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VITAMIN D, VITAMIN OR HORMONE?
LA VITAMINE D, VITAMINE OU HORMONE ?

Vitamin D and Cancer[*]

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Abstract – Epidemiological studies, mostly ecological but also case-control and prospective studies show a negative association between residential sun exposure and incidence (or fatality) of major cancers: colon, breast, and prostate cancer, and non-Hodgkin lymphoma. And it has been suggested that this reduction in risk could be influenced by vitamin D synthesized in the skin as a result of sun exposure. Low serum vitamin D levels are linked to an increase in risk of colon cancer, and to a lesser extent to risk of breast cancer, but not to risk of prostate cancer or non-Hodgkin lymphoma. Intervention trials consisting in daily supplementation in vitamin D for several years have all failed to demonstrate an effect on cancer incidence. Hence, it is not clear whether the reduction in cancer risk associated with sun exposure is mediated by vitamin D or by another factor influenced by sun exposure such as inflammation or immunosuppression, or whether a low vitamin D status is simply a consequence of ill health.

Keywords: Cancer / incidence / mortality / sun exposure / vitamin D

Résumé – Vitamine D et cancer. Les études épidémiologiques, essentiellement écologiques, mais aussi cas-témoins et prospectives, indiquent une association inverse entre l'exposition solaire résidentielle et l'incidence (ou la mortalité) de plusieurs cancers : cancers du colon, du sein et de la prostate, et lymphomes non-Hodgkiniens. Il a été suggéré que cette diminution du risque de cancer pouvait être du à la vitamine D synthétisée dans la peau lors de l'exposition solaire. De faibles taux sériques de vitamine D sont associés à une augmentation du risque de cancer du colon et, à un moindre degré, de cancer du sein, mais pas de cancer de la prostate ou de lymphome non-Hodgkinien. Aucun des essais d'intervention consistant en une supplémentation quotidienne en vitamine D pendant plusieurs années n'a démontré d'efficacité sur le risque de cancer. Il n'est donc pas déterminé si la réduction du risque de cancer associée à l'exposition solaire résulte d'un effet de la vitamine D, ou d'autres facteurs influencés par l'exposition solaire tels que l'inflammation ou l'immunosuppression, ou si de faibles taux sériques de vitamine D ne sont que la traduction d'un mauvais état de santé.

Mots clés : Cancer / incidence / mortalité / exposition solaire / vitamine D

1 Introduction

The observation by Garland and Garland (1980) of an inverse association between mortality from colon and breast cancer and levels of solar UVB irradiation in the USA raised the possibility that vitamin D produced as a result of sun exposure could play a role in the development of cancers. Further ecological studies, conducted mainly in the USA but also in Europe, showed that the incidence or the mortality of several cancers was inversely related to the latitude of residency, the geographic distribution of UVB irradiance matching the distribution of many of the cancer mortality maps. Eighteen anatomic sites of cancer were thus inversely associated with UVB irradiance, most of the results concentrating on colorectal, breast and prostate cancers and on non-Hodgkin lymphomas (Grant and Mohr, 2009). The hypothesis of a role for vitamin D in the control of development of cancers was supported by the demonstration of the antiproliferative, differentiating and pro-apoptotic effects of vitamin D (Frampton *et al.*, 1983), by the expression of vitamin D receptors in tumors (colon, breast, prostate) (Skowronski *et al.*, 1993), and by the discovery that several tissues are able to locally produce 1α,25 dihydroxyvitamin D3, the biologically active form of vitamin D (see IARC, 2008, for review).

But, soon, these results fuelled a controversy. Without waiting further to the confirmation of the negative influence of sun exposure on cancer occurrence, and to the evidence of involvement of vitamin D in the preventive effects of sun

exposure, some advocated an abandon or an amendment of public health policies advising limitation of sun exposure for the prevention of skin cancers and more especially melanoma, the most deadly form of skin cancer (Gillie, 2004, 2010), claiming that health benefits of both UVB and vitamin D, including reduced risk for infectious viral diseases, may substantially outweigh reasonably anticipated adverse effects of a few minutes per day of exposure to sunlight (Grant and Mohr, 2009). Moreover, the indoor tanning industry, arguing that most populations are "vitamin D insufficient", more especially in winter, advised for a correction of this insufficiency by exposure to UV-emitting tanning beds (Autier et al., 2011), dismissing the International Agency for Research on Cancer working group report demonstrating that exposure to artificial UV tanning increases melanoma risk by a 1.75 factor when use started before the age of 35 (IARC, 2006), and later the classification of UV-emitting tanning devices as a Group 1 carcinogen (IARC, 2009). Over the last three decades, the domain has been extremely active: a PubMed search on "Vitamin D and cancer" retrieves 7805 publications, of which 1664 are reviews and 104 meta-analyses, steadily increasing from 41 publications in 1980 to 524 in 2012, and already 489 in 2013!

In this context, the International Agency for Research on Cancer convened in 2008 a working group to review and evaluate the epidemiological literature on vitamin D and cancer and to conduct a meta-analysis of observational studies of serum levels of 25-hydroxyvitamin D and risk of colorectal, breast and prostate cancer (IARC, 2008). Based upon this review and more recent reviews (Espié et al., 2013; van der Rhee et al., 2009, 2013), the current evidence associating solar UVB exposure and serum levels of 25-hydroxyvitamin D with colorectal, breast and prostate cancers and non-Hodgkin lymphomas are briefly presented hereafter, as well as results of intervention studies aiming at a reduction in cancer incidence by dietary supplementation with vitamin D Details of the studies can be found in van der Rhee et al. (2013) and Espié et al. (2013).

2 Sunlight exposure and cancer prevention

Since Garland and Garland (1980) proposed the hypothesis that vitamin D, synthesized as a result of residential exposure to solar UVB radiation, could be a protective factor against colon and breast cancer, the inverse association between ambient solar radiation and cancer incidence and/or mortality has been described for many types of cancers in many countries, mostly in North America and in Europe. Most of these studies suggesting a link between sun exposure and cancer were ecological studies assessing correlation between latitude or, even better, measured ambient solar UV radiation and cancer incidence or mortality, and were reviewed elsewhere (IARC, 2008; van der Rhee et al., 2006, 2009). But causal inference from ecological studies is notoriously perilous as, among other things, these studies cannot adequately control for confounding by exposure to various cancer risk factors which may also vary with latitude or ambient solar radiation (e.g. clothing or dietary habits). For colorectal, breast, and prostate cancers and non-Hodgkin lymphomas, case-control and prospective studies are available.

2.1 Colorectal cancer

Among four case-control studies, one observed no statistically significant associations between sunshine exposure and colon cancer risk, but an analysis of the same subjects stratified by genetic variants of the androgen receptor (AR) found that men with low levels of sunlight exposure and more than 23 polyglutamine (CAG) repeats of AR had the greatest risk of colon cancer (OR = 1.51; 95% CI: 1.09–2.09). In a case-control study of 750 cases of rectal cancer, high levels of sunshine exposure were associated with a borderline protective effect for p53 tumor mutations (OR = 0.78; 95% CI: 0.59–1.02). A fourth case-control study found an inverse association between colon cancer mortality and exposure to sunlight.

Three prospective cohort studies found an inverse association between ambient residential UV exposure or recreative sun exposure and colon cancer risk: the US Radiologic Technologist Study in never/past (not in current) users of Hormone Replacement Therapy (RR for the highest versus lowest tertile = 0.40; 95% CI: 0.17–0.93), the Swedish Women's Lifestyle and Health cohort (non-significant lower risk for at least one week per year sunbathing vacation: RR = 0.81; 95% CI: 0.47–1.39), and the National Institutes of Health (NIH)-AARP Diet and Health Study in 450 934 white non-Hispanic subjects (HR = 0.88; 95% CI: 0.82–0.96). However, a recent publication from the NIH-AARP Diet and Health Study assessing the association between ambient residential UVR exposure and total and cause-specific mortality risks in 346 615 white, non-Hispanic subjects, 50–71 years of age, with accounting for individual-level confounders, suggests that sun exposure is associated with a 6% increase in risk of mortality from cancer: HR Q4 vs. Q1 = 1.06, 95% CI: 1.02, 1.11 (Lin et al., 2013).

2.2 Breast cancer

Four case-control studies observed negative correlations between the risk of breast cancer or breast cancer mortality and sun exposure, the risk reduction being of the order of 30%, and particularly associated with estrogen receptor +/progesterone receptor + tumors.

The prospective studies on breast cancer risk and sun exposure gave mixed results. Among the five studies performed in the USA, one found no consistent relation between breast cancer risk and the region of residence (however, women reporting less than 30 min outside had significantly higher risks than women who spent more than 2 h in daylight), and another one using ecological exposure data only, also found no regional differences in the risk of breast cancer, whereas a third one also using ecological data found that the mortality rates of breast cancer among older women were 8–10% higher in the West, Midwest and Northeast, respectively, than in the South. No association between residential UV exposure and breast cancer risk was found In the NIH-AARP Diet and Health. And only one found inverse associations between residential or recreational exposure and breast cancer risk.

Three Scandinavian studies gave also mixed results. One found no associations between personal sun exposure and breast cancer risk, while another analysis of the same cohort

showed reduced risks for women who, between the age of 10 and 30 years, spent at least 1 week every year on a sunbathing vacation. But the Norwegian Women and Career Study found no association between the risk of breast cancer and sun seeking vacations.

The French cohort study E3N, involving 67 721 women followed for 10 years, found significantly inverse association between residential exposure and breast cancer risk: women living in regions with the highest UV exposure having a 30% reduction in risk.

2.3 Prostate cancer

With one exception, all seven case-control and two prospective studies showed negative associations between sunlight exposure and the risk or survival of prostate cancer, the reduction in risk varying from 10 to 50%. It should however be noted that studies were mainly performed in relatively low solar UV environments, while the study showing positive association (OR = 2.07; 95% CI: 1.36–3.15) was done in Australia in a high ambient solar UV environment.

2.4 Non-Hodgkin lymphomas

A considerable number of studies have been conducted on the relationship between sun exposure and risk of non-Hodgkin lymphoma and gave conflicting results. While ecological studies had found both positive and negative associations, twelve out of seventeen case-control studies found a negative association, and a pooled analysis from the Inter-lymph consortium found that recreational exposure at the age of 18 to 40, or 10 years before diagnosis, significantly reduced risk of B cell lymphoma: OR = 0.76 (95% CI 0.63–0.91) for the highest exposure category (Kricker *et al.*, 2008). Three prospective studies in the USA found that residential exposure reduced the risk, while another one found no effect, and two Scandinavian studies found no reduction in incidence risk (one even found a modest increase in risk associated with residency in the South).

It should be noted that older studies usually found a positive association with sun exposure, non-melanoma skin cancers associated with chronic sun exposure being a lymphoma risk factor, while more recent studies found a negative association. In addition, recent changes in lymphoma classification may hamper comparison between studies.

2.5 Other cancers: melanoma

Even for melanoma, positively associated with sun exposure, there are some indications that sun exposure may result in a reduced progression and better survival. Berwick *et al.* (2005), exploiting the Connecticut cancer registry, found that the presence of solar elastosis in the vicinity of the tumor was associated with an increase in survival. Boniol *et al.* (2006), exploiting the New South Wales Cancer Registry, found that fatality from melanomas diagnosed in summer was lower than that of melanomas diagnosed in winter (relative risk of

death = 0.82; CI 95%: 0.72–0.94), suggesting that sun exposure at the time of melanoma diagnosis decreases risk of mortality from melanoma. And a recent publication showed that holidays in the sun were associated with thinner melanomas in women and reduced rates of relapse in both sexes (HR = 0.30; 95% CI: 0.10–0.87) (Gandini *et al.*, 2013). However, these results do not prove a direct causal effect of sun exposure on survival since other confounding factors, such as vitamin D serum levels and socio-economic status, may play a role. Other factors in sun seeking individuals may also possibly affect these results, and a meta-analysis suggests a possible significant role of Vitamin D receptor *FokI* and *BsmI* polymorphism in melanoma and non-melanoma skin cancer risk (Gandini *et al.*, 2009).

3 Association with vitamin D levels in serum

Most ecological studies assumed a latitude gradient in ground level UV radiation, and hence a gradient in vitamin D levels in the populations. Actually, studies from the USA show a weak association between latitude and vitamin D status and that other factor such as outdoor activities and obesity are better predictive factors of vitamin D status. In Europe, the opposite has been found, with a south to north increase in serum 25-hydroxyvitamin D that parallels a similar gradient in the incidence of colorectal, breast and prostate cancers. In addition, in people of the same age and skin complexion, there is considerable inter individual variation in serum 25-hydroxyviatmin D even with similar levels of sun exposure (IARC, 2008). Therefore, actual measurement of blood vitamin D levels should be preferred to ecological UV radiation data in the analysis of case-control and prospective studies.

3.1 Colorectal cancer

At least twelve prospective studies assessed the association between pre-diagnostic blood 25(OH) D level and colorectal cancer risk or mortality. With the exception of a Finnish cohort showing a significantly elevated risk for the highest versus lowest quartile of 25(OH)D levels (OR = 1.88; 95% CI: 1.07–3.22), all showed an inverse association, the relative risk for the highest versus lowest blood 25(OH)D levels being of a magnitude of 0.70, *i.e.* a 30% reduction, with a 10 ng/ml increment in blood 25(OH)D level conferring a 25% reduction in risk.

Similar results were obtained in the European EPIC cohort involving more than 520 000 persons, in which 1248 colon cancer cases were diagnosed during follow-up. A nested case-control study showed that 25-(OH)D blood levels were in strong inverse linear dose-response association with risk of colorectal cancer: a blood level < 25 nmol/L being associated with an increased risk (incidence ratio (IR) = 1.32; 95% CI: 0.87–2.1), whereas higher concentrations were associated with lower risk (75.0–99.9 nmol/L: 0.88 (0.68 to 1.13); ⩾100.0 nmol/L: 0.77 (0.56 to 1.06)). However, in subgroup analyses this association was noted for colon cancer but not rectal cancer (Jenab *et al.*, 2010). Participants with prediagnostic 25(OH)D levels in the highest quintile had a reduced

risk of colorectal cancer-specific mortality (HR = 0.69; 95% CI: 0.50–0.93) and overall mortality (HR = 0.67; 95% CI: 0.50–0.88), compared with the lowest quintile (Fedirko *et al.*, 2012).

3.2 Breast cancer

Five case-control studies of the relationship between 25(OH)D levels and the risk of breast cancer all showed inverse associations between the vitamin D blood levels and breast cancer risk. Of the prospective studies, four showed inverse associations and six found no association between vitamin D blood levels and breast cancer risk, while in the NHANES III cohort a 35% reduction in mortality risk was found (RR = 0.65; 95% CI: 0.18–2.38 for ⩾ 80 25(OH)D nmol/L *versus* < 50 nmol/L). These results are confirmed by the meta-analysis of Gandini *et al.* (2009) showing that the summary relative risk (SRR) for a 10 ng/ml increase of 25(OH)D levels was of 0.83 (95% CI: 0.79–0.87) for the case-control studies, and of 0.97 (95% CI: 0.92–1.03) for prospective studies.

3.3 Prostate cancer

Out of fourteen prospective studies on the relationship between 25(OH)D levels and the risk of prostate cancer, eleven studies found no association between prostate cancer risk and the blood levels of vitamin D, one observed no statistically significant trend in overall prostate cancer risk with increasing serum 25(OH)D level although greater serum concentrations were associated with an increased risk of aggressive disease, and two studies found negative associations. Two prospective studies on the relationship between vitamin D blood levels and mortality gave conflicting results: while one showed that higher levels (⩾ 80 nmol/L) was non significantly associated with an increased risk, the other found that men with the lowest 25(OH)D quartile were more likely to die of their cancer (HR = 1.59; 95% CI: 1.06–2.34). These results were confirmed by a meta-analysis (Gandini *et al.*, 2011) showing a summary relative risk (SRR) for a 10 ng/ml increase in serum 25-hydroxyvitamin D of 0.99 (CI 95%: 0.95–1.03) for prostate cancer risk.

3.4 Non-Hodgkin lymphomas

Few studies have investigated vitamin D serum levels in relation to non-Hodgkin lymphoma risk. But currently the results are mostly in favor of an absence of relation.

One case-control study and a prospective study found no associations between 25(OH)D levels and the risk of NHL. In the Finnish Alpha-Tocopherol Beta-Carotene Cancer Prevention Study cohort, an inverse association was found for cases diagnosed less than 7 years from baseline, but not for later diagnoses (OR = 0.43; 95% CI: 0.23–0.83). In addition, in a prospective study, no relation was found between 25(OH)D levels and mortality.

4 Intervention studies

Observational studies, of which several have been prospective, have linked low vitamin D status to an increased cancer risk, but intervention studies are necessary to test this hypothesis and reach any firm conclusion.

In this context, the trial published by Lappe *et al.* (2007) raised great expectations. This was a 4-year, population-based, double-blind, randomized placebo-controlled trial. The primary outcome was fracture incidence, and the principal secondary outcome was cancer incidence. The subjects were 1179 community-dwelling women randomly selected from the population of healthy postmenopausal women aged > 55 years in a 9-county rural area of Nebraska. Subjects were randomly assigned to receive 1400–1500 mg supplemental calcium/day alone (Ca-only), supplemental calcium plus 1100 IU vitamin D3/day (Ca + D), or placebo. Fifty women developed nonskin cancer during the course of the study: 20 in the placebo group (n = 228), 17 in the Ca-only group (n = 445), 13 in the Ca + D group (n = 446). In comparison to the placebo group, the relative risk (RR) of developing cancer at study end was 0.402 (95% CI: 0.20–0.82; P = 0.013) for the Ca+D group and 0.532 (95% CI: 0.27–1.03; P = 0.063) for the Ca-only group. However, it cannot be concluded from these results that vitamin D supplementation actually reduced cancer incidence since there was no vitamin D alone group, and since when the Ca-only group is pooled with the placebo group, the difference in cancer incidence is no longer significant.

But a large double-blind, randomized placebo-controlled intervention trial, involving 36 282 postmenopausal women from 40 Women's Health Initiative centers failed to show an effect of a daily supplementation in calcium and Vitamin D (400 IU) during 7 years on colorectal cancer incidence (Wactawski-Wende *et al.*, 2006).

While a recent meta-analysis of 18 randomized trials (57 311 participants) showed that a vitamin D supplementation (400 to 800 IU/day) is associated with a significant reduction in mortality (RR = 0.93; CI 95%: 0.87–0.99) (Autier *et al.*, 2012), a recent review showed that no vitamin D supplementation trial (10–20 μg/day, for 48 to 260 months) showed reduction in risk of colorectal, breast or skin cancer (Autier *et al.*, 2013).

4.1 Tanning bed use and cancer prevention

The UVB component of the radiation emitted by tanning beds used for artificial tanning induces vitamin D synthesis in the skin, and actually increases serum levels of 25(OH)D and it has been suggested that exposure to tanning bed could compensate a vitamin D insufficiency. But it should be kept in mind that artificial UV tanning is classified as a Group 1 carcinogen (IARC, 2009), to which 347 melanoma cases (4.6% of the incident cases) and 19 to 76 deaths can be attributed annually in France (Boniol *et al.*, 2012). Furthermore, a recent publication from the Nurses' Health Study II shows that tanning bed exposure has no effect on the risk of internal cancers (HR = 0.99; 95% CI, 0.95–1.04 for every 4 times/year use on average during high school/college and at ages 25–35), and no association

Table 1. Summary of associations of cancer risk with sun exposure and vitamin D levels.

Tumor	Negative association with sun exposure	Association with 25(OH)D blood levels	Intervention trials	Comments
Colorectal cancer	Fairly consistent from ecological, case-control and prospective studies	Consistent inverse relationship with serum 25-hydroxyvitamin D levels	No effect	The Lappe et al. (2007) intervention trial cannot disentangle effects of calcium alone supplementation from Ca + vitamin D supplementation
Breast	Observed in case-control studies Mixed results from prospective studies	Inverse association in case-control studies No association in prospective studies	No effect	Too low dose of vitamin D (400 IU/d) in WHI intervention trial?
Prostate	All but one case-control and prospective studies show negative association	No association	No evaluable trial	Studies on sun exposure conducted in relatively low UV environment; the only study showing a positive association conducted in Australia
Non-Hodgkin Lymphoma	Conflicting results	Few studies Current results in favor of an absence of association	No evaluable trial	

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was found for the risk of any individual major cancers, such as breast cancer, colorectal cancer, or non-Hodgkin lymphoma (Zhang et al., 2013).

5 Conclusion

As summarized in Table 1, there is an inverse association between sun exposure and incidence or progression of major cancers: colon, breast and prostate cancer, and possibly non-Hodgkin lymphomas. But the mechanism of such an association is far from being unraveled. Although a role of vitamin D in the reduction in cancer risk is biologically plausible, the serum levels of 25(OH)D are negatively associated with risk of colon cancer and to a lesser extent with risk of breast cancer, but not with risk of prostate cancer and non-Hodgkin lymphoma, and vitamin D supplementation studies all failed to demonstrate an effect on cancer risk. Currently, the question is to determine whether the reduction in cancer risk is mediated by vitamin D or by another factor influenced by sun exposure such as inflammation or immunosuppression, and whether a low vitamin D status causes an increase in cancer risk or is simply a consequence of ill health (van der Rhee et al., 2013). And indeed, as stated by Autier et al. (2013): "*The discrepancy between observational and intervention studies suggests that low 25(OH)D is essentially a marker of ill health. Inflammatory processes involved in disease occurrence and clinical course would bring down 25(OH)D, what would explain why low vitamin D status is encountered in a large variety of conditions. In elderly, the restoration of vitamin D deficits due to aging and changes in lifestyle induced by ill health could explain why small dose supplementation leads to modest gain in survival.*"

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