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Seasonal and geographical variations in lung cancer prognosis in Norway
Does Vitamin D from the sun play a role?

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Summary Vitamin D derivatives can modulate proliferation and differentiation of cancer cells. Our main source of Vitamin D is ultraviolet (UV) radiation-induced synthesis in skin following sun exposure. UV measurements show that the ambient annual UV exposures increase by about 50% from north to south in Norway. As judged from the incidence rates of squamous cell carcinoma, the same is true for the average personal UV exposures. Solar ultraviolet B (UVB) (280—320 nm) exhibits a strong seasonal variation with a minimum during the winter months. The present work aims at investigating the impact of season of diagnosis and residential region, both influencing the Vitamin D level, on the risk of death from lung cancer in patients diagnosed in Norway.

Data on all incident cases of lung cancer between 1964 and 2000 were collected. Risk estimates were calculated as relative risk (RR), with 95% confidence intervals using Cox regression model. The seasonal variation of 25-hydroxyvitamin D was assessed from routine measurements of 15,616 samples performed at The Hormone Laboratory of Aker University Hospital.

Our results indicate that season of diagnosis is of prognostic value for lung cancer patients, with a ≈15% lower case fatality for young male patients diagnosed during autumn versus winter (RR = 0.85; 95% CI, —0.73 to 0.99; $p = 0.04$). Residing in a high UV region resulted in a further lowering of the death risk than residing in a low UV region.

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We propose, in agreement with earlier findings for prostate-, breast- colon cancer and Hodgkins lymphoma, that a high level of sun-induced 25-hydroxyvitamin D can be a prognostic advantage for certain groups of lung cancer patients, notably for young men.

Lung cancer has for several decades been the leading cause of cancer-related mortality in men in Norway [1] and during the last two decades, became the second most common cause of cancer-related death in women [2]. There are two main types of lung cancer: small cell lung cancer for which chemotherapy is the primary treatment and non-small cell lung cancer, which in its early stages is treated primarily with surgery. Gender-related differences have been described in the literature with respect to survival after therapy, male gender being a significant independent negative prognostic factor [3]. In Norway the 5 years relative survival for localized tumours is about 30% for females and 20% for males.

Calcitriol, which is the most active form of Vitamin D, is involved in key regulatory processes such as proliferation, differentiation and apoptosis in a wide variety of cells [4—6]. Mechanisms for these actions have been proposed to be the interaction of active Vitamin D derivatives with a specific nuclear receptor (VDR receptor) and/or with membrane targets [4,7]. In vitro studies, performed with lung cancer cell lines, have shown an inhibitive effect of Vitamin D derivatives on cell-growth and proliferation [8]. Furthermore, animal studies have demonstrated the capability of these compounds to suppress invasion, metastasis and angiogenesis in vivo [9—11], suggesting that administration of Vitamin D derivatives may be used as adjuvant therapy for lung cancer.

Humans get optimal Vitamin D levels by exposure to sun or artificial ultraviolet B (UVB, 280—320 nm) sources [12], and possibly also by consumption of food rich in this nutrient (fat fish, eggs, margarine, etc.) or of vitamin supplements [13]. Among these sources, solar radiation appears to be the most important one [12]. Thus, the Vitamin D status (assessed by the serum levels of 25-hydroxyvitamin D, calcidiol) exhibits a strong seasonal variation that parallels the seasonal change in the fluence of solar UVB that reaches the ground. During winter, the UVB fluence rate in the Nordic countries (50—71°N) is below the level required for Vitamin D synthesis in skin [14]. The maximal level of calcidiol is reached between the months July and September, and is 20—120% higher than the corresponding winter level [15—24].

Recently we hypothesised that the seasonal variation of calcidiol might be of prognostic significance for colon-, breast- prostate cancer as well as for Hodgkins lymphoma in Norway. Patients diagnosed during summer and autumn have a better survival after standard treatment than patients diagnosed during the winter season [25,26]. This might be a consequence of a higher Vitamin D level. An American study investigated the effect of season of surgery and recent Vitamin D intake on the survival of non-small cell lung cancer patients. The authors reported a significant beneficial joint effect of summer season and high Vitamin D intake compared with winter season and low Vitamin D intake [27] while Vitamin D intake alone did not affect prognosis. Similar results were recently reported from a large study in United Kingdom involving over a million cancer patients including over 190,000 patients diagnosed with lung cancer [28].

Norway (58—71°N) has a significant north—south variation in UV fluence. This makes the country suitable for studies relating cancer epidemiology to UV levels [29,30].

We investigated whether variations in UV, and, consequently, in Vitamin D level, influence the prognosis of lung cancer, using season of diagnosis and residential regions as variables. Survival data obtained for patients diagnosed over a 40 years period were compared with variations in serum Vitamin D levels obtained from routine measurements performed in The Hormone Laboratory of Aker University Hospital during the period 1996—2001. Seasonal and gender variations in Vitamin D level have been estimated from the analyses.

1. Methods

1.1. Lung cancer population

Reporting of all new cancer cases to the Cancer Registry of Norway has been compulsory since the registry was established in 1953. Information regarding date of birth, sex, place of residence, primary tumour site and stage of disease at diagnosis is available throughout the study period. The case ascertainment is based on pathology, cytology and clinical reports. For the present study we have identified 49,518 lung cancer patients diagnosed between 1960 and 2001. From this, 3837 patients were excluded because of the following: report by autopsy or death certificate only, missing cause of death and no information on place of residence or date of birth. The final study population consisted of 45,681 eligible patients. The patients were followed from the date of diagnosis until death, emigration or December 31, 2001, whichever occurred first. Demographic characteristics of the eligible population are presented in Table 1. The mean follow-up period was 21 months for females and 17.5 months for males. In the analyses, we considered two age groups: younger and older than 50 years. The cut-off age was chosen based on the knowledge that the Vitamin D syn-

Table 1 Number of incident cases of lung cancer by season of diagnosis in the eligible population and seasonal variation of calcidiol concentration in samples drawn for routine analyses are shown

	Number of incident cases of lung cancer				Percentage change in serum calcidiol concentration in the samples from routine measurements	
	Women ($n = 12,277$)		Men ($n = 33,404$)		Women	Men
	≤50 ($n = 1086$)	>50 ($n = 11,191$)	≤50 ($n = 1943$)	>50 ($n = 31,461$)		
Winter (01 December–29 February)	288	2741	507	7619	0[a]	0[a]
Spring (01 March–31 May)	269	2785	478	7871	−4.3	−3.9
Summer (01 June–31 August)	233	2709	470	7789	3.9	11.2
Autumn (01 September–30 November)	296	2956	488	8182	6.7	16.6

[a] The mean winter concentration of serum calcidiol was 55 nmol/l for women and 46 nmol/l for men in the samples from routine measurements.

thetic capacity of human skin decreases with age [31] and allowed us to consider for the survival analyses, a group of young patients that presumably have a competent Vitamin D synthesis system.

1.2. Vitamin D population

Results from routine serum calcidiol measurements, performed in 15,616 persons (aged 16–80 years) at the Hormone Laboratory (Aker University Hospital, Oslo) from 1996 to 2001, were available and allowed estimations of age-, gender- and season-related variations. Calcidiol concentrations were determined by high performance liquid chromatography after ether extraction, essentially as described in ref. [32] with an inter assay variation of 12%.

1.3. Study variables and statistical analysis

The time-points for diagnosis were grouped in four seasons: winter (1 December–29 February), spring (1 March–31 May), summer (1 June–31 August) and autumn (1 September–30 November). For statistical reasons we have merged the summer and autumn season and the winter and spring season when performing analyses stratified by residential region. Norway was divided into three residential regions (Fig. 1) according to the calculated level of UV exposure (Fig. 2). Additionally, to control for the real UV exposure obtained by different populations, we have plotted the incidence rates (IR) of squamous cell carcinoma of the skin (SCC) versus the calculated UV dose (Fig. 3) in each of the Norwegian coun-

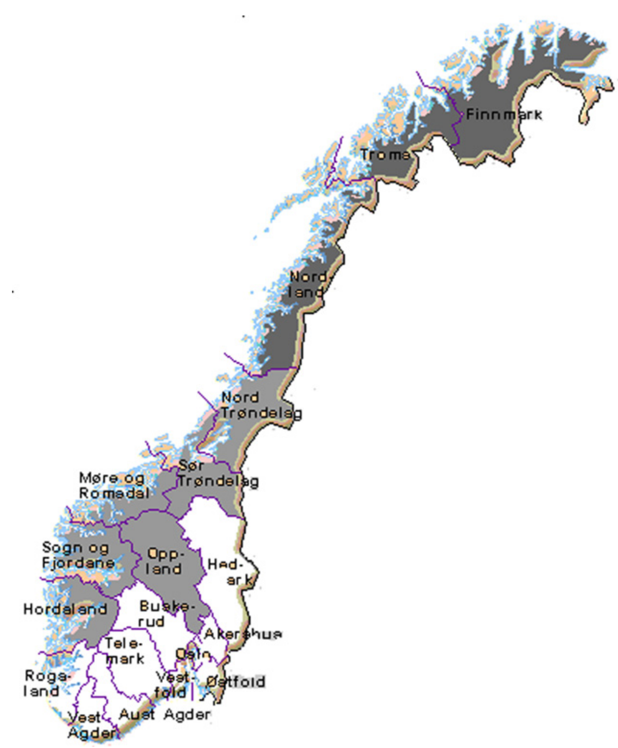

Fig. 1 A map of Norway showing the three residential regions (□, southeast region, high incidence rates of SCC; ▪, midwest region, medium incidence rates of SCC; ▪, north region, low incidence rates of SCC).

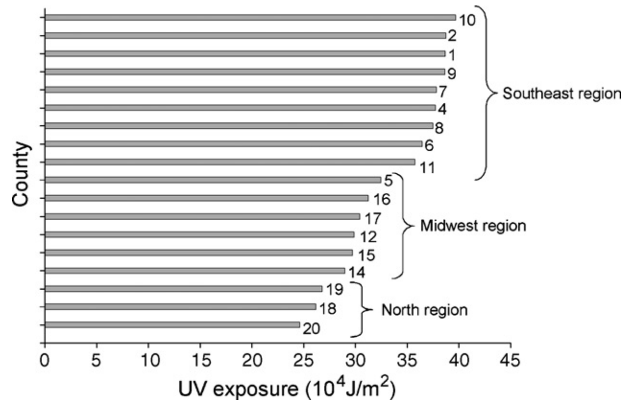

Fig. 2 The UV exposure from the sun, determined by using the CIE reference spectrum of erythema. The number in the brackets gives the county's number.

ties. The incidence rates were age-adjusted and the values plotted represent an average of the period 1957—2001. log—log plots are usually used for incidence—annual UV dose relationships in the case of skin cancer. The reason for this is that the relationship is not linear, but closer to quadratic. In fact, in most cases it follows the equation: $\log(\text{incidence}) = A_b \log(\text{dose})$, where A_b is the so-called biological amplification factor [29]. The main city, Oslo, was excluded from all analyses, to reduce errors that may arise from different sun exposure habits and high immigration rate. Oslo has the highest proportion of immigrants with 18% of its population being of non-western origin [33].

The global solar UV irradiance (i.e. direct + diffuse radiation on a horizontal surface) was calculated with a radiative transfer model [34,35]. Daily total ozone column amounts measured by TOMS satellite instruments were used in the model. The daily cloud cover for each site used in the calculations was derived from measured reflectivities from an ozone insensitive channel of the same satellite instruments. The effect of snow cover at different regions in Norway was estimated by comparing the calculations with UV measurements from the Norwegian UV monitoring network. The

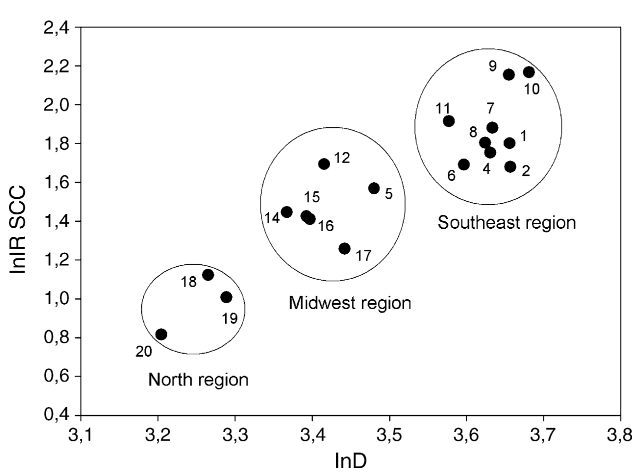

Fig. 3 Annual ambient UV exposure (D) vs. age adjusted rate of squamous cell carcinoma (R) in Norway (1957—2001). The relationship is described by the relationship $\ln R = A \times \ln D$, where A is the amplification factor [29].

calculated annual UV exposures are based on available satellite measurements in the period 1980—2000.

The number of incident cases of lung cancer corresponding to each season was collected. To assess the association between season of diagnosis and the risk of death from lung cancer, a Cox regression ran by SPSS for Windows (SPSS Inc., USA) was used. The relative risk of death for patients diagnosed in each season versus winter diagnosis was evaluated while considering the following potential confounding variables: age at diagnosis, stage of disease at diagnosis and histology which are known predictors of survival from lung cancer [36]. Additionally, adjustments for sex, period of diagnosis, birth cohort and residential region were performed. All analyses were done for the first 18 months of follow-up.

2. Results

It is widely accepted that UV from the sun is the main risk factor for SCC. Strong evidence points to a relationship between accumulated UV exposure and incidence rates of SCC [29,30,37—39]. When plotting the age adjusted incidence rates of SCC as a function of the calculated annual solar UV fluence, our data clustered in three groups (Fig. 3). The northern region was not included into the further analyses. People living in this region consume large quan-

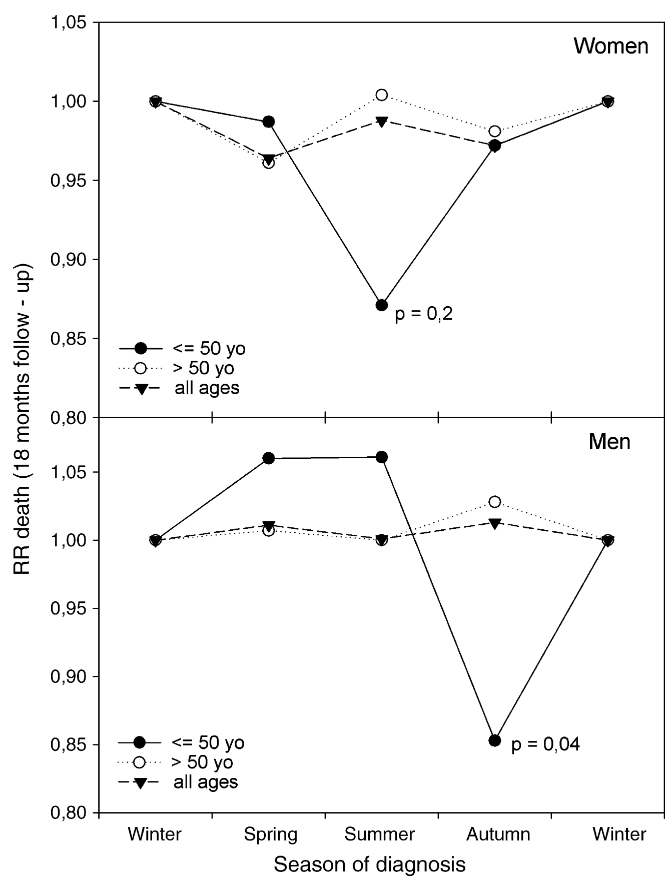

Fig. 4 Relative risk of death of lung cancer by season of diagnosis in Norway (winter is the reference season). Data were stratified by age and gender. (Upper panel) Data for males and (lower panel) data for women.

tities of cod and saithe liver, especially from late summer until spring. The season of cod fishing starts around mid-December and lasts until April. Saithe liver is consumed from late summer until September/October [15,40]. Therefore, the general intake of Vitamin D is around 17% higher in north Norway compared with that in southeast and midwest Norway [41].

The southeast region includes the population living in the counties with the highest calculated UV doses and the highest incidence rates of SCC (counties 1, 2, 4 and 6—11). The midwest region comprises the counties 5, 12 and 14—17. The third region (counties 18—20) is excluded from the analyses due to higher Vitamin D intake in this region than in the other ones [41]. Table 1 shows the number of new cases of lung cancer by season of diagnosis for the two age groups, in males and females. The results of multivariate analysis of the RR of death by season of diagnosis are shown in Fig. 4. We analysed the effect of age, gender and residential region on the seasonality of lung cancer prognosis. It is apparent that male patients, younger than 50 years, have a significant better survival if diagnosed during autumn or summer relative to those diagnosed in winter (Table 2). Region of residence also had a positive impact on the improved survival among cases diagnosed during fall. Residing in the southeast resulted in a further lowering of the risk of death compared with residing in the midwest. Identical analysis of the data for female patients showed no significant association between season of diagnosis and risk of death from lung cancer (Table 2).

Table 1 also presents the seasonal variation of calcidiol concentration, assessed in 15,616 serum samples mostly from routine analyses of patients with suspected bone or calcium disorders. In both genders the highest mean values for calcidiol were achieved in the autumn and the lowest in spring. An important gender-related difference can be observed in the amplitude of seasonality of serum calcidiol concentration, with the greatest amplitude for men.

3. Discussion

The present results support the hypothesis that sun-induced Vitamin D improves cancer prognosis. Male lung cancer patients, younger than 50 years, have a 15% reduced risk of dying from the disease within 18 months when diagnosed during the summer/autumn compared with patients diagnosed during winter/spring. Additionally, when analyzing separately the two residential regions with significant vari-

Table 2 Relative risk of death among lung cancer patients by season of diagnosis and residential region

	Women (mean age 65 years)			Men (mean age 66 years)		
	RR death	95% CI	*p*-Value	RR death	95% CI	*p*-Value
Midwest region						
Winter	1.00	Ref.		1.00	Ref.	
Summer	0.98	0.92—1.05	0.71	1.00	0.96—1.04	0.7
Southeast region						
Winter	0.89	0.82—0.95	0.002	0.94	0.90—0.98	0.01
Summer	0.9	0.83—0.97	0.006	0.95	0.90—0.99	0.02
	Women $\leq$ 50 years old			Men $\leq$ 50 years old		
	RR death	95% CI	*p*-Value	RR death	95% CI	*p*-Value
Midwest region						
Winter	1.00	Ref.		1.00	Ref.	
Summer	0.74	0.58—0.93	0.01	0.84	0.71—1.01	0.06
Southeast region						
Winter	0.82	0.64—1.05	0.1	0.82	0.69—0.99	0.04
Summer	0.88	0.68—1.14	0.3	0.75	0.62—0.90	0.003
	Women > 50 years old			Men > 50 years old		
	RR death	95% CI	*p*-Value	RR death	95% CI	*p*-Value
Midwest region						
Winter	1.00	Ref.		1.00	Ref.	
Summer	1.01	0.94—1.08	0.73	1.00	0.97—1.05	0.49
Southeast region						
Winter	0.89	0.83—0.97	0.006	0.95	0.91—0.99	0.02
Summer	0.91	0.84—0.98	0.01	0.96	0.92—1	0.07

Data for 18 months follow-up are shown. Spring and winter were merged into one season, here called ''winter'', which was set as the reference category. Summer and autumn were also merged and called ''summer''. (Upper table) Data for all ages, (middle table) data for patients younger than 50 years at diagnosis and (lower table) data for patients older than 50 years at diagnosis.

ations in the levels of UV and SCC, it became apparent that living in the southeast represents a further benefit.

3.1. Season of diagnosis as a predictor of survival

Our hypothesis is based on the fact that the level of sun-induced Vitamin D exhibits a strong seasonal variation and on the evidence that Vitamin D derivatives act as potent anticancer agents for lung cancer [8—11,27]. Similar correlations between the season of cancer diagnosis and survival have been observed for breast-, colon-, prostate cancer and Hodgkins lymphoma diagnosed in Norway [25,26,42] and, very recently, in UK [28].

Our measured seasonal variation of the Vitamin D status is in agreement with what is found in a number of other Scandinavian investigations showing a 20—120% increase in the serum calcidiol from winter to summer [15—24]. During winter, the fluence rate of solar UVB is too low in Norway to induce any skin synthesis of Vitamin D [43]. This is reflected in a low level of calcidiol. Our calcidiol analyses illustrate a gender difference in the Vitamin D status. The data should be interpreted with caution, since most of the samples were from individuals at increased risk of a Vitamin D insufficiency. Furthermore, no information on place of residence and Vitamin D intake was recorded.

For females, our analyses revealed no beneficial prognostic effect of being diagnosed during autumn/summer. A similar gender difference has been observed for Hodgkins lymphoma and colon cancer patients (data not shown). This might be a consequence of the gender difference in the seasonality of calcidiol (Table 1). The higher amplitude of calcidiol seasonality observed for males versus females could be explained by the different sun exposure patterns, with males exposing themselves more than females.

Since Vitamin D synthesis in skin is age-dependent, we have analysed survival separately in two age groups. Holick et al. showed that a given UVB dose induces four times more serum calcidiol in a young population (20—30 years) compared with in an older population (62—80) [44] and that the epidermis content of 7 dehydrocholesterol (7DHC, Vitamin D_3's precursor) decreases drastically with age [31]. Moreover, elderly are likely to be housebound, and, therefore, are less sun exposed than young people [23]. The mean age in our oldest group was close to 70, possibly explaining the lack of association between season of diagnosis and survival among the patients in this age group.

The reason why the best prognosis seems to be associated with a time of diagnosis that is slightly later than the time of maximal calcidiol concentration in serum is not known. However, it should be noted that the calcidiol maximum in many investigations occurs after mid-summer [45—47], which may be related to late vacations and/or to the delay time caused by the physiological and biochemical reactions leading from previtamin D_3 formation in the skin to production of calcidiol in the liver and release into the blood. Calcidiol is taken up by cells in tumours and in a number of other target tissues, and is then transformed to calcitriol. It has been proposed that calcitriol is trapped in the cells until it is degraded [48]. This may result in a further delay, as observed here.

3.2. Residential region

We investigated the fatality among cases in the southeast and midwest regions, in a similar manner as we analysed the data for the whole country. Our results show that residing in the southeast adds an extra beneficial effect to the improved summer survival.

We have previously found a seasonal variation in the prognosis of breast, colon and prostate adenocarcinomas and in that of Hodgkins lymphoma [25,26,42]. The prognosis was significantly better for summer/autumn diagnosis. This was tentatively attributed to a high Vitamin D status in these seasons as compared with the winter. Our findings are in agreement with other epidemiological studies indicating that cancer mortality decreases with increasing sun exposure [49—56].

Until now, mainly calcitriol derivatives have been considered for adjuvant cancer therapy. For these compounds, development of secondary hypercalcemia is a limiting factor for clinical application [57]. Calcitriol is believed to be the biologically most active Vitamin D derivative in relation to the calcium metabolism [12]. The main source of calcitriol is hydroxylation of calcidiol in the kidneys. However, a number of other normal and malignant tissues, including lung cancer cells [58], produce calcitriol that control differentiation, multiplication and cell growth by autocrine mechanisms [59—61]. Once formed, calcitriol binds to well-known nuclear or putative membrane receptors and performs its function. Calcidiol, which is found in 500—1000 times higher concentrations in serum compared to calcitriol, has a lower affinity for the nuclear receptors [59,62]. This has been the rationale for choosing calcitriol in clinical testing [57].

The measurements from Hormone Laboratory, Aker University Hospital, Oslo, show no seasonal variation of the calcitriol concentration (data not shown). Other investigations agree with this [17,21,63,64]. Therefore, we have hypothesized that calcidiol may be a more important Vitamin D derivative than calcitriol in view of cancer prognosis [25,26,42]. Calcidiol might act either directly by binding to VDR receptors (since its high concentration might compensate for the lower receptor affinity) or by supplying cancer cells with the precursor of calcitriol. Hence, the role of calcidiol should be considered in further experimental and clinical studies.

In summary, our results suggest that Vitamin D status at time of lung cancer diagnosis is of prognostic value. From this perspective, further epidemiological and experimental studies are warranted to evaluate the role of sun-induced Vitamin D in cancer progression. The circulating level of Vitamin D derivatives (calcidiol) needed to reduce cancer risk and improve prognosis is currently not known. The present work seems to indicate that levels as found in summer play a positive role. Levels higher than previously thought to be sufficient for skeletal health have been suggested [65—68]. Safety and efficiency of different Vitamin D sources should be further investigated.

Conflict of interest statement

None declared.

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