Ultraviolet Exposure and Mortality among Women in Sweden

Ling Yang1,2,3, Marie Lof1, Marit Bragelien Veierød4, Sven Sandin1, Hans-Olov Adami2,5, and Elisabete Weiderpass1,3,6,7

Abstract

Background: Ecological studies have reported possible effects of sunlight on the risk of several diseases. Little evidence is available on the association between mortality and solar and artificial UV exposure by individual level from prospective studies.

Methods: The Swedish Women’s Lifestyle and Health cohort study included women aged 30 to 49 years in 1991–1992. Participants completed a questionnaire and were followed-up through linkages to national registries until the end of 2006. Cox models were used to estimate adjusted HRs and 95% CIs for all-cause mortality and for cancer and cardiovascular disease (CVD) mortality.

Results: During 15 years of follow-up, among the 38,472 women included in the present study, 754 deaths occurred: 457 due to cancer and 100 due to CVD. When combining the information on sun exposure from age 10 to 39 years, women who got sunburned twice or more per year during adolescence had a reduced all-cause mortality, compared with women who had been sunburned once or less. A reduced risk for all-cause and CVD mortality was observed in women who went on sunbathing vacations more than once a year over three decades. Solarium use once or more per month for at least one decade increased the risk of all-cause mortality, when compared with women who never used a solarium.

Conclusions: Solar UV exposure was associated with reduced overall and CVD mortality, whereas artificial UV exposure was associated with increased overall and cancer mortality among Swedish women.

Impact: Moderate sun exposure may protect against cause-specific mortality. Cancer Epidemiol Biomarkers Prev; 20(4); 683–90. ©2011 AACR.

Introduction

The convincing evidence for a causal relationship between UV exposure, be it solar or artificial, and the risk of skin cancer (1–6) has stimulated extensive public campaigns against excessive sunbathing. Nevertheless, most people depend on sun exposure to synthesize the amounts of vitamin D required for optimal health. In the skin, UV-B photons are absorbed by the precursor 7-dehydrocholesterol and converted to vitamin D3. Vitamin D3 is thereafter metabolized to 25(OH)D (25-hydroxyvitamin D) in the liver and then converted to its biologically active form, 1,25(OH)2D in the kidney (7). Solar UV-B is thought to contribute about 90% of serum vitamin D levels, as few foods naturally contain it (8). Artificial tanning by solarium use can also increase vitamin D synthesis (8).

During the last decades, there has been accumulating evidence that UV exposure, via its effect on the body’s vitamin D metabolic synthesis pathway, might have a wide range of beneficial effects on several conditions, such as multiple sclerosis, osteoporosis, cardiovascular disease (CVD), diabetes type 1 and several cancers, including breast, ovary, prostate, colon, and non-Hodgkin lymphoma (8–24). However, existing evidence is derived mostly from ecological studies and includes only a few case-control or prospective studies with individual data on both UV exposure and dietary vitamin D intake. Hence, uncertainties persist about the relationship between UV exposure and mortality, such as whether the associations differ according to UV exposure in different periods of life, and factors related to UV transmission and absorption, such as host characteristics related to UV sensitivity, and dietary or supplementary vitamin D intake.

The Swedish Women’s Lifestyle and Health (WLH) cohort allows us to address these questions using detailed...
data on solar and artificial UV exposure during different periods of life, host pigmentary characteristics, and vitamin D intake from foods and supplements.

Materials and Methods

Study cohort

Enrollment into the Swedish WLH cohort took place in 1991–1992. As previously described in detail (25), 96,000 women aged 30 to 49 years residing in the Uppsala Health Care Region were randomly selected from the Swedish Central Population Registry at Statistics Sweden and sent an extensive questionnaire. A total of 49,259 women (52%) returned a completed questionnaire which included demographic data, anthropometric characteristics, and information on a variety of lifestyle factors.

UV exposure and other relevant data

By means of the questionnaire, the women reported their history of sunburn, sunbathing vacations, and frequency of solarium use at ages 10 to 19, 20 to 29, 30 to 39, and 40 to 49 years. For each age period, sunburn history was retrieved from questions on the average number of times per year (none, 1, 2–3, 4–5, or ≥6 times) that the participant had been sunburned so severely that it resulted in pain or blisters that subsequently peeled. Sunbathing vacations were recorded as the average number of weeks per year (none, 1, 2–3, 4–6, or ≥7 weeks) spent in southern latitudes (typically southern Europe, e.g., Spain or Greece) or within Sweden for each age period. The participants also reported their average solarium use during each age period (never, rarely, once, twice, 3–4 times per month, or more than once per week).

Study participants were asked to categorize their natural hair color (dark brown/black, light brown, blond or red) and eye color (brown, gray/green, or blue) in the questionnaire. Information on skin pigmentation, based on reactions to both acute sun exposure in the beginning of the summer (brown without red, red, or red with pain or blisters) and chronic or long-lasting sun exposure (light or never brown, brown, or deep brown) were also asked. The questionnaire at baseline included a validated self-administered food frequency questionnaire assessing habitual diet during the 6 months preceding the woman’s enrollment into the study. It covered the frequency and quantity of consumption of about 80 food items and beverages as well as multivitamins (26). Individual dietary intake of vitamin D was calculated by linking the amount of foods assessed by means of the questionnaire to the food composition database from the National Food Administration (1989). Vitamin D supplement intake information was obtained from the question on overall multivitamin supplement, without specification of the dose of vitamin D in the multivitamin (and thus only results for overall multivitamin use can be reported).

Follow-up

Follow-up for deaths among the study participants was conducted through linkages with existing nationwide population and health registries, using the individually unique national registration number assigned to all residents in Sweden. Follow-up was virtually complete with respect to death and emigration. Information on dates and causes of death for women who died during the follow-up period was abstracted from the nationwide Causes of Death Register. The cause of death was coded to 3 digits using the 9th version of the International Classifications of Disease (ICD-9) from 1991 to 1996 and the 10th version (ICD-10) thereafter. Dates of emigration for women who moved out of Sweden were provided by the Emigration Register.

The following causes of death were considered as endpoints in the present study: all-cause, CVD (ICD-9: 390–459, ICD-10: I00-I99), and cancer (ICD-9: 140–208, ICD-10: C00-C98). Due to small numbers, no other specific cause of death was analyzed.

The start of follow-up was defined as the date of receipt of the returned baseline questionnaire and person-years were calculated until the date of death, the date of emigration, or the end of follow-up (31 December 2006), whichever came first. For the current study, we excluded 5,763 women with a history of major chronic disease reported at baseline (1,212 cancer, 158 heart attack or stroke, 4,393 diabetes), 843 subjects with a total energy intake outside the 1st and 99th percentiles and 9 participants who did not report any UV exposure information. We further excluded 4,172 participants with missing information on any of the covariates involved in the analyses. The final study cohort comprised 38,472 women (78% of those who returned the questionnaire).

Statistical analysis

We assessed the association between all-cause, CVD, and cancer mortality and UV exposure, host characteristics, and vitamin D intake by calculating HRs as estimates of relative risks, with associated 95% CIs by the Cox proportional hazards model. We combined the UV exposure across each of the 3 decades of life recorded for all participating women (10–19, 20–29 and 30–39 years of age; ref. 27). The first 4 categories of annual number of sunburns and annual number of weeks spent on sunbathing vacations represent exposure accumulating over successive decades (10–39 years), whereas the fifth category corresponds to exposure in adult years only (i.e., 20–39 years). For solarium use, we used 4 categories representing cumulative exposure (10–39 years). The proportional hazard assumption was checked by plotting the Schoenfeld residuals (28). Attained age was used as the time scale in the models. The models were further successively adjusted for education, smoking, alcohol drinking, body mass index (BMI), and physical activity. The potential confounding effect of hair and eye color, and skin response to acute and chronic sun exposure, was further controlled in the models estimating risk of death from...
all-causes, CVD, or cancer. Subgroup analyses were confined to subjects with a low consumption of vitamin D, defined as a dietary vitamin D intake of less than 5 μg/d and no consumption of multivitamin supplements. When fitting the cause-specific models, death due to other causes were treated as censoring. All tests of statistical hypothesis were 2-sided with a 5% level of significance. The SAS software version 9.1 was used for all statistical analyses.

Ethics
This study was approved by the Data Inspection Board in Sweden and by the regional Ethical Committee. Consent was assumed by the return of the postal questionnaire.

Results

Characteristics of the study population
The 38,472 women included in this analysis were followed for an average of 14.9 years. During follow-up, a total of 754 deaths occurred: 457 (60%) due to cancer and 100 (13%) due to CVD. The baseline characteristics for the women in the entire cohort, as well as per cause of death are presented in Table 1. The patterns of mortality are in agreement with those expected on the basis of existing knowledge, in that mortality increases with smoking and BMI, and decreases with education and physical activity. At baseline, the mean dietary intake of vitamin D was 4.1 μg/d (SD = 1.7) and 15% of the women reported use of multivitamins. During the time period from age 10 to 39 years, 56% of the women reported having been sunburned once or more per year, 50% reported to have spent 1 week or more on sunbathing vacations every year, and 30% of women reported that they had used a solarium once or more per month (data not shown).

UV exposure and mortality
Table 2 shows all-cause mortality and mortality from CVD and cancer per annual number of sunburns, annual number of weeks spent on sunbathing vacations, and solarium use between ages 10 and 39 years. Women who got sunburned twice or more per year during adolescence had a 30% lower all-cause mortality (HR = 0.7, 95% CI: 0.5–0.9) than women who had been

![Table 1. Characteristics of the study population at baseline and by cause of death during follow-up (from 1991–1992 through 2006), the Swedish WLH cohort study](https://www.aacrjournals.org/cebp/article-pdf/20/4/685/15458099/685.pdf)
sunburned once or less per year between age 10 and 39 years. No statistically significant associations between annual number of sunburns and CVD or cancer mortality were found.

Women who had spent more than 1 week on sunbathing vacations per year between 10 and 39 years had a decreased all-cause mortality (HR = 0.9) compared with women who never went on sunbathing vacations. Similar results were found for CVD mortality, but no statistically significant effect was observed.

Solarium use once or more per month during 2 or 3 decades of life between 10 and 39 years of age was associated with an increased all-cause mortality (HR = 1.9, 95% CI: 1.3–2.7) for solarium use during 2 or 3 decades compared with women with no solarium use; Table 2; 𝑃_{trend} < 0.01). Similar associations were found for cancer mortality, but no statistically significant effect was observed for CVD mortality.

Table 3 shows relevant host characteristics related to UV sensitivity and vitamin D intake in relation to mortality. Compared with women with dark brown or black hair, women with blonde hair had a higher all-cause and cancer mortality. No effect was found for eye color. A statistically significantly increased risk for CVD mortality (HR = 2.3, 95% CI: 1.2–4.3) was found in women who were more likely to get a deep brown tan after chronic sun exposure compared with women who got light brown or never browned. We observed a statistically significantly reduced risk for CVD mortality in relation to skin color after acute sun exposure, with women turning red with pain or blisters having a lower HR than those turning brown without red (HR = 0.5, 95% CI: 0.3–0.9); for those whose skin turned red the results were of borderline statistical significance (HR = 0.6, 95% CI: 0.4–1.0).

When we mutually controlled for hair and eye color, or skin color after acute and chronic sun exposure in the analyses, the HRs presented in Tables 2 and 3 changed only marginally (data not shown). These variables were not strongly correlated with each other (all <0.30, except for skin color after acute and chronic sun exposure, 0.44). Vitamin D intake (either from diet or supplement) was not associated with all-cause mortality or any cause-specific mortality (Table 3). When we confined the analyses to women with low vitamin D intake, the observed associations between UV exposure and mortality were basically not altered (data not shown).

Discussion

In this large prospective study of middle-aged Swedish women, natural sun exposure during sunbathing vacations was associated with reduced all-cause mortality and CVD mortality, whereas artificial UV exposure (by solar-
After 8.7 years of follow-up. After adjustment for potential confounders (11, 35).

In ecological studies, an inverse correlation was found between regional UV-B radiation and mortality due to cancer mortality. The associations were not essentially altered by adjustment for host characteristics of UV sensitivity or vitamin D intake. Because UV exposure is the major source of vitamin D, studies on the association between circulating vitamin D and disease risk may be informative. A recent published study of a cohort of 13,331 adults aged over 20 years from the Third National Health and Nutrition Examination Survey (NHANES III) examined the association between serum levels of 25(OH)D and mortality (36) after 8.7 years of follow-up. After adjustment for baseline demographics and other lifestyle risk factors, 25(OH)D deficiency increased all-cause mortality (relative risk = 1.3, 95% CI: 1.1–1.5, the lowest vs. highest quartile), but not the mortality from CVD and cancer. However, in yet another study based on the NHANES III, Ginde and colleagues (37) reported that serum levels of 25(OH)D had an independent inverse association with CVD and all-cause mortality. On the basis of a male cohort study, Giovannucci and colleagues reported an inverse association between vitamin D dietary intake and the risk of cancer and myocardial infarction (38, 39). The overall inverse association between sun exposure and all-cause or CVD mortality found in the present study is consistent with those studies (36, 39), as well as with newly published studies from the Nordic countries, where diet and sun exposure are relatively similar to those in our cohort. In Finland, Virtanen and colleagues reported an increased all-cause and CVD mortality among men and women with low concentrations of 25(OH)D (40) and Kilkkinen and colleagues (41) reported low vitamin D levels to be associated with a

### Table 3. Multiadjusted HRs and 95% CIs of different causes of death according to hair color, eye color, and skin color after chronic or acute sun exposure, and dietary and supplementary vitamin D intake, the Swedish WLH cohort study follow-up from 1991 to 1992 through 2006

<table>
<thead>
<tr>
<th>Study sample</th>
<th>All-cause mortality</th>
<th>Total CVD</th>
<th>Total Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>HR (95%CI)</td>
<td>No.</td>
</tr>
<tr>
<td>Hair color</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dark brown/black</td>
<td>10,700</td>
<td>197 Ref.</td>
<td>36</td>
</tr>
<tr>
<td>Light brown</td>
<td>16,549</td>
<td>336</td>
<td>1.1 (0.9–1.3)</td>
</tr>
<tr>
<td>Blond</td>
<td>9,595</td>
<td>194</td>
<td>1.2 (1.0–1.4)</td>
</tr>
<tr>
<td>Red</td>
<td>1,201</td>
<td>21</td>
<td>1.0 (0.6–1.6)</td>
</tr>
<tr>
<td>Eye color</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brown</td>
<td>5,202</td>
<td>96 Ref.</td>
<td>17</td>
</tr>
<tr>
<td>Gray/green</td>
<td>13,457</td>
<td>273</td>
<td>1.1 (0.8–1.3)</td>
</tr>
<tr>
<td>Blue</td>
<td>19,108</td>
<td>377</td>
<td>1.0 (0.8–1.3)</td>
</tr>
<tr>
<td>Skin color after long-lasting or chronic sun exposure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Light or never brown</td>
<td>8,293</td>
<td>162 Ref.</td>
<td>15</td>
</tr>
<tr>
<td>Brown</td>
<td>23,802</td>
<td>441</td>
<td>0.9 (0.8–1.1)</td>
</tr>
<tr>
<td>Deep brown</td>
<td>6,212</td>
<td>146</td>
<td>1.2 (1.0–1.5)</td>
</tr>
<tr>
<td>Skin color after acute sun exposure at the beginning of summer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brown without red</td>
<td>8,898</td>
<td>203 Ref.</td>
<td>38</td>
</tr>
<tr>
<td>Red</td>
<td>18,465</td>
<td>349</td>
<td>0.9 (0.8–1.1)</td>
</tr>
<tr>
<td>Red with pain or blisters</td>
<td>10,974</td>
<td>199</td>
<td>0.9 (0.7–1.1)</td>
</tr>
<tr>
<td>Vitamin D dietary intake</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1 (&lt;2.906 µ/d)</td>
<td>9,293</td>
<td>171 Ref.</td>
<td>24</td>
</tr>
<tr>
<td>Q2 (2.906–3.935 µ/d)</td>
<td>9,792</td>
<td>207</td>
<td>1.2 (1.0–1.5)</td>
</tr>
<tr>
<td>Q3 (3.936–5.109 µ/d)</td>
<td>9,828</td>
<td>189</td>
<td>1.1 (0.9–1.4)</td>
</tr>
<tr>
<td>Q4 (&gt;5.110 µ/d)</td>
<td>9,559</td>
<td>187</td>
<td>1.2 (0.9–1.4)</td>
</tr>
<tr>
<td>Multivitamin user</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>32,751</td>
<td>653 Ref.</td>
<td>92</td>
</tr>
<tr>
<td>Yes</td>
<td>5,721</td>
<td>101</td>
<td>1.0 (0.8–1.3)</td>
</tr>
</tbody>
</table>

*Adjusted for education, smoking, physical activity, alcohol drinking, and BMI.
higher risk of a fatal CVD event, particularly cerebrovascular death. Worryingly, in Sweden, Michaelsson and colleagues reported that both high and low concentrations of plasma 25(OH)D were associated with an elevated risk for all-cause and cancer mortality among men (42). In the North of Norway, Hutchinson and colleagues reported increased all-cause mortality among nonsmokers (but not among smokers) with low 25(OH)D (43). Newly published studies from other parts of the world also reported a decreased risk of all-cause and CVD mortality: in Italy, Semba and colleagues reported a decreased all-cause mortality and CVD mortality in 1 study from the Chianti Region among men and women (44); in Baltimore, Semba and colleagues (45) found that low serum 25(OH)D concentrations were associated with greater all-cause mortality in women. In Germany, Pilz and colleagues (46) reported that low 25(OH)D levels were associated with all-cause and CVD mortality. In Japan, 25(OH)D levels were found to be independent risk factors for all-cause mortality among women (47). However, at least 2 other methodologically well-conducted studies did not find such associations in California (48) and several states in the United States (49).

We did not find any protective effect of sun exposure on cancer mortality, in agreement with data on 25(OH)D from the NHANES III study (50) and the Norwegian study (43), but in contrast with other studies (9, 31, 38, 42, 51, 52).

Solarium use has been reported to increase the risk of melanoma and nonmelanoma skin cancer in fair-skinned populations (1, 27, 53). The present study also observed that solarium use was associated with an increased risk of all-cause and cancer mortality, after controlling for other lifestyle risk factors or host characteristics related to UV sensitivity. Also noteworthy, solarium use once or more per month over a period of 2 or 3 decades was associated with a 1.6-fold increased risk of CVD mortality (95% CI: 0.6–4.2) compared with never users. This finding is difficult to explain biologically. It could be a chance finding or it could be due to residual confounding from some lifestyle factor that we did not control for.

We would have expected that women who are more susceptible to sunburn (i.e., those with light or red hair, those whose skin response to acute sun exposure was turning red with pain or blisters, and those with skin that is light or never brown after long-lasting or chronic sun exposure) would avoid sun exposure due to increased risk of melanoma and therefore have lower circulating 25(OH)D levels, as observed in the United Kingdom (54). However, that did not seem to affect the outcomes of our study, as women with light or red hair or with skin reacting strongly to sun exposure did not have an increased mortality compared with women with other hair and skin characteristics. Women whose skin turned deep brown after long-lasting or chronic sun exposure had an increased risk for CVD, a fact that remains to be explained.

Low estimated vitamin D intake did not modify the associations between UV exposure and mortality in our study. The lack of association between multivitamin intake and mortality in our study is not consistent with the results of a meta-analysis based on 18 randomized clinical trials of vitamin D supplementation, in which a 7% decreased risk of all-cause mortality appeared among people using vitamin D supplementation (6). However, in a recently published study on an 8-year follow-up of the Women’s Health Initiative cohort, multivitamin use was shown to have little or no influence on the risk of death from common cancers, CVD, or all causes (55). Nevertheless, the presence of any association between oral vitamin D intake and disease risk is complex, given that the amount of vitamin D obtained through use of supplements may differ substantially between studies. Moreover, the relative contribution to serum vitamin D from diet or supplement and UV exposure varies by latitude and seasonal variations; UV exposure being the most important source in most countries. We only had information on multivitamin supplement use, without specification of the dose of vitamin D. The dose of vitamin D in multivitamins in Sweden in the early 1990s, when the study women answered the questionnaire, was probably too low (200 IU/d, 5 μg/d) to produce any significant effect on mortality, for which doses of 1,000 IU/d (25 μg/d) would be needed (18, 56, 57).

Several mechanisms might be responsible for the association between UV exposure, through the vitamin metabolic pathway, and the risk of disease and death. Vitamin D deficiency is associated with hypertension, diabetes mellitus, insulin resistance, and an elevated BMI (58), all of which are risk factors for CVD and all-cause mortality. A protective effect of vitamin D on CVD mortality may arise due to inhibition of vascular smooth muscle proliferation, suppression of vascular calcification, down-regulation of proinflammatory cytokines, upregulation of anti-inflammatory cytokines, and action of vitamin D as a negative endocrine regulator of the renin-angiotensin system (59).

Strengths of our study include its large size, prospective design, and virtually complete follow-up through linkages to national registries. The information on UV exposure at different periods in life and relevant data on host characteristics and lifestyle factors is also an important strength. A strong association between our questionnaire-based UV exposure measures and risk of malignant melanoma shown in previous analyses from this study (27, 60) suggested that those questions assessing sun and solarium exposure are appropriate. The lack of information about the changes in the exposure and other risk factors after the baseline survey is a major limitation. Moreover, although adjusted for the major traditional risk factors for mortality, some relevant risk factors have not been taken into account in the disease-specific analyses such as blood pressure. Nevertheless, the NHANES III study (36) indicated that adjustment for hypertension and diabetes mellitus did not change the
results of the mortality risk estimates associated with vitamin D levels.

In conclusion, in this large prospective study of Swedish women, natural sun exposure during sunbathing vacations was associated with a reduced overall mortality and CVD mortality, whereas artificial UV exposure (by solarium use) was associated with an increased overall mortality and cancer mortality.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References


Grant Support

The survey was supported by the Swedish Cancer Society and the Swedish Research Council.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received September 24, 2010; revised January 12, 2011; accepted January 19, 2011; published OnlineFirst February 4, 2011.


Correction: Ultraviolet Exposure and Mortality among Women in Sweden

In this article (Cancer Epidemiol Biomarkers Prev 2011;20:683–90), which was published in the April 2011 issue of Cancer Epidemiology, Biomarkers & Prevention (1), the authors request the following corrections: (i) Dr. Hans-Olov Adami is affiliated with the Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden and the Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts. Dr. Adami is not affiliated with the Clinical Trial Service Unit and Epidemiological Studies Unit, University of Oxford, Oxford, United Kingdom. (ii) In Table 2, under "Annual number of weeks spent on sunbathing vacations," the authors want to replace "≥ 1 week, 20–29, and 30–39" with "≥ 1 week, 20–29, and/or 30–39."

Reference


Published OnlineFirst May 17, 2011. ©2011 American Association for Cancer Research. doi: 10.1158/1055-9965.EPI-11-0404
Ultraviolet Exposure and Mortality among Women in Sweden

Ling Yang, Marie Lof, Marit Bragelien Veierød, et al.

Cancer Epidemiol Biomarkers Prev 2011;20:683-690. Published OnlineFirst February 4, 2011.

Updated version
Access the most recent version of this article at:
doi:10.1158/1055-9965.EPI-10-0982

Supplementary Material
Access the most recent supplemental material at:
http://cebp.aacrjournals.org/content/suppl/2011/03/24/1055-9965.EPI-10-0982.DC1

Cited articles
This article cites 55 articles, 19 of which you can access for free at:
http://cebp.aacrjournals.org/content/20/4/683.full#ref-list-1

Citing articles
This article has been cited by 12 HighWire-hosted articles. Access the articles at:
http://cebp.aacrjournals.org/content/20/4/683.full#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.