abnormalities affecting CDKN2A and CDK4 genes shared by other neoplasms, previous family associated neoplasms as retinoblastoma, Li–Fraumeni syndrome, and Lynch syndrome type II recommends new research lines.[4-7]

The presence of other noncutaneous neoplasms does not seem to increase the risk of melanoma; however, it seems to be associated with the development of other hematological, brain, breast, uterine, and prostatic neoplasms.[6]

The International Agency for Research on Cancer (IARC) was established in 1965 by the World Health Assembly, as independently financed organization with the structure of the World Health Organization (WHO). IARC develops research programs to study cancer epidemiology and potential human carcinogens. One of its units prompts and coordinates cancer registration worldwide.

Cancer incidence in five continents is a publication edited periodically by IARC since 1966 in collaboration with the International Association of Cancer Registries that includes information about cancer incidence in 5 years period. Information is obtained from cancer registries in different countries worldwide that satisfy basic quality requirements. Before inclusion of the registries, data are evaluated by the Editorial Committee of International Experts.[8]

Although ecological studies have several limitations and bias, they are considered simple studies and frequently used to investigate new health problems and exposures.[9] These studies are exploratory and hypothesis generating, meanwhile experimental and analytical studies are considered confirmatory for these hypotheses. Advantages of these studies include availability of data and possibility to evaluate multiple levels of exposure in different geographic areas. Several authors such as Susser suggest that ecological studies have several advantages because they investigate health problems in environmental context as the health of the population is more than pooling of individual patients. These studies have great importance in epidemiology and public health.[10]

The objective of the present study is to evaluate the geographic association between incidences of cutaneous malignant melanoma and 24 localizations of cancer in forty European countries in 2008.

METHODS

An ecological transversal study was conducted with the database of GLOBOCAN Project 2008 (IARC). Our study included the registries of forty European countries: Albania, Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Byelorussia (Belarus), Chez Republic, Croatia, Cyprus, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Island, Italy, Latvia, Lithuania, Luxemburg, Macedonia, Malta, Moldavian Republic, Montenegro, Norway, Poland, Portugal, Romania, Russia, Serbia, Slovenia, Spain, Sweden, Switzerland, The Netherlands, Ukraine, and The United Kingdom.

Registration systems of all included European countries fulfilled the quality criteria of IARC.

Of the mentioned registries, we utilized incidence rates of age-adjusted and gender-stratified for the following localizations of cancer identified with their International Classification of Diseases-10: Brain and nervous system (C70-72), colon and rectum (C18-21), esophagus (C15), stomach (C16), liver and intrahepatic biliary system (C22), Hodgkin lymphoma (HL) (C81), larynx (C32), leukemia (C91-95), cutaneous melanoma (C43), multiple myeloma (C88 and C90), nasopharynx (C11), non-HL (NHL) (C82-85, C96), oral cavity (C00-08), pancreas (C25), prostate (C61), trachea, bronchial tree, lung (C33-34), kidney and ureter, testicles (C62), thyroid (C73), urinary bladder (C67), gall bladder and extrahepatic biliary system (C23-24), breast (C50), uterine cervix (C53), uterus (C54), and ovary (C56).

Correlations were calculated using Pearson's correlation test.[10] All tests were considered statistically significant for $P < 0.05$.[11] All statistical analyses were performed using the Statistical Package for Social Sciences version 15.0 (SPSS Inc., Headquarters, Chicago, Illinois, USA).

RESULTS

The mean incidence of cutaneous malignant melanoma in males of the included European countries was 7.9 ± 4.6 per 100,000 habitants (hbs), with maximum incidence rates in Switzerland (18.1 per 100,000), Norway (17.9 per 100.000), and Sweden (16.1 per 100,000). Minimum incidence rates were reported in Cyprus (2.6 per 100,000), Greece (2.5 per 100,000), and Albania (2.2 per 100,000).

The mean incidence of cutaneous malignant melanoma in females of the included European countries was 8.4 ± 5.4 per 100,000 hbs, with maximum incidence

rates in Denmark (21.9 per 100,000), Switzerland (20.5 per 100.000), and The Netherlands (39 per 100,000). Minimum incidence rates were reported in Albania (1.7 per 100,000), Greece (2.5 per 100,000), and Cyprus (16.1 per 100,000).

The maximum correlation between mean age/sex-adjusted incidence rates of cutaneous malignant melanoma in males was shown with testicular cancer 5.4 (±2.9), cancer prostate 65 (±31.4), NHL 8.2 (±3.2), and myeloma 2.8 (±1.2).

In females, the maximum correlation between mean age/sex-adjusted incidence rates of cutaneous malignant melanoma was shown with colorectal cancer 22.9 (±5.6), breast cancer 66 (±20.6), and NHL 5.8 (±2.2).

Tables 1 and 2 show, in descending order, the highest twenty incidence rates of cancers correlated with cutaneous malignant melanoma. Of every cancer, we included countries with incidence rates over the mean incidence rate with 1 or 2 standard deviations.

Analyzing incidence rates of cutaneous malignant melanoma in males, maximum correlation was found with testicular cancer ($r = 0.83$ [95% confidence interval (CI): 0.68–0.89]) followed by myeloma ($r = 0.68$ [95% CI: 0.46–0.81]), cancer prostate ($r = 0.66$ [95% CI: 0.43–0.80]) and NHL ($r = 0.63$ [95% CI: 0.39–0.78]). All these correlations were statistically significant with $P < 0.05$.

In females, cutaneous malignant melanoma had maximum correlations with breast cancer ($r = 0.80$ [95% CI: 0.64–0.88]), colorectal cancer ($r = 0.72$ [95% CI: 0.52–0.83]), and NHL ($r = 0.71$ [95% CI: 0.50–0.83]). All these correlations were statistically significant with $P < 0.05$.

DISCUSSION

Currently, identification of cutaneous malignant melanoma risk factors is the most crucial problem in the epidemiology of the disease. The present study aims to evaluate the geographic association between cutaneous malignant melanoma and other 24 types of localizations of cancer.

Potential limitations and objections of the methodology of our study should be considered before interpreting the results. Many investigators consider that ecological studies could only raise hypotheses. Our results only belong to forty European countries and could not be generalized although the methodology can be applied in other continents. Another possible bias is the instability of calculated rates for a relatively rare disease such as cancer. We should also consider the cyclical oscillation of rates over time. We tried to avoid these possible biases including only registration systems that fulfilled the quality criteria of the IARC and WHO.

The associations found could be attributed to the fact that some cancers are consequence or secondary to other type of cancer. Chemotherapy and/or radiotherapy could produce an iatrogenic effect and the presentation of second cancer because of improved life expectancies with modern treatments.

Table 1: Males' incidence rates per 100.000 adjusted by age and sex of 5 cancers in 20 European countries (Descending order)

Country Melanoma	Country Testicle	Country Myeloma	Country Prostate	Country NHL
Switzerland 18,1	Norway 12,1	Iceland 5,7	Ireland 126,3	Luxemburg 13,6
Norway 17,9	Denmark 10,3	Norway 4,8	France 118,3	Finland 13,1
Sweden 16,1	Slovenia 9,3	France 4,6	Iceland 112,1	Norway 12,8
Denmark 15,4	Switzerland 9,0	The Netherlands 4,5	Norway 104,1	Belgium 12,8
The Netherlands 14,7	Slovakia 8,8	Belgium 4,4	Belgium 100,5	UK 12,4
Slovenia 14,1	Luxemburg 8,8	Italy 4,3	Sweden 95,5	The Netherlands 12,3
Czech Republic 13,3	Czech Republic 8,7	UK 4,1	Switzerland 91,3	Italy 12,2
UK 11,9	Germany 8,5	Ireland 4,1	Finland 83,2	Ireland 12,0
Germany 11,9	Ireland 8,1	Sweden 3,9	Germany 82,7	Cyprus 11,7
Finland 11,8	The Netherlands 8,0	Slovenia 3,8	Luxemburg 74,8	France 11,6
Iceland 11,6	Hungary 7,7	Slovakia 3,8	Denmark 72,5	Denmark 11,4
Ireland 10,9	Austria 7,4	Finland 3,5	Austria 70,7	Switzerland 10,6
Hungary 9,9	France 7,1	Germany 3,4	The Netherlands 67,7	Sweden 10,0
Slovakia 9,5	Croatia 7,1	Luxemburg 3,4	Lithuania 66,7	Iceland 10,0
Italy 9,2	Cyprus 6,8	Spain 3,4	Czech Republic 66,6	Spain 9,6
Austria 8,4	UK 6,6	Switzerland 3,3	Latvia 66,4	Malta 9,4
Croatia 8,3	Italy 6,4	Denmark 3,2	UK 64,0	Germany 9,3
Luxemburg 8,3	Sweden 6,1	Lithuania 3,1	Slovenia 62,8	Portugal 9,0
Belgium 8,1	Bulgaria 5,6	Czech Republic 2,8	Italy 58,4	Austria 8,5
France 7,4	Iceland 5,5	Estonia 2,8	Spain 57,2	Slovenia 7,9

Table 2: Females' incidence rates per 100.000 adjusted by age and sex of 4 cancers in 20 European countries (Descending order)

Country Melanoma	Country Colorectal	Country Breast	Country NHL
Denmark 21,9	Norway 34,0	Belgium 109,2	Ireland 9,8
Switzerland 20,5	Denmark 33,5	Denmark 101,1	Italy 9,4
The Netherlands 18,8	The Netherlands 32,3	France 99,7	Finland 9,2
Norway 16,5	Hungary 30,8	The Netherlands 98,5	Luxemburg 9,0
Sweden 16,1	Italy 29,9	Iceland 95,5	UK 8,7
Slovenia 15,2	Belgium 29,5	Ireland 93,9	The Netherlands 8,6
Ireland 14,7	Slovakia 29,2	Switzerland 89,4	Belgium 8,6
UK 13,2	Ireland 28,8	UK 89,1	Norway 8,3
Iceland 12,9	Czech Republic 27,5	Finland 86,3	Denmark 8,1
Belgium 12,7	Germany 27,3	Italy 86,3	France 7,9
Germany 12,6	Slovenia 26,2	Luxemburg 82,3	Sweden 7,4
Czech Republic 12,0	Luxemburg 25,9	Germany 81,8	Spain 7,3
Luxemburg 11,1	UK 25,3	Sweden 79,4	Portugal 7,1
Finland 10,2	Sweden 25,0	Norway 73,5	Germany 7,0
France 8,9	Croatia 24,3	Malta 72,2	Slovenia 7,0
Italy 8,7	France 24,1	Czech Republic 70,9	Cyprus 6,6
Slovakia 8,4	Portugal 24,1	Cyprus 67,5	Estonia 6,5
Malta 7,8	Iceland 23,4	Slovenia 64,9	Malta 6,4
Austria 7,4	Bulgaria 23,3	Croatia 64,0	Switzerland 6,3
Croatia 7,3	Spain 22,9	Austria 62,1	Czech Republic 6,1

Lens and Newton-Bishop conducted a systematic review about the association between cutaneous malignant melanoma and other types of cancer.[12,13] All reviewed studies included the risk of second cancer in the evolution of cutaneous malignant melanoma and NHL. One of the possible causes of this association could be the exposure to UV rays, known risk factor for cutaneous malignant melanoma. In addition, there is a clear interaction between exposure and inheritance, as well as CDKN2A gene. This gene is quite frequent in Australian and European patients with cutaneous malignant melanoma and usually associated with defects in MCIR gene which codes hair color and susceptibility to sunburns. In addition, UV radiations affect the immune response both systematically and locally in the skin. UV-B (270–320 nm) radiation has the ability to impair the cutaneous immune system activity altering the antigen-presenting cells in the skin and reducing the hypersensitivity response as well as T-lymphocytes.[14-18]

The selection of countries in this study has been based on the homogeneity in terms of geographical location together with the importance of phenotypes of Nordic countries as a risk factor for cutaneous malignant melanoma.[19,20]

A possible selection bias could be attributed to the nonrandom choice of countries to study. Our goal was not to include the European countries as representative of the population worldwide but rather extrapolate the results only for the studied population.[19-22]

Our results show associations between cutaneous malignant melanoma and other hormone-related cancers such as breast, testis, and prostate. This confirms recent concepts that skin should be considered the largest peripheral endocrine organ.

Series of data were reported that make plausible relationship between estrogen and risk of cutaneous malignant melanoma, especially from the epidemiological point of view[23] such as highest prevalence among females (ratio men:women 1:1.8), rise from menarche and decline after menopause, and higher survival in women. The physiological plausibility includes changes in nevi melanocytic, chloasma, and increased pigmentation in other areas such as areolas, linea alba, and perineal skin during pregnancy,[24] and hyperpigmentation of the face in 8–29% of oral contraceptives users. Moreover, *in vitro* studies shows that estradiol (E2) favors proliferation of melanocytes and reduces tyrosinase activity and melanin content, presence of hormonal receptors for E2 (estrogen receptor [ER]) in melanocytes and cutaneous malignant melanoma,[25-28] and presence of ER type β in malignant and benign melanocytic lesions.[26]

To date, the presence of ER in cutaneous malignant melanoma is a controversial issue although it has been demonstrated that there are subgroups of cutaneous malignant melanoma cells expressing it.[29,30]

In vitro studies of cutaneous malignant melanoma suggest that estrogens have effects on cell growth; however, results are difficult to interpret because of insufficient knowledge about the effects of the stimulation of ER-β and its interaction with the activation of the ER-α. In case of endometrial carcinoma and breast cancer, the nucleic and nonnucleic effects of ER have been demonstrated. Recently, it was reported that ER-α produces epigenetic alterations in cutaneous malignant melanoma through hypermethylation of the gene and consequently progression of the tumor.[31]

Epidemiology is another approach for formulating the question of whether there is a link between sex steroids and cutaneous malignant melanoma. Till date, only a few epidemiological studies about this association deserve to be highlighted. The largest prospective study of Feskanich *et al.* included 183,693 women and 252 cutaneous malignant melanomas.[32] They carried out logistic regression analysis to control possible confounding factors such as skin type, hair color, number of nevus, family

history family of melanoma, history of burns, body mass index, weight, and parity. The authors concluded that premenopausal white women with >10 years use of anovulatory anticonceptives had significantly higher risk of developing cutaneous malignant melanoma.

Gefeller *et al*. conducted a meta-analysis pooling 18 case–control studies to examine the same association, but they did not confirm the association between anticonceptives and the risk of cutaneous malignant melanoma.[33] In concordance, Karagas *et al*. carried out an aggregated analysis of case studies and controls that comply with requirements such as controlled confusion biases, community-based population, and included at least 100 cases and controls. The ten studies that fulfilled these inclusion criteria confirmed that oral contraceptives use does not increase the risk of developing cutaneous malignant melanoma.[34]

CONCLUSIONS

The correlation found between cutaneous melanoma and other malignancies of different embryonic origin raises hypothesis about its etiology. Our results call for further investigation of cutaneous melanoma etiology and possible risk factors; future epidemiological studies should be conducted on large prospective cohorts to improve their internal validities.

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Conflicts of interest
There are no conflicts of interest.

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