Sun Exposure and Cancer Survival in Norway: Changes in the Risk of Death with Season of Diagnosis and Latitude
Alina Carmen Porojnicu,* Arne Dahlback and Johan Moan

Abstract
Epidemiological and experimental studies suggest that derivatives of vitamin D may improve prognosis of a number of cancer types. Sun is our most important source of vitamin D. Seasonal variations and latitudinal gradients of calcidiol (the marker of vitamin D status) have been reported. We wanted to investigate if season and latitude play any role for survival from seven different cancer types in Norway. Seasonal and geographical variations of vitamin D were estimated by calculations and were compared with clinical data. For the survival analyses, 249373 cancer patients were followed for three years after diagnosis and the risk of death was analyzed separately for summer- and winter diagnosis, as well as for two geographical regions with different UV exposures. We found a 15-25 % better survival for patients diagnosed during summer and a slight beneficial effect for residents of the high UV region for some of the cancer forms investigated.

Based on our results we suggest that calcidiol concentration at the time of cancer diagnosis is related to survival and discuss briefly ways to improve the vitamin D levels in the general population.

Introduction
Solar radiation, a recognized skin carcinogen,1 may also reduce mortality from internal cancers. This intriguing suggestion was first published by Apperly in 1941.2 He observed that cancer patients living at high latitudes in USA had a higher mortality risk compared with those living in the south. Later, in 1980, Garland and Garland3 surveyed the association between solar exposure and risk of dying from colon cancer and hypothesized that the negative association between these two may be related to the level of vitamin D. A number of similar ecological studies were carried out in the following years, most of them supporting the proposed association.4-9 The level of solar exposure were either approximated by using latitude, UV satellite measurements, UV indexes (the case of ecological work), assessed through records of personal history of sun exposure or estimated by structural changes in the skin.10 A number of cancers were investigated throughout this period and in a recent publication fifteen cancer types were found to be sun-sensitive with respect to progression.11

A north-south gradient seems to be present in USA as well as in Europe12,13 and even in Japan.14

*Corresponding Author: Alina Carmen Porojnicu—Department of Radiation Biology, Institute for Cancer Research, Montebello, Oslo, Norway. Email: a.c.porojnicu@usit.uio.no

These epidemiological observations triggered experimental work aimed at understanding the mechanistic background. As suggested by Garland and Garland a possible link between the level of solar exposure and cancer mortality is vitamin D. It is well known that sun is our main source of vitamin D. Our epidermis and dermis contain 7-dehydrocholesterol (7-DHC), a precursor of both vitamin D and cholesterol. When UVB (ultraviolet B, 280-320 nm) photons from the sun or from artificial sources, hit the skin, 7-DHC absorbs energy and is structurally changed to previtamin D which is unstable and isomerizes in a temperature dependent process to vitamin D. Vitamin D is transported by the blood flow, bound to DBP (vitamin D protein), first to the liver and then to the kidneys. The molecule undergoes steps of enzyme-catalyzed hydroxylation, resulting in the formation of 25 hydroxyvitamin D (calcidiol) in the liver and 1,25 dihydroxyvitamin D (calcitriol) in the kidneys. Calcidiol is used in the clinical vitamin D monitoring, since its formation is not tightly regulated. Therefore it is reflecting the vitamin D status.

The seasonal variation of calcidiol is a well documented fact. In a healthy, adult population living in Norway the percent increase from winter to summer is 15-50%. From October to April solar vitamin D synthesis does not take place in this part of the world and vitamin D deficiency will become manifest unless adequate amounts of the vitamin are ingested. The maximal serum levels of calcidiol are usually achieved during the months September-October, reflecting a delay from the maximal solar UVB fluence rate midsummer.

Materials and Methods

The purpose of our work was to study the association between the level of solar exposure and cancer prognosis in Norway. The exposure level changes with season and residential region. Outcome was calculated using Cox proportional hazards regression model and expressed as relative risk of death (RR). The category with the lowest solar exposure was chosen as reference and set to 1. Analyses were adjusted for a number of possible confounders, as outlined below.

Cancer Database

In our study we used data from The National Cancer Registry of Norway, a population-based registry that since 1953 collects data on cancer incidence and survival. Information is obtained from three sources: diagnosing physician, pathology laboratories and Statistics Central Bureau and this assures a high degree of reliability. The Registry records information on patients characteristics (date of birth, sex, residence), date of diagnosis, primary tumor site, stage of diagnosis and follow up for vital status.

After 1960, each Norwegian inhabitant received a unique identification number. This allowed us to link the Cancer Database to The Population Registry whenever we were interested in obtaining further socio-demographic information.

In our work we included all patients diagnosed with prostate-, breast-, colon-, lung-, ovarian- and bladder cancer, as well as with Hodgkin lymphoma. Description of the period of inclusion, number of cases and number of deaths from cancer is presented in Table 1.

Using the date of diagnosis, the season of diagnosis was defined as follows: winter (December 1-May 31) and summer (June 1-November 30).

Solar Exposure in Norway

The main factors influencing the ultraviolet (UV) irradiances at ground level are solar zenith angle (variable with season, latitude and time of day), cloud and snow cover and the thickness of the ozone layer.

In this study, the global solar UV irradiance was calculated using a radiative transfer model. Total ozone amounts used in this model were measured by TOMS satellite instruments. The daily cloud cover varies in Norway, with coastal regions being cloudier than the inland regions. The