



ELSEVIER

Is the seasonal variation in cancer prognosis caused by sun-induced folate degradation?

Arnfinn Hykkerud Steindal ^{a,*}, Alina Carmen Porojnicu ^{a,b},
Johan Moan ^{a,c}

^a Department of Radiation Biology, Institute for Cancer Research, Health Enterprise, Rikshospitalet – Radiumhospitalet, Montebello, N-0310 Oslo, Norway

^b Department of Biophysics and Cell Biotechnology, Carol Davila University of Medicine and Pharmacy, 15-205 Bucharest, Romania

^c Department of Physics, University of Oslo, N-0316 Oslo, Norway

Received 4 July 2006; accepted 6 July 2006

Summary Recently, we have documented that the season of diagnosis affects the prognosis of Hodgkin's lymphoma, colon-, breast- and prostate-cancer patients in Norway. The relative risk of death was lower for the patients diagnosed during summer and autumn when compared with the winter diagnosis. We here hypothesise that UV (ultraviolet) induced degradation of folate may be the reason for the observed seasonal variations in cancer prognosis. It is known that folic acid, a synthetic form of folate, is degraded by UV radiation. We have also found that the most common folate derivative in the human body, 5-methyltetrahydrofolate, is UV sensitive.

© 2006 Elsevier Ltd. All rights reserved.

Introduction

We have found that prognosis of several cancer forms varies with the season of diagnosis and therapy start [1–3]. The relative risk of death after an 18 month follow-up was 20–50% lower for the cases diagnosed during summer and autumn compared with winter diagnosis. A recent study from UK, looking at cancer prognosis by season of diagnosis in over 1 million patients, found similar results [4]. We

proposed that this seasonal variation might be related to the variation in the UV induced vitamin D₃ production. It is well known that the main source of vitamin D₃ in humans is exposure to sun. In Norway as in many other countries there is significantly more (20–120%) calcidiol (25 hydroxyvitamin D₃) in human serum in summer and autumn than in winter and spring [5].

We here propose an alternative explanation of our cancer survival data, one related to folate photodegradation. Solar radiation can degrade folate, a vital B-vitamin derivative [6]. Furthermore, antagonists of folate, such as metotrexate, are used in cancer therapy [7]. The rationale for this is that all cell division (i.e. DNA synthesis) is

* Corresponding author. Tel.: +47 22934443; fax: +47 22934270.

E-mail address: arnfinn.hykkerud.steindal@rr-research.no (A.H. Steindal).

dependent on folate and folate derivatives. Folate antagonists slow down cell division, and since cancer cells often divide fast, tumours are presumably selectively affected. The synthetic form of folate, folic acid, is known to be sensitive to UV radiation [8]. However, the photobiophysics of organic derivatives of folate is hardly investigated at all. Our preliminary experiments indicate that these derivatives are UV sensitive. Scientists have suggested that the evolutionary reason for the brown skin colour of people living near the Equator is protection of folates in the blood from sun-induced degradation [9].

Hypothesis

The observed seasonal variation in survival rate of several types of cancer in Norway is due to photodegradation of folate by sun exposure. Thus, the folate levels in the serum of these patients may be lower in summer and autumn than in winter.

Evaluation of the hypothesis

(a) Folate-cancer connection

Folate is necessary for the biochemical formation of thymidine, one of the four bases in DNA [10], being therefore an essential factor in DNA replication and cell division. In tissues with rapidly dividing cells, such as cancer tissues, a low folate level would be expected to alter the DNA synthesis and to induce an inhibition of tumour growth and an increase in the chance of survival. This has been

the rational for using antifolate derivatives (such as methotrexate) as anticancer agents in clinical practice [11]. Clinically, it has been reported that folate treatment of children with acute leukaemia results in an accelerated evolution of the cancer [12]. Animal experiments support this view, showing that folate deficiency delays tumour progression [13,14].

(b) UV degrades folate in vitro

Folic acid (FA), a synthetic form of folate, is sensitive to UV radiation [8]. We have also found that 5-methyltetrahydrofolate (5MTHF), the most common folate derivative in the human body (80–90%), is UV sensitive (unpublished data). Upon UV exposure, 5MTHF is oxidized to 5-methyldihydrofolate and, after continuous irradiation, 5-methyldihydrofolate is broken down to *p*-aminobenzoyl glutamic acid and a pterin moiety [6]. 5-methyldihydrofolate is probably not re-entering the folate pool in the human body [15], so the first step of photolysis is enough to degrade the folate.

FA is even degraded by UVA radiation (320–400 nm), although 5MTHF absorbs little UVA, mainly UVB (280–320 nm, Fig. 1). UVB is not penetrating deeply into the skin, and, therefore, very little of the UVB reaches the blood stream. This means that direct photodegradation of 5MTHF may not be efficient enough to be of biological significance. On the other hand, indirect degradation of folates may take place. 5MTHF has a high antioxidant activity [16]. We have found that 5MTHF is quickly oxidized to 5MDHF during light exposure in the presence of photosensitizers (unpublished data). Therefore, reactive oxygen species (ROS)

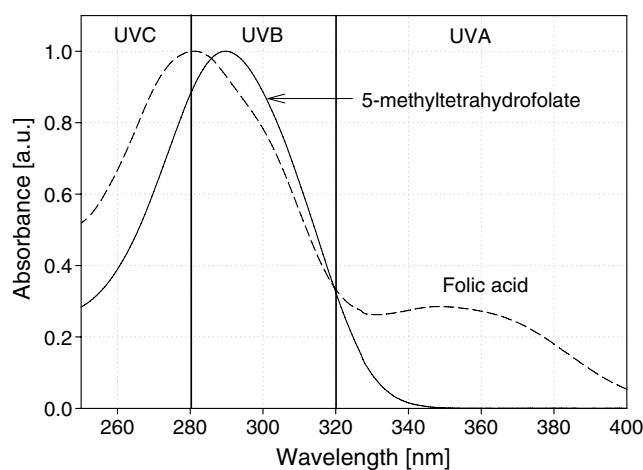


Figure 1 Normalized absorption spectra of 5-methyltetrahydrofolate (solid line) and folic acid (dashed line) in PBS at pH 7.4. Folic acid absorbs both UVA and UVB, while 5-methyltetrahydrofolate mostly absorbs UVB.

produced in human tissues by UVA radiation may degrade 5-methyltetrahydrofolate. Possibly, even radiation of longer wavelengths than those in the UVA region may degrade 5MTHF. Such radiation penetrates well to the blood vessels in the dermis. Several photosensitizers are present in low concentrations in human serum: porphyrins, flavins, bilirubin and substances in food.

(c) Seasonal variation in UV fluences

In Norway, there is a large variation in solar UV radiation. The daily UV-dose in Oslo (60 °N) averaged for the period 1995–2001 was 2232 and 82 J/m² in summer (June–August) and winter (December–January), respectively [17]. The corresponding values for Tromsø (70 °N) are 1550 and 19 J/m².

(d) UV might degrade folate in vivo

The birth rate of children with neural tube defect (NTD), a disease closely related to folate deficiency, varies with season [18]. A proposed mechanism of this seasonality has been the UV induced folate degradation [19]. UV is even included in a mathematical model for NTD incidence [20]. These findings may certainly have other reasons than direct UV exposure. Van Rootselaar suggested that the herpes virus might be involved in the connection between UV exposure and NTD [20].

In vivo photodegradation of folate has been seen also in psoriasis patients undergoing UV treatments. We have measured a slightly lower amount of erythrocyte folate in eight out of ten patients after several UVB phototherapy sessions (unpublished work).

There are some indications of seasonal variations in the folate level. Hao et al. found that the folate concentrations (both in serum and in erythrocytes) were lower in fall than in spring for people living in the southern China [21]. The result was opposite for the northern China, but this can be explained by limited supply of fresh vegetables during winter and spring for the rural population in the north. Ronnenberg et al. found a lower folate concentration during summer among Chinese women of childbearing age [22]. One point that has to be stressed is the fact that folate intake through diet may vary with season, because of changes in vegetable intake.

If our hypothesis is correct, sun-induced degradation of blood folate might act beneficial with regard to cancer prognosis. Prospective studies examining blood levels of folate at the moment

of diagnosis in relation to subsequent death risk appear warranted.

Acknowledgement

Steindal AH and Porojnicu AC were financially supported by the Research Foundation of the Norwegian Radium Hospital.

References

- [1] Moan J, Porojnicu AC, Robsahm TE, et al. Solar radiation, vitamin D and survival rate of colon cancer in Norway. *J Photochem Photobiol B* 2005;78:189–93.
- [2] Porojnicu AC, Robsahm TE, Ree AH, Moan J. Season of diagnosis is a prognostic factor in Hodgkin's lymphoma: a possible role of sun-induced vitamin D. *Brit J Cancer* 2005;93:571–4.
- [3] Robsahm TE, Tretli S, Dahlback A, Moan J. Vitamin D₃ from sunlight may improve the prognosis of breast-, colon- and prostate-cancer (Norway). *Cancer Cause Control* 2004;15:149–58.
- [4] Lim HS, Roychoudhuri R, Peto J, Schwartz G, Baade P, Moller H. Cancer survival is dependent on season of diagnosis and sunlight exposure. *Int J Cancer* 2006.
- [5] Moan J, Porojnicu AC. The photobiology of vitamin D – a topic of renewed focus. *Tidsskr Norske Laege* 2006;126:1048–52.
- [6] Lucock M, Yates Z, Glanville T, Leeming R, Simpson N, Daskalakis I. A critical role for B-vitamin nutrition in human developmental and evolutionary biology. *Nutr Res* 2003;23:1463–75.
- [7] Priest DG, Bunni MA. Folates and folate antagonists in cancer chemotherapy. In: Bailey LB, editor. *Folate in health and disease*. New York: Marcel Dekker; 1995.
- [8] Off MK, Steindal AE, Porojnicu AC, et al. Ultraviolet photodegradation of folic acid. *J Photochem Photobiol B* 2005;80:47–55.
- [9] Jablonski NG, Chaplin G. The evolution of human skin coloration. *J Hum Evol* 2000;39:57–106.
- [10] Lucock M. Folic acid: nutritional biochemistry, molecular biology, and role in disease processes. *Mol Genet Metab* 2000;71:121–38.
- [11] Kamen B. Folate and antifolate pharmacology. *Semin Oncol* 1997;24:518.
- [12] Farber SIDN. Some observations on the effect of folic acid antagonists on acute leukemia and other forms of incurable cancer. *Blood* 1949;4:160–7.
- [13] Le Leu RK, Young GP, McIntosh GH. Folate deficiency reduces the development of colorectal cancer in rats. *Carcinogenesis* 2000;21:2261–5.
- [14] Glynn SA, Albanes D. Folate and cancer: a review of the literature. *Nutr Cancer* 1994;22:101–19.
- [15] Ratanasthien K, Blair JA, Leeming RJ, Cooke WT, Melikian V. Serum folates in man. *J Clin Pathol* 1977;30:438–48.
- [16] Rezk BM, Haenen GR, van der Vijgh WJ, Bast A. Tetrahydrofolate and 5-methyltetrahydrofolate are folates with high antioxidant activity. Identification of the antioxidant pharmacophore. *FEBS Lett* 2003;555:601–5.
- [17] Johnsen B, Mikkelsen O, Hannevik M, Nilsen LT, Saxebøl G, Blaasaas KG. The Norwegian UV monitoring

- program. Perid 1995/96 to 2001. StrålevernRapport 2002:4. Østerås: Norwegian Radiation Protection Authority, 2002.
- [18] Marzullo G, Fraser FC. Similar rhythms of seasonal conceptions in neural tube defects and schizophrenia: a hypothesis of oxidant stress and the photoperiod. *Birth Defects Res A Clin Mol Teratol* 2005;73:1–5.
- [19] Jablonski NG. A possible link between neural tube defects and ultraviolet light exposure. *Med Hypotheses* 1999;52: 581–2.
- [20] Van Rootselaar FJ. The epidemiology of neural tube defects. A mathematical model. *Med Hypotheses* 1993;41: 78–82.
- [21] Hao L, Ma J, Stampfer MJ, et al. Geographical, seasonal and gender differences in folate status among Chinese adults. *J Nutr* 2003;133:3630–5.
- [22] Ronnenberg AG, Goldman MB, Aitken IW, Xu X. Anemia and deficiencies of folate and vitamin B-6 are common and vary with season in Chinese women of childbearing age. *J Nutr* 2000;130:2703–10.

Available online at www.sciencedirect.com

