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Acne in late adolescence is not associated with a raised risk of subsequent malignant melanoma among men

Teresa Mota Garcia[a], Ayako Hiyoshi[b,*], Ruzan Udumyan[b], Hugo Sjöqvist[b,c], Katja Fall[b,d], Scott Montgomery[b,e,f]

[a] Faculty of Health Sciences of the University of Beira Interior, Av. Infante D. Henrique, 6200-506 Covilhã, Portugal
[b] Clinical Epidemiology and Biostatistics, School of Medical Sciences, Örebro University, SE 701 82 Örebro, Sweden
[c] Department of Statistics, Örebro University, 701 82, Örebro, Sweden
[d] Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, SE 171 77, Stockholm, Sweden
[e] Clinical Epidemiology Unit, Department of Medicine, Karolinska University Hospital, Solna, Karolinska Institutet, SE 171 76 Stockholm, Sweden
[f] Department of Epidemiology and Public Health, University College, WC1E 6BT London, UK

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ABSTRACT

Background: To evaluate the association of acne in late adolescence with the risk for subsequent malignant melanoma (MM) in men.

Methods: Swedish register-based cohort study of 242,096 males born between 1952 and 1956, who took part in compulsory assessments for Swedish military conscription in late adolescence between 1969 and 1975, with subsequent diagnoses of MM (n = 1,058) up to December 31, 2009. Covariates included measures of childhood circumstances and information from adolescence on presence of acne, physical fitness, cognitive function, body mass index (BMI), and a summary of diagnoses. Cox regression was used for the analysis.

Results: In total 1,058 men were diagnosed with MM. Acne was not associated with subsequent MM, with an adjusted hazard ratio (and 95% confidence interval) of 0.95 (0.61 to 1.49). Men with parents who were agricultural workers, and men who lived in northern Sweden, had lower physical fitness, or lower cognitive function had a lower risk of MM. Overweight and obesity was associated with a raised risk, with an adjusted hazard ratio of 1.39 (1.14, 1.71).

Conclusions: Acne in late adolescence is unlikely to represent a raised risk for subsequent MM in men. Overweight or obesity was identified as a raised risk for MM, possibly due to the associated increased skin surface area.

1. Introduction

Malignant melanoma (MM), once an uncommon disease, has increased in incidence (160,000 new diagnoses per year throughout the world) and with increased mortality rates over the last few decades [1]. The incidence has been notably higher in countries further north or south from the equator, including northern Europe, Australia and New Zealand [1]; and there is growing concern about the possible causes of MM to develop preventive measures. Although ultraviolet exposure, skin phenotype and genetics indicated by family history are known risk factors for MM [2], it may have a heterogeneous aetiology due to differing involvement of the immune and the hormonal systems [3,4], including immune system influences on inflammation in MM [5–7]. Melanoma risk may be influenced by androgens, the steroid hormones [3]. It is therefore of interest to examine the association of acne with MM because both are influenced by the immune and endocrine systems. Acne is often caused by Propionibacteria acnes (P. acnes) [8], a commensal bacteria responsible for activation of T-cells and production of proinflammatory cytokines [9–11] and corticotropin releasing hormone (CRH) [12] and individuals with acne tend to have higher levels of androgens [13].

There is evidence that P. acnes can be used intratumorally as a therapeutic agent that may cause regression of MM in an animal model [14]. However, in human studies, the results remain inconclusive. A study by Zhang et al. (Nurses' Health Study II – NHSII) found that teenage acne was associated with a 30–40% increased risk of developing MM [15]. In contrast, Beral et al. reported that acne has an inverse association with MM [16]. Elwood et al. did not find an association between the acne and MM [17]. Potential limitations of these studies include that the Nurses' Health Study was limited to women

* Corresponding author at: Clinical Epidemiology and Biostatistics, School of Medical Sciences, Örebro University, 703 62, Örebro, Sweden.
E-mail address: ayako.hiyoshi@oru.se (A. Hiyoshi).

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[15] while other studies identified acne retrospectively, so they may have suffered from recall/reporting bias.

Zhang et al. speculated that androgen levels may be important in explaining the raised risk of MM associated acne in adolescence: Zhang's study and the study by Beral et al. were of women, although the study by Elwood et al. involved both sexes. Therefore, little is known about P. acnes infection in men and MM risk; also there remains a paucity of studies using prospectively recorded data with long duration of follow-up and adequate statistical power. We do not know of any studies that specifically examined associations of acne in adolescence, when it is common, with MM in later adulthood.

This study uses a prospectively recorded measure of acne in adolescence, performed during a medical examination for compulsory military conscription among a large and representative cohort of males from the general population in Sweden, with follow-up into middle-age to identify associations with MM using national registers.

2. Methods

2.1. Study design and population

This is a register-based cohort study of the majority of males born between 1952 and 1956 and resident in Sweden when they took part in assessments for compulsory Swedish military service conscription (SMSC) from 1969 to 1975, typically at ages 18–19 years. A subsequent diagnosis of malignant melanoma was assessed from immediately after the date of SMSC to December 31, 2009 (up to age 57 years).

A total of 284,257 cohort members were identified and 42,161 were excluded due to: errors in personal identification number, uncertain vital status or female sex (n = 2,848); emigration or death before the date of SMSC (n = 162); did not attend the conscription assessment between ages 17 and 20 years (n = 5,379); diagnosis of malignant melanoma or any other cancer before the date of SMSC (n = 206); missing data for variables used in the analysis or an incomplete summary health score (n = 33,566). Some 242,096 men remained for analysis.

2.2. Measures

This first lifetime diagnosis of MM was obtained from the Swedish Cancer Register using International Classification of Diseases (ICD) revision 7. The diagnosis was clinical, morphological, or from laboratory examination. The diagnostic code for malignant melanoma of the skin is 190; and in situ melanoma of the skin was not included. The Swedish Cancer Register began in 1958, has national coverage, and records more than 99% of cancer diagnoses made in Sweden.

The 1960 Population and Housing Census provided information on childhood circumstances, which was used to adjust for socioeconomic characteristics in childhood [18,19]. *Head of household's (parents') occupation* was classified into manual workers, agricultural workers, farm owners/managers, officer workers, business owners/managers, and other/unknown. *Household crowding* was calculated by dividing the number of household members by the number of habitable rooms divided into quarters of the distribution.

The Total Population Register provided information on geographical region of residence – grouped into northern, southern and central Sweden – which is associated with MM risk [20–22]. This register also provided information on dates of death, immigration and emigration to censor follow-up duration.

The SMSC Register has been described in greater detail elsewhere [23] and provided information on physical and psychological characteristics in late adolescence. *Acne* was identified through medical examination, history and record review (as were other diagnoses) and defined using ICD-8: 706.00, 706.01, 706.10, 706.11, 706.12 and 706.20; and these codes can be used to differentiate between severe and non-severe acne. The codes were combined for the main analysis, and severe acne investigated only in a sensitivity analysis. *Physical fitness* was tested using a bicycle ergometer, classified into three categories – from 1 (lowest fitness) to 3. *Cognitive function* was measured by evaluating spatial recognition, linguistic understanding, general knowledge and ability to follow mechanical instructions [22]. The result was a normally distributed nine level scale, classified into three categories. *Body mass index* (*BMI*) [24–26] was calculated from height and weight, then classified into three categories, according to WHO criteria: underweight (≤ 18.49 kg/m^2); normal weight (18.5–24.99 kg/m^2); overweight/obese (≥ 25 kg/m^2). A *disease summary score* was evaluated by a physician following record review and examinations. This score identified diagnoses – principally of any chronic or clinically significant diseases – producing a score that reflected the extent to which the diseases were limiting in daily life. This produced a score of 0–9, which was subsequently classified into four categories: significant problem (2–3), fairly significant problem (4–5), no serious problem (6–8), no diagnosis (9). Individuals with ill-defined problem (n = 23) were excluded.

2.3. Statistical analysis

The χ^2 test was used to assess the associations between acne during adolescence and the other measures. Cox regression was used to assess the association between acne in adolescence and subsequent risk of MM. Follow up was from conscription assessment to the first diagnosis of MM, death, emigration or December 31, 2009, whichever occurred first. The Schoenfeld residuals test was used to assess the proportional hazards assumption for the association of acne with MM and did not indicate a violation of proportionality (p = 0.479). Adjustment was performed using the covariates. All tests are two-sided and p values < 0.05 or confidence intervals not including 1.00 were considered statistically significant. IBM SPSS (version 22) and Stata 14 were used to perform the statistical analysis. This study was approved by Uppsala Regional Ethics Committee (Dnr 2014/324).

3. Results

Mean age at the start of follow-up was 18.6 years (standard deviation (SD) 0.5) and 55.5 (SD 1.4) years at the end of follow-up. In total 1058 men (0.4%) were diagnosed with MM during follow-up.

Table 1 summarises the characteristics of the study population divided by presence of notable acne in late adolescence. The χ^2 test identified statistically significant association with presence of acne for BMI, cognitive function, parental occupation and county of residence in childhood. None of the men with acne had 'no diagnosis' in the disease summary score, due to the diagnosis of acne: the majority with a diagnosis of acne were categorized as having no serious problem.

Table 2 shows the unadjusted and adjusted associations between acne in late adolescence and subsequent MM. Acne was not associated with MM in the unadjusted model and the estimate was almost unaltered following adjustment for all covariates. Exclusion of the variables that did not have a statistically significant association with MM, to produce a more parsimonious model, did not alter any of the other estimates notably. The adjusted hazard ratio (and 95% confidence interval) for the association of acne with MM is 0.94 (0.60–1.47; p = 0.791). A sensitivity analysis examined those with more *severe* acne in adolescence (n = 39), but none of these men received a diagnosis of MM. In the unadjusted model, the hazard ratio for MM (and 95% confidence interval) is 0.95 (0.61–1.47; p = 0.805) for acne, but no estimate could be produced for severe acne due to an empty cell (p = 1.00). In the adjusted model, the estimates are 0.96 (0.61–1.50; p = 0.856) and p = 1.00.

Exclusion of men with another cancer diagnosis prior to first MM did not alter the results notably (data not shown). In the adjusted model, a higher risk of MM was associated with overweight and obesity, living in southern Sweden, higher level physical fitness, and higher