Protocol for retrospective study assessing the relationship between serum Vitamin D levels and severity of malignant melanoma

Research question: Is there a relationship between serum Vitamin D level and clinical / histological indicators of severity in malignant melanoma?

Background:

Cutaneous malignant melanoma is a potentially aggressive tumour originating from melanocytes. The incidence is increasing rapidly on a global scale [Gladfelter, 2017] and is currently the third most common cancer in Europe after cancers of the colon/rectum and the lung [Ferlay, 2012; Whiteman, 2016].

Various different risk factors have been showed to be associated with cutaneous malignant melanoma. The strongest risk factors are a family history of melanoma, multiple benign or atypical naevi and a previous melanoma [Bataille, 2008]. Additional risk factors include immunosuppression and exposure to UV light [Gandini, 2005].

The most important predictor for melanoma relapse and melanoma specific survival is Breslow thickness of the primary tumour at diagnosis [Elder, 2005]. The AJCC (American Joint Committee on Cancer) staging system for malignant melanoma also includes other important prognostic factors, including the presence of mitoses and ulceration status [Balch 2009].

Vitamin D, a fat-soluble seco-steroid, has two sources. The main source, vitamin D3 (cholecalciferol) is the skin. The other source, vitamin D2 (ergocalciferol) and D3, is exogenous and is ingested via dietary intake or supplements. The endogenous pathway is the most important source of vitamin D for humans. 7-dehydrocholesterol (7-DHC), a provitamin in the epidermis, is photoactivated by ultraviolet B (UVB) radiation into provitamin D3. A series of modifications in the skin, liver and kidneys metabolizes vitamin D2 and vitamin D3 (dietary and endogenous) into the active substance 1α,25 dihydroxyvitamin D3 (calcitriol, 1,25(OH)2D3). 1,25(OH)2D3 and retinoid X receptor form a heterodimer and have an effect on gene expression by binding to the vitamin D receptor [Field S, 2011].

The impact of vitamin D deficiency has been reported for various different types of cancer [Holick, 2006, Chen, 2003] and several studies have shown that higher vitamin D levels at diagnosis are associated with thinner primary melanomas [Newton-Bishop, 2009; Gambichler, 2013]. A recent publication in the British Journal of Dermatology showed that primary tumours in Vitamin D deficient patients were associated with higher mitotic rate and ulceration [Lo, 2017].

Aims

a) To evaluate relationship between Vitamin D levels and malignant melanoma clinical outcomes including staging and metastasis over a 2 year period
b) To evaluate the relationship between Vitamin D levels and histological features including Breslow thickness, mitosis and ulceration over a 2 year period
c) To respond to BJD paper by Lo *et al.* including data from Nottingham and more appropriate statistical analysis.

Outcome

Primary

Relationship between Vitamin D levels and Breslow Thickness

Secondary outcomes

Relationship between Vitamin D levels and:

- Mitosis
- Ulceration
- Pathological staging
- Metastatic Spread
- Clinical stage
- Histological sub-type
- Tumour site
- Age
- Gender

Methodology:

The study design is a retrospective case-note series of patients with malignant melanoma diagnosed between 1st August 2015- 1st August 2017.

Data collection was performed by doctors working in the Dermatology department at the NHS Treatment centre Nottingham. All patients diagnosed with a cutaneous invasive malignant melanoma between 1st August 2015 and 1st August 2017 were analysed. The online NOTIS (Nottingham University Hospitals Electronic Results System) was used to access medical records for the cohort of patients identified, including histology results and clinic letters. An excel spreadsheet was created in order to record patient demographics including sex, and age. Date of diagnosis and date of vitamin D level will also be recorded. The Vitamin D level closest to the date of malignant melanoma diagnosis was used. Those with no vitamin D levels on NOTIS were excluded from the data set. Clinical and histological data collection will include; Vitamin D levels, Breslow thickness, Tumour site, Histological sub-type, pathological stage, metastatic status, clinical stage, ulceration and number of mitosis.

Analysis

Pearson's correlation will be calculated for two continuous variables. T-test or ANOVA will be conducted for continuous and categorical variables. If the data are non-normal then non-parmaetic methods (Spearman's correlation coefficient, Mann-Whitney and Kruskal-Wallis) will be used instead.

References

Gladfelter P, Darwish NHE, Mousa SA. Current status and future direction in the management of malignant melanoma. Melanoma Res. 2017 Oct;27(5):403-410.

Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 2013;49:1374–40.

Whiteman DC, Green AC, Olsen CM. The growing burden of invasive melanoma: projections of incidence rates and numbers of new cases in six susceptible populations through 2031. J Invest Dermatol 2016;136:1161–7.

Bataille, de Vries. Melanoma—Part 1: epidemiology, risk factors, and prevention. BMJ 2008;337:a2249.

Gandini S, Sera F, Cattaruzza MS, Pasquini P, Zanetti R, Masini C, Boyle P, Melchi CF. Meta-analysis of risk factors for cutaneous melanoma: III. Family history, actinic damage and phenotypic factors. Eur J Cancer. 2005 Sep;41(14):2040-59.

Elder DE[1], Gimotty PA, Guerry D. Cutaneous melanoma: estimating survival and recurrence risk based on histopathologic features. Dermatol Ther. 2005 Sep-Oct;18(5):369-85.

Balch CM, Gershenwald JE, Soong SJ et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol. 2009; 27:6199–206.

Field S, Newton-Bishop JA. Melanoma and vitamin D. Mol Oncol. 2011;5:197–214.

Holick MF: Vitamin D: Its role in cancer prevention and treatment. Prog Biophys Mol Biol 92: 49-59, 2006.

Chen TC, Holick MF: Vitamin D and prostate cancer prevention and treatment. Trends Endocrinol Metab 14:423-430, 2003.

Newton-Bishop JA, Beswick S, Randerson-Moor J, Chang YM, Affleck P, Elliott F, Chan M, Leake S, Karpavicius B, Haynes S, Kukalizch K, Whitaker L, Jackson S, Gerry E, Nolan C, Bertram C, Marsden J, Elder DE, Barrett JH, Bishop DT. Serum 25-hydroxyvitamin D3 levels are associated with Breslow thickness at presentation and survival from melanoma. J Clin Onc. 2009;27(32):5439–44.

Gambichler T, Bindsteiner M, Hoxtermann S, Kreuter A. Serum 25-hydroxyvitamin D serum levels in a large German cohort of patients with melanoma. British J Dermatol 2013; 168:625–8.

Lo MCI, Maraka J, Garioch J, John WG, Moncrieff M. Monitoring vitamin D in the patient with melanoma: impact of sun avoidance on vitamin D levels of patients with melanoma at a U.K. tertiary-referral melanoma service. British Journal of Dermatology (2017) 177, pp282–283.