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Folate degradation due to ultraviolet radiation: possible implications for human health and nutrition

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Folate is essential for human health in the prevention of megaloblastic anemia and neural tube birth defects and plays important roles in cardiovascular disease and cancer. Therefore, research into environmental factors that may impact folate status, such as solar ultraviolet (UV) radiation, is of great health significance. In vitro studies have shown that UV radiation can degrade folate and folic acid in human blood and this has been confirmed in several human studies. Despite these findings, there is a dearth of epidemiological research into investigating the relationship between folate status and the links to solar UV exposure.

INTRODUCTION

Folate is a water-soluble B-vitamin that plays an important role in human health. Classically, folate deficiency is associated with an increased risk of neural tube birth defects (such as spina bifida) and megaloblastic anemia.[1,2] Low folate status may also be a risk factor for some cancers and cardiovascular disease, although the role of folate in these diseases is controversial, with studies showing conflicting results.[3–7] The health impacts of low folate status necessitate further investigation of the possible determinants of folate status, with such research being especially important for the populations most vulnerable to folate deficiency, such as pregnant women and the elderly. One little-known factor that may potentially decrease folate status is exposure to solar ultraviolet (UV) radiation, with recent research showing that UV radiation has the capacity to degrade folate in human blood and skin.[8,9] The relationship between UV radiation and folate degradation is complicated by the fact that UVB (ultraviolet B, 280–315 nm) radiation, while being able to degrade the main biological form of folate found in blood, 5-methyltetrahydrofolate (5MTHF), is unable to penetrate to the dermal circulation to impact blood levels.[10,11] Conversely, the longer-wavelength UVA (ultraviolet A, 315–400 nm) radiation is able to penetrate to the dermal circulation but it is unable to directly degrade 5MTHF.[10] The recent discovery of an indirect degradation pathway via UVA-derived generation of reactive oxygen species (ROS) able to oxidize and, therefore, indirectly degrade 5MTHF, has led to renewed interest in the field.[10–13] Other mechanisms such as the direct degradation of folic acid, the synthetic form of folate, in the blood by UVA and the effect of folate depletion in the skin from chronic UV exposure are also important pathways that appear to impact folate status in humans.[9,14] The public health consequences of solar UV-induced degradation of folate in humans are potentially enormous, especially in a country such as Australia, which has high annual UV exposures.[15] Despite in vitro findings showing the role of UV radiation in the degradation of folate in the human body, there is a dearth of population-based research in this potentially important area. The present review investigates the major research findings in the area of UV radiation and folate, with a particular focus on in vivo research, and discusses the strengths and weaknesses of the major studies conducted in this important field. It also identifies existing gaps in the research and provides recommendations for possible future studies of UV radiation and its impact on folate status.

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Folate is obtained exclusively from dietary intake or supplementation.[16] Via the small intestine, folate enters the circulation and is absorbed by cells where it is converted to active forms such as 5MTHF.[17] In its active tetrahydrofolate forms, its role as a one-carbon carrier is essential in methylation reactions, which include DNA synthesis (for a more detailed treatment of folate metabolism and forms please refer to Ulrich et al. 2008[7]).[16] Folate in food primarily exists in polyglutamate forms, with leafy green vegetables being a rich source of folate; however, other fruits and vegetables such as broccoli, cauliflower, and oranges are good sources, and liver, yeast, and beer are also sources of folate.[18] The synthetic form of folate used in (the majority of) supplements and food fortification is folic acid (also known as pteroylmonoglutamic acid or PGA), as this form has greater bioavailability and stability than the natural folates found in foods.[16] Folic acid is reduced to the active 5MTHF form; however, high doses (>200 µg) result in the appearance of unmetabolized folic acid in the bloodstream before its conversion to 5MTHF.[19] To account for differences in higher bioavailability of folic acid compared to food folate, dietary folate equivalents (DFE) have been developed, whereby 1 DFE = 1 µg food folate, or 0.6 µg folic acid added to food as a fortificant, or 0.5 µg of folic acid taken as a supplement when fasting.[14,20] Many countries fortify foods with folic acid; for example, fortification of flour has been mandatory in the United States and Canada since 1998, and other countries, such as Australia, have followed and have more recently introduced mandatory folic acid fortification.[21,22] The National Institutes of Health in the United States have set the recommended daily intake (RDI) level for folate at 400 µg a day for adults, with higher levels of 600 µg/day recommended for pregnant women to reduce the risk of neural tube defects (NTDs).[23] Table 1 provides a summary of the folate content (as DFE) of selected foods and multivitamin supplements.

HEALTH IMPLICATIONS OF FOLATE STATUS

Low serum folate levels, caused by either an inadequate dietary intake or conditions such as malabsorption or liver disease, are classically associated with the development of megaloblastic (large cell type) anemia and, in fetuses of folate-deficient mothers, NTDs such as spina bifida.[1,2] Indeed, it is the prevention of NTDs, particularly following the landmark Medical Research Council's vitamin study that showed folic acid supplementation reduced NTD risk by 72% (95% CI 0.12–0.71) in pregnant women when taken before and following conception, that has led many countries to introduce the mandatory folic acid fortification of foods described above.[21,22,24]

Since folate plays an important role in the metabolism of the amino acid homocysteine, which is classified as an independent risk factor for cardiovascular disease, there has been much research interest in the role of folate in reducing cardiovascular disease risk via the lowering of total homocysteine levels in the blood.[16] Early studies with folic acid supplementation showed much promise by significantly lowering homocysteine levels while observational studies reported significant increases in cardiovascular risk as a result of elevated homocysteine.[3,25] However, more recent data from randomized control trials has consistently shown a null effect from folate and other B-vitamins on cardiovascular disease risk; for instance, results from a recent large meta-analysis (eight trials composed of 37,485 participants) show that homocysteine-lowering intervention via vitamin B supplementation (including folate) had no statistically significant effects on cardiovascular disease risk or mortality.[4,6] To explain this null effect shown by the casual evidence, Blom and Smulders[26] have proposed an interesting hypothesis suggesting that the high levels of folic acid supplementation used in homocysteine-lowering trials may lead to increased inflammation and proliferation, stimulating atherosclerotic plaque growth and destabilization. This would have the effect of negating any improvements in cardiovascular disease risk from lowering homocysteine levels.

Table 1 **Dietary folate equivalents (DFEs) of selected foods and supplements.**

Food	DFEs (µg) per 100 g	Weight/serving to provide RDI (400 µg/day)
Wholemeal bread (fortified-Australia)	248	160 g (approx. 5 slices)
Asparagus (cooked)	133	300 g (approx. 20 spears)
Spinach (cooked)	105	381 g (approx. 4 cups)
Orange	31	1,300 g (approx.12 oranges)
Lentils (cooked)	182	220 g (approx. 1 cup)
Beef liver	218	183 g
Multivitamin supplement	200–500 per capsule/tablet	1–2 capsules/tablets

Data from Suitor and Bailey (2000)[20] and Food Standards Australia New Zealand (2010)[60].

Folate's essential role in DNA synthesis and repair has also made its role in cancer carcinogenesis of great research interest, with folate appearing to provide a protective effect on some cancers (e.g., colorectal) early in carcinogenesis.[7] For example, a large prospective analysis of cancer mortality and morbidity in Western Australia ($N = 1{,}988$) showed independent associations between decreased folate levels and increased risk of prostate cancer mortality and breast cancer morbidity over 20 years of follow-up.[27] While adequate folate is essential to human health, there is also increasing focus on the health effects of excess folate, particularly in its folic acid form. The ability of folic acid to mask the hematological signs of vitamin B_{12} deficiency is a major concern, as this can lead to a missed diagnosis and progression of the neurological damage associated with vitamin B_{12} deficiency.[28] There is also some evidence that too much folic acid may increase risk of some cancers; for example, results from the Prostate, Lung, Colorectal and Ovarian screening trial showed a 20% increased risk for breast cancer development in females taking supplements containing ≥400 µg/day of folic acid compared to females who were not taking supplements.[29] Several other studies have also shown possible deleterious effects of folic acid supplementation on colon and prostate cancer, although there is a lack of consensus, and evidence in this area remains mixed.[30,31] While the exact mechanisms for the apparent dual health effects of folate on cancer are unknown, folate, through its role in DNA synthesis and repair, is thought to protect against cancer initiation, but once preneoplastic tumors become established, it may aid cancer progression.[28] It is important to note that even high intakes of natural folates found in food are rarely, if ever, implicated in increased cancer risk; however, the paucity of quantitative folate intake data from diet makes any conclusion regarding the different health effects of folate from food versus folic acid difficult.[28] While there is a lack of consensus in this area, the growth of mandatory food fortification with folic acid makes further research into the possible health risks of folic acid essential.

For determining folate status, the following pathological measurements are used: serum folate and erythrocyte folate. Serum folate provides a short-term assessment of folate status and is, thus, determinant of recent folate intake, while erythrocyte folate provides a longer-term assessment of folate status (past 2–3 months of intake).[18] Traditionally, immunoassay methods have been used to test folate status, but this technique is unable to distinguish between the different folate metabolites and to detect the presence of unmetabolized folic acid in the circulation; thus, high performance liquid chromatography is needed when data on specific forms of folate are required.[19,32] The Royal College of Pathologists of Australasia uses reference ranges of 7–45 nmol/L for serum folate and 360–1,400 nmol/L for erythrocyte folate, to define normal folate status.[33] However, both erythrocyte and serum folate status cutoffs for deficiency are poorly defined for health outcomes, and various researchers have used different cutoff levels to define deficiency or "low" folate status.[1,17] An example of various cutoffs to define low serum and erythrocyte folate is provided in Table 2.[1]

Table 2 **Classification of low and normal serum and erythrocyte folate levels.**

Classification	Serum folate (nmol/L)	Erythrocyte folate (nmol/L)
Very low	<6.8	<370
Moderately low	6.8–<11.0	370-<513
Normal	≥11.0	≥513

Data from Flood et al. (2005).[1]

FOLATE AND ULTRAVIOLET RADIATION: OVERVIEW

With folate's role in many aspects of human health, environmental factors that may affect folate status are of great interest from a health perspective. One of these environmental factors is the photosensitivity of folates upon exposure to UV radiation. While there has been a recent upsurge of research in the area of UV-induced folate degradation, interest in this area is not a recent phenomenon. Branda and Eaton[34] proposed a relationship between UV sun exposure and the evolution of human skin color in 1978, suggesting that maintenance of genetic characteristics such as dark skin color requires continuous positive selection. Therefore, there must be strong evolutionary pressures favoring retention of highly melanized skin in people living in areas of intense solar radiation. This hypothesis is based on the observation that populations with more heavily melanized skin evolved in and near to equatorial regions, most likely because darker skin provided these populations with a survival advantage by reducing photodegradation of folate and, possibly, other nutrients by solar UV exposure.[35] Other explanations for the retention of dark skin color, such as the protection that dark skin provides against the carcinogenic effects of UV, are likely not to have impacted reproduction, and therefore selection, while micronutrient deficiencies, particularly of folate, are known to play essential roles in fetal development and fertility and are consequently much more likely to drive selection pressures.[34] Following publication of that article, several other authors published reports supporting the theory of a photoprotective role of melanized skin for reducing micronutrient degradation and its resulting impact on the evolution of human skin color.[35–38] Similarly, it has been hypothesized that lighter skin provided a survival advantage *away* from the equator

at higher latitudes; in this case, by improving UV-induced vitamin D synthesis, which is reduced in more heavily melanized populations.[39]

FOLATE AND ULTRAVIOLET RADIATION: LABORATORY STUDIES

Several experimental studies have proven that folate is vulnerable to UV degradation. For instance, in vitro studies have shown that folic acid (the synthetic form of folate) is photosensitive to UVA radiation.[13,40–44] These studies have shown that when folic acid is exposed to UVA, it undergoes photolysis and is cleaved into several photoproducts.[43] Laboratory studies have also shown that biological metabolites of folate found in the human body, such as 5MTHF, are sensitive to UVB (280–320 nm) radiation, but not UVA (320–400 nm).[10] Figure 1 illustrates this by showing the absorbances of both 5MTHF and folic acid when exposed to different UV wavelengths; both UVA and UVB are absorbed by folic acid and UVB is absorbed readily by 5MTHF, but absorbance by 5MTHF in the UVA spectrum is minimal.[45] UVC (ultraviolet C, 100–280 nm) radiation is absorbed by both folic acid and 5MTHF, but because it is absorbed by the earth's atmosphere, it does not reach the earth's surface to affect the skin.[10] Thus, based on absorbance data alone, UVB would appear to be the main UV wavelength responsible for folate degradation. This, however, does not take into account the fact that UVB does not penetrate deeply enough into the skin to reach the dermal circulation and is therefore unlikely to influence blood folate levels directly.[10] The longer-wavelength UVA, although able to penetrate the skin to a greater depth and reach the dermal circulation, is unable to directly degrade 5MTHF, resulting in the inability of solar UV radiation to directly impact 5MTHF levels in blood.[14]

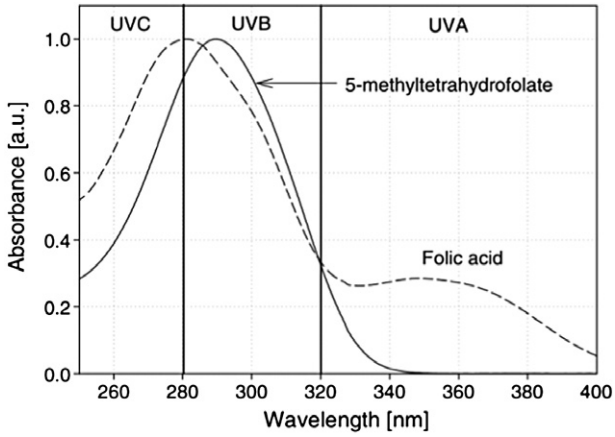

Figure 1 **Absorbances for UVA and UVB radiation in 5MTHF and folic acid.** Reproduced from Steindal et al. (2007)[45] with permission.

The recent discovery of photosensitizers such as flavins and porphyrins that have the ability to indirectly degrade 5MTHF during UV exposure has provided a biologically plausible mechanism for in vivo UV degradation of folate.[11,12] Both flavins and porphyrins are natural photosensitizers in human blood, which produce reactive oxygen species (ROS), such as singlet oxygen, when exposed to UV radiation.[11,12] It is the production of these ROS that has been proposed as a mechanism that leads to the degradation of 5MTHF to the oxidized inactive form methyl 5,6 dihydrofolate.[12] As UVB radiation will not penetrate deeply enough into the dermis to affect circulating photosensitizers, it is proposed that it is UVA that indirectly degrades 5MTHF through the generation of ROS (particularly singlet oxygen) from photosensitizers (see Figure 2 for explanation of UVA's role in folate degradation).[12] Thus, combined with laboratory studies showing direct degradation of folic acid by UVA, this discovery provides a second, indirect mechanism whereby UVA can potentially degrade folate, although epidemiological studies are needed to confirm whether UV radiation in vivo, via sun exposure or sunbeds, can significantly decrease folate levels in humans.

While most of the few studies in the area are focused on blood levels of folate, folate levels in the skin are particularly vulnerable to degradation by ultraviolet radiation, both via direct photodegradation and indirect degradation via ROS.[9,46] The depletion of folate in skin may have significant health impacts; for instance, Williams and Jacobson[9] recently conducted an experiment with a cultured keratinocyte cell model, showing that keratinocytes depleted of folate had a decreased capacity to repair DNA damage when exposed to solar simulated light. Thus, folate depletion in the skin, combined with UVR exposure, appears to favor the development of the genomic instability associated with early skin carcinogenesis, a situation that was shown to be reversed by the addition of folate (in the form of folic acid) to keratinocytes, which reestablished repair of DNA damage in these cells.[9] While the capacity of UV radiation to damage skin is not a new concept, the direct role of UV radiation in the degradation of folate in the skin and the observation of enhanced photo and oxidative damage in folate-depleted cells requires much further investigation. The increased skin folate repletion demands caused by intense UV radiation exposure may be another pathway leading to depletion of circulatory folate, because blood folate needs to replete lost folate in the skin (see Figure 2). Further research into UV-induced folate depletion of skin is therefore needed to further existing knowledge of its role in carcinogenesis and the potential for decreasing circulatory folate.

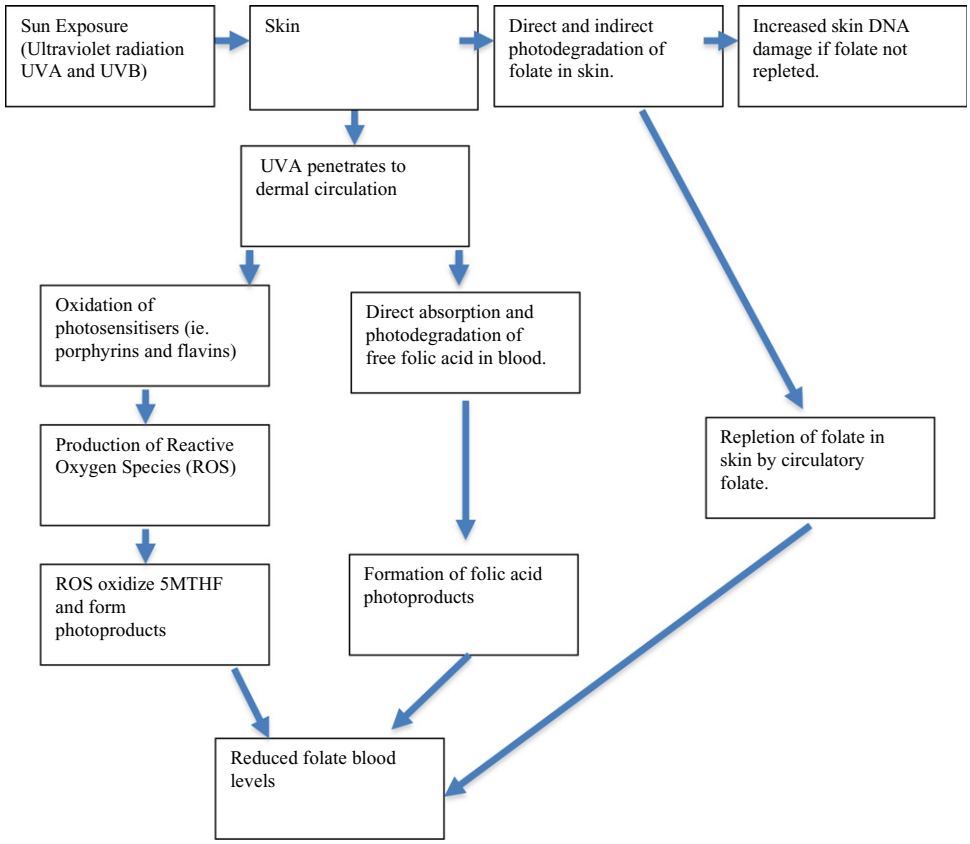

Figure 2 **Proposed pathway for blood folate degradation in human blood and skin.**

FOLATE AND ULTRAVIOLET RADIATION: SEASONAL EVIDENCE

A number of ecological studies have shown seasonal variation between folate levels, with lower serum folate and/or erythrocyte folate reported during summer or spring compared to winter and autumn, when UV exposure is lower.[47–49] Research has also shown seasonal differences in NTDs, with lower levels of NTDs reported during winter (higher serum folate) compared to summer (lower serum folate).[49] Seasonal differences in cancer diagnosis and mortality have also been the focus of recent folate research.[45] As reported earlier, higher folate status appears to be protective in early stages of carcinogenesis; however, higher folate status during later stages of carcinogenesis may decrease cancer survivability for some types of cancer.[28,45] Indeed, the inhibition of folate metabolism plays a major role in cancer treatment, with the use of chemotherapeutic agents such as methotrexate in cancer therapy.[50] It is through the theory of lower folate status possibly improving cancer survival at certain stages in carcinogenesis that Steindal et al.[45] proposed the hypothesis that cancer mortality is linked to seasonality via UV radiation's role in folate photodegradation. For instance, several Norwegian studies have shown that the relative risk of death for some cancers was 20–50% lower for cases if diagnosed in summer, compared with winter (after 18 months of follow-up).[50–53] Steindal et al.[45] suggest that lower folate status in summer, resulting from increased solar UV folate degradation, is a possible reason for the improved cancer prognosis seen in these studies. While these studies were primarily investigating the role of vitamin D and seasonality in cancer prognosis, the Norwegian data provides an interesting alternative hypothesis, particularly considering folate's important role in cancer. It is also important to consider that both hypotheses are not mutually exclusive; for instance, both higher vitamin D and lower folate status in summer may contribute to the improved cancer prognosis seen in ecological research designs. Further investigation in this important area is therefore needed into how solar-induced degradation of blood folate may be a factor in improving prognosis in some forms of cancer or preneoplastic tumors.

FOLATE AND ULTRAVIOLET RADIATION: SUNBED AND SOLAR ULTRAVIOLET STUDIES

Only a few small population-based studies have been conducted into UV-induced folate degradation (see Table 3). These include a study by Gambichler et al.[54] showing that both single and serial exposure to UVA

Table 3 **Summary of published in vivo studies of folate degradation and UV exposure.**

Reference	Country	Radiation treatment/cumulative dose (unless otherwise specified)	Blood testing protocol	Study participants	Results
Gambichler et al. (2001)[54]	Germany	UVA from sunbed twice weekly for 3 weeks/96 J cm^2	Serum folate tested with automated immunoassay	$N = 24$ healthy participants; $n = 8$ participants randomized into UVA treatment group	No significant differences in serum folate observed between exposed and non-exposed groups
Shaheen et al. (2006)[58]	Egypt	Narrowband UVB with 36 exposures/ 76 J/cm^2	Serum folate tested by HPLC	$N = 40$ vitiligo patients ($n = 20$ study group; $n = 20$ control)	Significant decrease in serum folate following UV treatment (baseline 18.3 ± 5.9 nmol/L versus 13.4 ± 3.4 nmol/L after UV)
Fukuwatari et al. (2009)[14]	Japan	Solar UV from outdoor exposure between the hours of 11:00 and13:00 for two days in summer/ UVA: 12 J/cm^2	Serum folate tested with microbioassay	$N = 7$ female students taking 0.25 mg of folic acid supplements at each meal for 2 days and morning of blood test Control: same protocol and participants but no sun exposure on another day	Significant decrease in serum folate following sun exposure (38.0 ± 7.2 nmol/L versus 28.1 ± 4.6 nmol/L)
Rose et al. (2010)[56]	United Kingdom	Narrowband UVB with minimum of 18 exposures/UVB average 2.3 J cm^2 per visit (Note: dose varied depending on participant's clinical response to UVB phototherapy)	Serum and erythrocyte tested with immunoassay	$N = 35$ psoriasis patients	No significant decreases in serum or erythrocyte folate following UVB exposure
Cicarma et al. (2010)[57]	Norway	Narrowband UVB from photocabinet with a total of 9–15 treatments/ 2.35–13.4 J/cm^2 (Note: dose varied depending on participant's skin type and clinical response to UVB phototherapy).	Serum and erythrocyte folate with immunoassay; 25(OH)D with radioimmunoassay	$N = 19$ dermatological patients	Significant increase in 25(OH)D but no effect on blood folate status
Juzeniene et al. (2010)[32]	Norway	Study 1 : Solar UV from outdoor exposure/UV not measured Study 2: UV from sunbed 4 sessions 2 × 10 min and 2 × 20 min Study 3: Broadband UVB photocabinet single exposure/ UVB 0.18–0.46 J/cm^2; UVA 0.04–0.46 J/cm^2 Study 4: Broadband UVB photocabinet 7–22 exposures/ varied dose (maximum dose 115–220 J/cm^2)	Serum and erythrocyte folate; homocysteine and 25(OH)D	Study 1: $N = 17$ (4 psoriasis patients and 13 healthy participants). Study 2: $N = 6$ healthy males Study 3: $N = 9$ psoriasis patients Study 4: $N = 10$ psoriasis patients	No statistically significant effects of solar or artificial UV exposure on blood folates in all 4 studies. Slight reduction in blood folate levels reported in psoriasis patients

radiation via a sunbed did not significantly affect serum folate levels in healthy participants. Small study numbers ($N = 24$; with only eight volunteers exposed to UVA radiation) and the use of UVA radiation, which is not able to photodegrade 5MTHF, the main form of circulatory folate in the human body, may have impacted the results. While this study agrees with the laboratory data showing that 5MTHF is not vulnerable to direct photodegradation by UVA (although some indirect degradation may have been expected), other forms of folate may be more susceptible. For instance, the finding that folic acid is sensitive to UVA irradiation is extremely important due to the use of this form for supplementation and food fortification. The findings from in vitro studies reported earlier, showing higher UVA absorption in folic acid compared to 5MTHF, led Fukuwatari et al.[14] to hypothesize that humans taking folic acid supplements would be at increased risk for degradation of folate by sunlight (via UVA exposure). To test this hypothesis, a series of experiments was conducted using a sample of Japanese college students between the ages of 21 and 24 years who were asked to bathe in sunlight between 11am and 1pm, while also taking 0.25 mg of folic acid supplements at each meal for 2 days prior to and once on the day of blood testing.[14] Folate concentrations were decreased when participants ($n = 7$) bathed in sunlight, while when participants were not exposed to sunlight, folate concentrations remained the same (for participants exposed: plasma folate pre-test = 38.0 ± 7.2 nmol/L versus post-test = 28.1 ± 4.6 nmol/L).[14] The studies also showed no difference in plasma folate post sun exposure when folic acid was not taken as supplements by participants. This corresponds to the data collected by Gambichler et al.[54] and in vitro studies showing no significant absorption and degradation of 5MTHF by UVA irradiation. While there are several limitations in the study by Fukuwatari et al.,[14] particularly the small numbers of participants and lack of randomization, data collected from the study points to the possibility that people supplementing with folic acid are at greater risk of folate degradation than those who are not. This is of particular concern for pregnant women (especially those with high sun exposure) who often obtain a significant proportion of their folate intake from folic acid supplementation.[16] The data from both of these studies also raise questions about the degree of the in vivo impact of indirect degradation of 5MTHF via generation of ROS, as no significant change in folate status following UV exposure was demonstrated (with the exception of the significant change if folic acid was taken).[14,54]

Several studies have also examined the effect of UVB radiation exposure on folate status by enrolling psoriasis patients, for whom UVB radiation therapy is often used as a treatment.[55] Narrowband UVB phototherapy was used to investigate the effect of UVB on serum and erythrocyte folate status in patients with psoriasis by Rose et al.[56] ($N = 35$) and in a mixed sample of dermatological patients by Cicarma et al.[57] ($N = 19$), but no effect was observed in either of these studies. An earlier study by Shaheen et al.,[58] however, reported a significant 27% decrease in serum folate following exposure of 20 vitiligo patients to 36 narrowband UVB sessions. All three studies used similar equipment, with the UVB source provided by standard narrowband UVB bulbs (Philips TL-01 fluorescent lamps) that have an emission peak of 311 nm. One likely explanation for the differences is the larger number of phototherapy sessions and higher cumulative UVB exposure used in the Shaheen et al.[58] study to treat the exposure group.[59] It is also worth noting that the different types of dermatological conditions used in each of these studies may have affected the results; however, little research is available regarding how any of these conditions may impact the vulnerability of folate to ultraviolet radiation.

To test the effect of broadband UVB exposure (280–400 nm), a recent study was conducted by Juzeniene et al.[32] in which both erythrocyte and serum folate were measured via a series of experiments in both healthy volunteers and psoriasis patients in Oslo, Norway. Both broadband UVB exposure from sunbeds and sunlight exposure during summer were shown to have no influence on healthy participants, but a small decrease in folate level was observed in psoriasis patients following broadband UVB exposure.[32] Once again, small study numbers ($N = 5$–13) and the lack of measurement of dietary and supplemental folate intake in the sample (to allow for adjustment) were some limitations. Also, as noted by Juzeniene et al.,[32] the use of high performance liquid chromatography rather than the more standard immunoassay method for analyzing erythrocyte folate would have allowed observation of how UVB and sunlight affected different folate fractions such as 5MTHF, folic acid, and the oxidized methyl 5,6 dihydrofolate. This study, combined with previous research, is important as it provides evidence that only very high doses of UVB are required to photodegrade 5MTHF. Because UVB is unable to penetrate to the dermal circulation, it is possible that skin-derived depletion of folate (see Figure 2) or possibly another mechanism, for instance, an increased vulnerability to UVB in people with some dermatological conditions, is responsible for this degradation.

With so few epidemiological studies conducted, the ability of sun exposure to affect folate status at clinically significant levels that would impact human disease is impossible to ascertain. There is also conjecture as to whether UV sun exposure's impact on folate status would have provided the necessary selection pressure to provide a role in the evolution of human skin color. Research in

countries with higher UV intensities and exposures may be an important next step, as most of the epidemiological research conducted to date has been at higher latitudes where UV intensities, even in summer, are quite low.

CONCLUSION

The question of whether UV radiation can affect folate status at clinically significant levels in vivo is of great health importance. While laboratory findings have allowed the elucidation of possible mechanisms of UV-induced folate degradation and ecological studies have pointed to possible health effects from UV-induced folate degradation, in vivo data has shown mixed results. Population-based studies have mainly focused on the use of sunbeds with only a few studies testing the impact of solar UV exposure on folate status. Further complicating matters is the lack of consensus regarding folate reference ranges and the need to measure different types of folate due to the varied impacts of UVA and UVB radiation on the different forms of folate, such as 5MTHF and folic acid. However, recent findings showing UV photodegradation of the synthetic folic acid in vivo when people are exposed to solar UV is of great health significance since mandatory folic acid fortification of food is in place in many countries and there is a reliance on folic acid supplementation, particularly by pregnant women, to provide a significant proportion of folate needs.

Larger epidemiological studies are needed that will allow researchers to observe the effects of UV on the folate status of free-living individuals. These larger studies would build on the research already conducted in this area and would enable researchers to observe any statistically significant population-level effects between solar UV exposure and folate status. This, combined with a research emphasis on groups who are most vulnerable to folate deficiency, for example, pregnant women taking folic acid supplements, would provide much needed data into the possible consequences of folate photodegradation on human health. Improving understanding of the various mechanisms of UV-induced folate degradation in blood will also be important as this would allow elucidation of the relative contributions of direct and indirect UVA mechanisms of photodepletion of folate. The impact of folate depletion in the skin by both UVA and UVB radiation and its impact on skin cancer as well as contribution to decreased blood folate status via increased skin folate demands is another area of folate research in need of further investigation.

Future studies need to consider appropriate folate assay methodology as research has shown varying impacts of UV radiation on different forms of folate. For instance, much of the current research has focused on measurement of blood levels of 5MTHF, while other important metabolites, such as folic acid, which is more vulnerable to UVA degradation, are rarely tested or not distinguished in standard serum folate and erythrocyte folate assays. Thus, the use of assays that allow researchers to distinguish between different folate metabolites will be important. Another important consideration is that, so far, much of the interest in and performance of folate and UV research has been largely confined to Northern Europe and Japan, two regions in which populations experience significantly less UV exposure than countries such as Australia; thus, research into the effects of sunlight exposure on the folate status of populations in high-UV environments is a priority. Future research in this field will also benefit greatly if dietary and supplemental folate intake is collected, since both the type and the amount of folate consumed have major implications for UV and folate studies.

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