Solar UVR and Variations in Systemic Immune and Inflammation Markers

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The characterization of the effects of solar UVR on a broad set of circulating markers in systemic immunity and inflammation may provide insight into the mechanisms responsible for the UVR associations observed for several benign and malignant diseases. We examined the associations between exposure to solar UVR and circulating levels of 78 markers among 1,819 individuals aged 55–74 years who participated in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial using multiplex assays. Solar UVR was derived by linking the geocoded locations of 10 screening centers across the continental United States and the date of blood draw to the National Solar Radiation Database from 1993 to 2005. We assessed associations between ambient solar UVR and dichotomized marker levels using adjusted weighted logistic regression models and applied a 5% false discovery rate criterion to P-values. UVR exposure was associated (P < 0.05) with 9 of the 78 markers. CCL27, CCL4, FGF2, GM-CSF, IFN-γ, soluble IL4R, IL-7, and IL-11 levels were lower with increasing UVR tertile, with adjusted ORs ranging from 0.66 to 0.80, and the significant association for CCL27 withstood multiple comparison correction. In contrast, CRP levels were elevated with increasing UVR. Solar UVR was associated with alterations in systemic immune and inflammation marker levels.

INTRODUCTION

In addition to causing direct DNA damage (Sinha and Håder, 2002), exposure to solar UVR can modulate the immune system both locally in the skin and systemically at sites distant from the location of exposure (Bernard et al., 2019). UVR is well established as the primary environmental cause of common skin cancers (Green and Whiteman, 2017) and increasingly recognized to play a role in rare cutaneous malignancies with confirmed or suspected viral etiology, such as Merkel cell carcinoma (Clarke et al., 2015), Kaposi sarcoma (Cahoon et al., 2017), and sebaceous carcinoma (Sargen et al., 2021, 2020), which occur disproportionately in individuals with severe immunosuppression. However, exposure to UVR has also been associated with lower risks of non-Hodgkin lymphoma (Park et al., 2019), Hodgkin lymphoma (Monnereau et al., 2013), and several systemic autoimmune conditions (Norval and Halliday, 2011; Tremlett et al., 2018). In addition, phototherapy has been used to treat a number of inflammatory and autoimmune skin conditions, including psoriasis (Racz and Prens, 2015), atopic dermatitis (AD) (Thyssen et al., 2015), vitiligo (Bae et al., 2017), and cutaneous T-cell lymphoma (Marka and Carter, 2020). The mechanisms involved in these associations, assuming that they are causal, represent an active area of ongoing research (Hart et al., 2019; Matsushima et al., 2019).

Short-term exposure to UVR results in erythema or reddening of the skin, alteration of vascular responses, production of inflammatory mediators, increased tissue sensitivity, and infiltration of inflammatory cells (Hruza and Pentland, 1993). Exposure to UVR also induces the production of vitamin D, a hormone that has been found to modulate innate and adaptive immune responses (Bernard et al., 2019). Experimental studies have examined the association between discrete wavelengths of artificial UVR and immune function in murine models (de Gruijl et al., 1993; Hart and Norval, 2018; Kripe and Fisher, 1976), and other studies in humans have examined the impact of phototherapy on immune marker levels in keratinocytes (Vieyra-Garcia et al., 2016) and serum of patients treated for psoriasis and AD (Narbutt et al., 2013; Walters et al., 2003). In an experimental study in 105 healthy volunteers repeatedly exposed to UVB lamps or solar-simulated radiation, Narbutt et al. (2005) found that levels of IL-8 and TNF-α were increased after 10 days of exposure. A recent observational study nested in a vitamin D trial of 82 infants has investigated the role of solar UVR on levels of 25 markers in cell culture supernatants, finding that higher ambient UVR exposure was significantly associated with lower levels of IL-2, GM-CSF, and eotaxin (Ruetter et al., 2019). There is very limited epidemiological evidence to suggest a role for UVR in the etiology of the broader set of systemic inflammation and immunity markers studied here.
data on the associations between solar UVR and circulating markers for systemic immune function and inflammation in a population-based setting.

The characterization of the effects of solar UVR on a broad set of circulating markers in systemic immunity and inflammation may provide insight into the mechanisms responsible for the UVR associations observed for several benign and malignant diseases. We examined the associations between exposure to solar UVR and circulating levels of 78 markers, using data from 1,819 individuals who participated in the population-based Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. To our knowledge, this is the largest study of solar UVR and levels of a broad set of circulating markers of immune, metabolic, and inflammatory function and a population-based study in adults.

RESULTS

Compared with the eligible PLCO screening arm, participants included in this study (N = 1,819) were older, had lower body mass index, and were more likely to be current smokers (Table 1). When weights were applied, the distributions of these factors became similar to the whole eligible PLCO screening arm population, suggesting that these weights help account for the nonrepresentative sampling, and our results could be generalized to the entire non-Hispanic white PLCO screening arm.

Solar UVR exposure was associated ($P < 0.05$) with 9 of the 78 markers based on testing trend in association across ordinal UVR tertiles (Table 2; see Supplementary Table S1 for all markers; Supplementary Table S2 using the bootstrap method with 1,000 replicates): CCL27 (also called CTACK), CCL4 (also called MIP-1β), FGF2, GM-CSF, IFN-γ, IL-7, IL-11, soluble IL4R (sIL4R), and CRP. For most of these markers (8/9), levels were lower with increasing UVR tertile with ORs (95% confidence interval [CI]) ranging from 0.66 (95% CI = 0.50–0.88) to 0.80 (95% CI = 0.67–0.95). In contrast, CRP levels were elevated with increasing UVR tertile (OR = 1.46, 95% CI = 1.12–1.90, $P$ for trend = 0.019). After applying the FDR correction, only CCL27/CTACK remained significant. The nine nominally significant markers were very weakly to moderately correlated with each other.

Table 1. Participant Characteristic in Subjects with Measured Marker Data, after Weights Were Applied, and in Eligible Participants in the PLCO Screening Arm

| Characteristic                  | Sample Population | %     | Sample Population, Weighted to PLCO Screening Arm | %     | PLCO Screening Arm | %     |
|--------------------------------|-------------------|-------|---------------------------------------------------|-------|--------------------|-------|
| Total number                   | 1,819             | —     | 58,264                                           | —     | 58,264             | —     |
| Case-control status            |                   |       |                                                   |       |                    |       |
| Case                           | 877               | 48.2  | 699                                               | 1.2   | —                  | —     |
| Control                        | 942               | 51.8  | 57,565                                           | 98.8  | —                  | —     |
| Sex                            |                   |       |                                                   |       |                    |       |
| Women                          | 814               | 44.8  | 28,331                                           | 48.6  | 28,331             | 48.6  |
| Men                            | 1,005             | 55.3  | 29,933                                           | 51.4  | 29,933             | 51.4  |
| Age, y                         |                   |       |                                                   |       |                    |       |
| ≤59                            | 401               | 22.1  | 19,081                                           | 32.8  | 20,056             | 34.4  |
| 60–64                          | 527               | 29.0  | 19,472                                           | 33.4  | 17,954             | 30.8  |
| 65–69                          | 534               | 29.4  | 11,490                                           | 19.7  | 12,877             | 22.1  |
| ≥70                            | 357               | 19.6  | 8,221                                            | 14.1  | 7,377              | 12.7  |
| BMI category, kg/m²            |                   |       |                                                   |       |                    |       |
| <25                            | 639               | 34.1  | 18,009                                           | 30.9  | 18,914             | 32.4  |
| 25–30                          | 792               | 43.5  | 26,941                                           | 46.2  | 24,753             | 42.5  |
| ≥30                            | 367               | 20.2  | 12,474                                           | 21.4  | 14,015             | 24.1  |
| Missing                        | 21                | 1.2   | 845                                              | 1.5   | 582                | 1.0   |
| Smoking status                 |                   |       |                                                   |       |                    |       |
| Never                          | 548               | 30.1  | 27,221                                           | 46.7  | 27,389             | 47.0  |
| Ex                             | 857               | 47.1  | 25,380                                           | 43.6  | 25,032             | 43.0  |
| Current                        | 414               | 22.8  | 5,663                                            | 9.7   | 5,843              | 10.0  |

Abbreviation: BMI, body mass index; PLCO, Prostate, Lung, Colorectal and Ovarian.

Weighted estimates were calculated using the combined lung cancer, non-Hodgkin’s lymphoma, and ovary cancer weight. Previous studies did not report the exact number.
except FGF2 and GM-CSF (weighted Pearson correlation coefficient [rho] = 0.44) and FGF2 and IFN-γ (0.58). Weighted rho ranged from −0.09 for CCL27/CTACK and IL-7 to 0.58 for FGF2 and IFN-γ (Table 3).

In analyses of continuous UVR by different periods of exposure, significant associations were found in 9 of 78 markers. UVR was significantly and consistently associated with lower levels of CCL27/CTACK and IFN-γ (Table 4). No association was found for other markers across different periods of UVR exposure. Although UVR was also significantly associated with higher levels of CRP, the association became nonsignificant for durations longer than 1–3 days before blood draw.

### DISCUSSION

To evaluate the immune, inflammatory, and metabolic effects of ambient UVR and to provide potential mechanistic insights into observed associations between UVR and a range of health outcomes, we conducted an epidemiological study of ambient UVR and a broad set of circulating markers among 1,819 men and women aged 55–74 years residing across the continental United States. We found nine markers to be nominally associated with ambient solar UVR, including CCL27/CTACK, CCL4/MIP-1β, FGF2, GM-CSF, IFN-γ, IL-7, IL-11, sIL4R (inverse associations), and CRP (positive association). CCL27/CTACK withstood multiple comparison correction. These markers have been found to mediate immune and inflammatory responses through cell signaling, cell growth, differentiation, and tissue repair. Our study provides population-based evidence that UVR may have a number of effects on systemic immunity and inflammation.

We found that increasing UVR was associated with a reduction in levels of several markers considered to be proinflammatory, including IFN-γ, IL-7, IL-11, sIL4R, CCL4/ MIP-1β, and CCL27/CTACK. Although the roles of many of these markers have not been fully characterized, many were elevated in patients with various diseases, such as AD and psoriasis (IFN-γ, IL-11, CCL4/MIP-1β, CCL27/CTACK) (Farrera et al., 2020; Johnson-Huang et al., 2012; Kakinuma et al., 2003; Lv et al., 2014; Toda et al., 2003), cutaneous T-cell lymphoma (IL-7, CCL27/CTACK) (Fujita et al., 2006; Yamanaka et al., 2006), inflammatory bowel disease (IFN-γ, IL-7) (Barbaro et al., 2016; Kader et al., 2005), and multiple sclerosis (IL-11, CCL27/CTACK) (Khaiboullina et al., 2015; Zhang et al., 2015) such that lower levels are consistent with a therapeutic or protective effect from exposure to UVR (DeStefano et al., 2019; Staples et al., 2010). Our results are also consistent with a recent epidemiological study nested in a vitamin D trial of 82 infants that higher UVR exposure during infancy was correlated with lower levels of GM-CSF in cell culture supernatants (Rueter et al., 2019). The effects of phototherapy on immune and inflammatory markers have been reported in a number of experimental studies among patients diagnosed with a range of inflammatory skin

### Table 2. OR and 95% CI of High Versus Low Marker Level Per Same-Day Ambient UVR Tertile for 9 of 78 Markers Examined

| Markers       | OR (95% CI) | P-Trend |
|---------------|-------------|---------|
| CCL4/MIP-1β   | 0.71 (0.59–0.86) | 0.002   |
| CCL27/CTACK   | 0.76 (0.62–0.93) | <0.001  |
| FGF2          | 0.73 (0.58–0.92) | 0.003   |
| GM-CSF        | 0.78 (0.63–0.97) | 0.022   |
| IFN-γ         | 0.75 (0.61–0.92) | 0.004   |
| IL-7          | 0.66 (0.50–0.88) | 0.026   |
| IL-11         | 0.67 (0.51–0.87) | 0.005   |
| sIL4R         | 0.80 (0.67–0.95) | 0.020   |
| CRP           | 1.46 (1.12–1.90) | 0.019   |

Abbreviation: CI, confidence interval; sIL4R, soluble IL4R.

### Table 3. Weighted Pearson Correlation Matrix among the Top Nine Markers in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Study

| Markers       | CCL4/MIP-1β | CCL27/CTACK | FGF2 | GM-CSF | IFN-γ | IL-7 | IL-11 | sIL4R | CRP |
|---------------|-------------|-------------|------|--------|------|------|------|-------|-----|
| CCL4/MIP-1β   | 1           | —           | —    | —      | —    | —    | —    | —     | —   |
| CCL27/CTACK   | −0.02       | 1           | 0.00 | —      | —    | —    | —    | —     | —   |
| FGF2          | 0.29        | 0.00        | 1    | —      | —    | —    | —    | —     | —   |
| GM-CSF        | 0.17        | −0.05       | 0.44 | 1      | —    | —    | —    | —     | —   |
| IFN-γ         | 0.16        | 0.01        | 0.58 | 0.33   | 1    | —    | —    | —     | —   |
| IL-7          | 0.14        | −0.09       | 0.13 | 0.16   | 0.10 | 1    | —    | —     | —   |
| IL-11         | 0.17        | −0.01       | 0.11 | 0.09   | 0.13 | 0.05 | 1    | —     | —   |
| sIL4R         | 0.21        | 0.21        | 0.17 | 0.14   | 0.32 | 0.23 | 0.03 | 1     | —   |
| CRP           | 0.00        | 0.03        | 0.06 | 0.02   | 0.06 | −0.03| −0.04| 0.03  | 1   |

Abbreviation: sIL4R, soluble IL4R.
conditions and in murine models. Phototherapy is a long-standing treatment for patients with AD and psoriasis, although the mechanisms are not fully understood. Decreased levels of IFN-γ in keratinocytes were reported in patients with psoriasis (Walters et al., 2003) or AD (Tintle et al., 2011) treated with phototherapy. Evidence from murine models suggest that overexpression of IL-7 may play a pathogenic role for inflammatory skin diseases (Heufler et al., 1993; Mackall et al., 2011; Matsue et al., 1993; Williams et al., 1997), also supporting a therapeutic role of UVR. In groups treated for severe AD with UVA1, serum levels of soluble IL-2R and sIL4R decreased significantly after phototherapy, with more pronounced response for sIL4R (von Kobyletzki et al., 1999). Our findings of reduced levels of CCL27/CTACK, a chemokine produced almost exclusively by keratinocytes and involved in effector memory T-cell trafficking to the skin (Meller et al., 2005), with increasing UVR correlated with lower levels of GM-CSF in cell culture supernatants (Rueter et al., 2019). GM-CSF is an important hematopoietic GF and immune modulator (Bhattacharya et al., 2015), and overexpression of GM-CSF has been shown to lead to severe inflammation (Wicks and Roberts, 2016). It is thought that the efficacy of UVB treatment for psoriasis is due in part to the suppression of the cutaneous TH1/TH helper 23 pathway, which is the same pathway that many of the biologics that treat psoriasis also target (Langer-Gould et al., 2018). We did not find any association between IL-17 levels in the blood and ambient UVR. However, these previous studies assessed IL-17 signaling in the skin, and levels of inflammatory markers in the skin could potentially differ from levels in the blood. Our study panel did not

Table 4. ORs (95% CI) of High Versus Low Circulating Marker Level and Ambient UVR for 1–60 Days for Nine Statistically Significant Markers

| Markers         | Estimate | OR   | OR   | OR   | OR   | OR   | OR   | OR   | OR   |
|-----------------|----------|------|------|------|------|------|------|------|------|
|                 |          | 1–2  | 3–7  | 1–14 | 1–30 | 1–60 |
| CCL4/MIP-1β     |          | 0.91 | 0.93 | 0.94 | 0.97 | 0.96 |
| 95% CI          | 0.86–0.97| 0.87–0.99 | 0.88–1.01 | 0.90–1.05 | 0.88–1.05 | 0.89–1.07 |
| CCL27/CTACK     | 0.89    | 0.89 | 0.88 | 0.87 | 0.84 | 0.82 |
| 95% CI          | 0.83–0.95| 0.83–0.96 | 0.81–0.95 | 0.80–0.95 | 0.76–0.92 | 0.74–0.92 |
| FGF2            | 0.90    | 0.87 | 0.88 | 0.91 | 0.90 | 0.91 |
| 95% CI          | 0.84–0.96| 0.80–0.95 | 0.81–0.96 | 0.82–1.01 | 0.81–1.00 | 0.81–1.02 |
| GM-CSF          | 0.93    | 0.93 | 0.95 | 0.99 | 0.96 | 0.97 |
| 95% CI          | 0.84–0.96| 0.86–1.00 | 0.88–1.03 | 0.90–1.08 | 0.87–1.06 | 0.86–1.07 |
| IFN-γ           | 0.91    | 0.88 | 0.87 | 0.88 | 0.87 | 0.90 |
| 95% CI          | 0.83–0.99| 0.82–0.94 | 0.81–0.94 | 0.81–0.95 | 0.80–0.95 | 0.80–0.96 |
| IL-7            | 0.90    | 0.92 | 0.93 | 0.93 | 0.92 | 0.94 |
| 95% CI          | 0.83–0.99| 0.84–1.02 | 0.84–1.02 | 0.84–1.04 | 0.82–1.03 | 0.83–1.06 |
| IL-11           | 0.88    | 0.87 | 0.87 | 0.88 | 0.87 | 0.91 |
| 95% CI          | 0.81–0.96| 0.79–0.96 | 0.79–0.97 | 0.78–0.98 | 0.77–0.98 | 0.78–1.01 |
| sIL4R           | 0.94    | 0.94 | 0.95 | 0.91 | 0.91 | 0.93 |
| 95% CI          | 0.89–0.99| 0.88–1.00 | 0.82–1.09 | 0.84–0.99 | 0.83–0.98 | 0.85–1.02 |
| CRP             | 1.10    | 1.11 | 1.20 | 1.02 | 1.03 | 1.02 |
| 95% CI          | 1.02–1.19| 1.02–1.21 | 0.98–1.48 | 0.92–1.12 | 0.93–1.15 | 0.91–1.13 |

Abbreviation: CI, confidence interval; sIL4R, soluble IL4R.

1Adjusted for 5-year age group, sex, involvement of case-control studies (lung cancer study, non-Hodgkin lymphoma study, and ovarian cancer study), smoking status (former and current vs never smokers), body mass index (<18.5, 18.5–25, 25–30, ≥30 vs ≥18.5–25 kg/m2), coffee consumption (<2.5 and ≥2.5 cups per day vs nondrinkers), and time of blood draw (afternoon vs morning).

2An example of per 100 watt-h/m2 could be the difference between UVR in Washington DC on a typical day in July (monthly median of 709 watt-h/m2) and September (614 watt-h/m2).
include some of the downstream signaling proteins of the IL-17/IL-23 pathway (e.g., signal transducer and activator of transcription 3), and therefore, UVR potentially could be affecting the downstream mediators of this signaling pathway but not IL-17.

CRP is a nonspecific marker of systemic inflammation produced in the liver with a plasma half-life of 19 hours (Pepys and Hirschfield, 2003), in comparison with various half-lives ranging from 0.5–24 hours for the other eight significant markers (Beenken and Mohammadi, 2009; Chuang et al., 2020; Foon et al., 1985; Jacobs et al., 1991; Kanda et al., 2005; Martin et al., 2013; Rapisarda et al., 2002). A study of acute exposure of erythemal UVB in healthy human subjects also reported an increase in serum CRP levels (Laihia et al., 2005). Our findings of decreased risk with >3-day averaged ambient UVR is consistent with metabolic studies of CRP synthesis rate (Pepys and Hirschfield, 2003). In contrast, two studies in patients with psoriasis found that narrow band UVB phototherapy was either associated with lower levels of CRP (Mehta et al., 2018; Romani et al., 2012) or not associated (Weinhold et al., 2016), possibly because levels of CRP were higher in patients with psoriasis compared with individuals without psoriasis (Romani et al., 2012) or had longer exposure times (52 weeks) than our study (Mehta et al., 2018). Indeed, we observed that CRP levels waned for a 7-day averaged UVR and appeared to be null for UVR averaged over 60 days (OR = 1.00, 95% CI = 0.90–1.12) in our population-based samples.

**Strengths and limitations**

The main strengths of our study include a large population-based setting with a comprehensive list of circulating markers of systemic immune and inflammatory function using a well-characterized technology and a refined two-stage design to reweight analyses to the population-based PLCO screening arm. The study population resided in a wide range of latitudes and had their blood drawn throughout the year so that they were exposed to a wide range of ambient solar UVR. Furthermore, we were able to control an extensive number of potential confounders using prospectively collected demographic and lifestyle data. Although evidence from experimental studies among patients with inflammatory conditions has suggested anti-inflammatory/immunosuppressive effects after exposure to artificial UV light, these studies have often been limited to a small number of participants with perturbed immune profiles because of underlying autoimmune dysfunction, such as mycosis fungoides (Goteri et al., 2012), Sézary syndrome (Masui et al., 2007), vitiligo (Tembré et al., 2013), or psoriasis (Jones et al., 1996; Sigmundsdottir et al., 2005). The association between solar UVR exposure and circulating markers had not been assessed in a population-based epidemiological setting in adults.

The primary limitation of our study is a lack of data on personal UVR exposure. However, solar UVR on the basis of ambient modeled measures has been significantly positively associated with UVR exposure as measured by personal dosimeter (Cahoon et al., 2013). Misclassification of exposure may also have resulted because solar UVR was linked to location of screening center only at the date of blood draw. In addition, outcomes were only collected at one point in time per individual, so we were unable to assess alterations in marker concentrations prospectively with changes in exposure to solar UVR. For example, we found no associations of UVR and IL-8 and TNF-α, in contrast to an experimental study in 105 healthy volunteers repeatedly exposed to UVB lamps or solar-simulated radiation (Narbutt et al., 2005). Narbutt et al. (2005) measured marker levels at least on two occasions (before and after exposure to UVB) and found that levels of IL-8 and TNF-α were increased after 10 days of exposure. All markers of systemic immunity and inflammation were not measured, nor could we evaluate UVR associations with marker variations occurring in the skin. The low abundance (censoring) of the Luminex system may be a concern (Breen et al., 2015) because a few markers had a sizable fraction of values below the lowest limit of detection (LLOD). However, the censoring would not affect our key findings substantially because of very low proportions of CCL27, CCL4, sIL4R, and CRP levels below LLOD. Existing methods for handling the problem that measurements of biomarkers often fall below the assay’s LLOD can perform poorly, including multiple imputation (Arunajadai and Rauh, 2012), parametric regression (Dinse et al., 2014), and deletion (Nie et al., 2010). Better for LLOD censoring is the method we employed (categorizing the variable with a level to include missingness). Circadian rhythm has been found to play a role in the acute effect of UVR exposure (Bustamante et al., 2019). We did not find that time of blood draw (afternoon vs. morning) was a confounder or effect modifier of the associations between ambient UVR exposure and circulating marker levels. Our study was limited to non-Hispanic white PLCO participants. Understanding the race-specific effect of UVR on circulating immune markers could shed light on the underlying role of UVR for cancer outcomes and autoimmune conditions with UVR effects that vary by race/ethnicity. The correlations we noted between the markers imply that some associated tests (of correlations with UVR) were not independent (FGF2 and GM-CSF, and FGF2 and IFN-γ) such that the upper bound on the expected false discovery rate that we estimated via the Benjamini-Hochberg procedure (Benjamini and Hochberg, 1995) may not be valid.

This population-based study shows that solar UVR exposure was associated with lower circulating concentrations of several proinflammatory markers (CCL27/CTACK, CCL4/MIP-1β, FGF-2, GM-CSF, IFN-γ, IL-7, IL-11, sIL4R) and increased levels of CRP for a range of days to weeks of average ambient UVR exposure among older, non-Hispanic white adults. These findings may inform possible etiologic mechanisms involved in UVR-induced immunosuppression and malignancy and UVR-modulated autoimmune disease. However, they require replication in other studies that include personal UVR dosimetry and in populations with wider distributions of age and non-white race/ethnicity. Our findings support the broad effect of solar UVR exposure on immunosuppression and anti-inflammation and identify several potential circulating markers for future studies of UVR-related cancers and autoimmune disease.
MATERIALS AND METHODS

Study population
The PLCO Cancer Screening Trial recruited about 155,000 participants, aged 55–74 years, from the general United States population between 1993 and 2005 (Prorok et al., 2000). Serum blood samples were obtained from participants in the screening arm at baseline or at a follow-up visit (processed and frozen within 2 hours of collection and stored at −70 °C). This analysis included participants from the screening arm of PLCO who were selected as either cases or controls from three nested case-control studies of lung cancer (Shiels et al., 2013), non-Hodgkin lymphoma (Purdue et al., 2013), or ovarian cancer (Trabert et al., 2014). The dataset excluded 152 participants who did not report being non-Hispanic white, 31 participants with a personal history of cancer before randomization (at the same time of blood draw), 6 participants with duplicate records in two of the three case-control studies, and 11 participants with incomplete data on smoking or solar UVR for a total of 1,819 non-Hispanic white individuals (because of small numbers in other races/ethnicities). Demographic and lifestyle factors, such as smoking history, age, and weight, were ascertained on the baseline questionnaire. Detailed descriptions of the exclusion criteria, matching factors, and inflammatory markers measured in these case-control studies have been reported elsewhere (Shiels et al., 2014) and are presented in Supplementary Table S3.

The PLCO Cancer Screening Trial was approved by the Institutional Review Boards at each participating center and at the National Cancer Institute (Bethesda, MD), and all participants gave written informed consent.

Circulating markers
Circulating levels of 86 immune and inflammation markers were measured, including cytokines, chemokines, GFs, and soluble products of immune activation (Supplementary Table S4). These markers were selected on the basis of a methodologic study that evaluated the performance and reproducibility of multiplexed assays for measurement of inflammatory markers (Chaturvedi et al., 2011) and were measured using Luminex bead-based assays (EMD Millipore, Billerica, MA). Marker concentrations were calculated using either a four- or five-parameter standard curve. Serum samples were assayed in duplicate and averaged to calculate concentrations. Blinded duplicates in the lung cancer and non-Hodgkin lymphoma studies and duplicate measurements on study subjects in the ovarian cancer study were used to evaluate assay reproducibility through coefficients of variation and intra-assay correlation coefficients calculated on log-transformed values of the markers. Log-transformed intra-assay correlation coefficients were >0.8 in 91% (Purdue et al., 2013), 91% (Shiels et al., 2013), and 78% (Trabert et al., 2014) of evaluable markers in the lung cancer, non-Hodgkin lymphoma, and ovarian cancer studies, respectively. We analyzed 78 markers after excluding 8 markers with >90% of values below the LLOD. Because a few markers had a sizeable fraction of values below the LLOD, we precluded analysis of these markers as continuous outcomes. Separately by study, marker levels were dichotomized as above or below the median value or as detectable and undetectable if > 50% of the values were below the LLOD.

Solar UVR
Daily noon solar UVR was derived by linking the geocoded locations of 10 screening centers across the continental United States (Washington DC, Colorado, Michigan, Minneapolis, Missouri, Pennsylvania, Utah, Wisconsin, Alabama, and Idaho) and the date of blood draw (same day and averaging 1–2, 1–3, 1–7, 1–14, 1–30, or 1–60 days before, respectively) to the National Solar Radiation Data Base (Wilcox, 2012) between 1993 and 2005. This ambient UVR data is weighted toward the UVB spectrum (280–315 nm) and modeled to represent the biological action spectrum associated with erythema.

Statistical analysis
We examined the associations between solar UVR tertile (T1–3: 68–325, 326–648, 649–1030 watt-h/m²) as an ordinal variable and each of the 78 dichotomous markers by calculating ORs and 95% CIs using weighted logistic regression models. Models categorizing UVR into quartiles or quintiles produced similar results. P-values for solar UVR were based on trend tests using continuous solar UVR. The following variables were considered potential confounders: age (5-year group), sex, involvement of case-control studies (lung cancer study, non-Hodgkin lymphoma study, and ovarian cancer study), smoking status (never, former, and current), coffee consumption (nondrinkers, <2.5, ≥2.5 cups per day), body mass index (<18.4, 18.5–24.9, 25.0–29.9, ≥30 kg/m²), physical activity level (<1, 1–2, ≥3 hours per week), tertile of daily maximum temperature (as an ordinal variable), alcohol drinking (0, <1, 1–3, or ≥4 drinks per day), education (less than a high school education, high school graduate or equivalent, some post-high school education, college graduate), nonsteroidal anti-inflammatory drug use, multivitamin use, and time (morning, afternoon) and season (December–February, March–May, June–August, September–November) of blood draw. Age, sex, involvement of case-control studies, smoking status, coffee consumption, and body mass index were included in all models a priori. Additional variables were evaluated on the basis of the Akaike information criterion (Lindsey and Jones, 1998). Final models were adjusted for 5-year age group, sex, involvement of case-control studies, smoking status, coffee consumption, body mass index, and time of blood draw (morning, afternoon). Nine markers with P-trend < 0.05 were retained for subsequent analyses. We used Pearson correlation coefficients to assess the weighted correlations between these nine markers. UVR-response effects after exposure to continuous solar UVR (per 100 watt-hour/m²) for 78 markers were assessed at different time periods (same day of blood draw and averaging 1–2, 1–3, 1–7, 1–14, 1–30, or 1–60 days before, respectively). Missing values for covariates were coded as separate categories and included as indicator variables in the models.

Propensity-score adjusting sampling weights were used to ensure that our analysis accounted for the inclusion/exclusion criteria and sampling plan for each study. The sampling weights, which have been described in detail elsewhere (Austin, 2011; Kitahara et al., 2014; Shiels et al., 2014), allowed us to include all participants with marker data and made our analysis as representative as possible of the non-Hispanic white PLCO screening arm population. Briefly, study-, sex-, and case-control status–specific logistic regression models adjusted for age, detailed smoking history, and vital status as of 31 December 2009 were used to estimate the probability that an eligible screening arm participant would be selected into any given case-control study. Combinations of study-specific weights were generated for markers that were measured in multiple case-control studies (e.g., all three studies, lung and non-Hodgkin lymphoma, lung and ovary, or non-Hodgkin lymphoma and ovary). Simulations showed that analyses using both weighting methods and additional regression adjustment for matching factors provide a good way to
adjust for nonrepresentative sampling in nested case-control studies (Steer and Samuelsen, 2013).

We conducted two additional analyses (data for both not shown because they did not substantially affect our results). We assessed multiplicative interactions of the associations for these nine markers by age (<65/65+ years), sex, smoking (ever/never), and study (lung cancer study/non-Hodgkin lymphoma study/ovarian cancer study) on the basis of the likelihood ratio test that compared nested models with and without interaction terms. We also investigated whether clinical cutoff points in some markers (Kakinuma et al., 2003; Takahashi et al., 2010) impacted our findings. We conducted a sensitivity analysis to examine whether our findings would be altered when bootstrapping with 1,000 replications. All statistical tests were two-sided with a specific type-I error of 0.05, and analyses were performed in SAS 9.4 (SAS Institute, Cary, NC). We applied a 5% false discovery rate criterion (Benjamini and Hochberg, 1995) to account for multiple comparisons.

Data availability statement
The datasets presented in this article are not readily available because the data that support the findings of this study are available from National Institutes of Health PLCO study group. Restrictions apply to the availability of these data, which were used under license for this study. Requests to access the datasets should be directed to https://cdas.cancer.gov/plco/.

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CONFLICT OF INTEREST
The authors state no conflict of interest.

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AUTHOR CONTRIBUTIONS
Conceptualization: ZMM; EKC; Data Curation: ZMM; EKC; Formal Analysis: ZMM; Funding Acquisition: ZMM; Investigation: ZMM; Methodology: ZMM; SNB; MPL; Supervision: EKC; Writing-Original Draft Preparation: ZMM; Writing - Review and Editing: ZMM; SNB; MPL; MRS, EKC

SUPPLEMENTARY MATERIAL
Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.xjidi.2021.100055.

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**Supplementary Table S1. OR and 95% CI of High Versus Low Marker Level and Same-Day Ambient UVR Tertiles**

| Markers    | OR¹ Per UVR Tertile | 95% CI       | P-Trend² Category³ |
|------------|---------------------|--------------|--------------------|
| Amylin     | 0.81                | 0.63–1.05    | 0.23 b             |
| BCA-1      | 0.96                | 0.78–1.20    | 0.84 a             |
| CCL13/MCP-4| 0.96                | 0.77–1.19    | 0.52 a             |
| CCL15/MIP-1d| 0.82                | 0.67–1.02   | 0.17 a             |
| CCL17/TARC| 1.18                | 0.95–1.46    | 0.13 a             |
| CCL19/MIP-3б| 0.92                | 0.75–1.14    | 0.58 a             |
| CCL2/MCP-1| 1.15                | 0.96–1.38    | 0.19 a             |
| CCL20/MIP-3α| 0.89                | 0.72–1.10    | 0.37 b             |
| CCL21/CKINE| 0.87                | 0.70–1.08    | 0.13 a             |
| CCL22/MDC| 0.92                | 0.75–1.12    | 0.34 a             |
| CCL27/CTACK| 0.76                | 0.62–0.93    | 0.001 a            |
| CCL3/MIP-1α| 0.85                | 0.63–1.15    | 0.35 d             |
| CCL4/MIP-1b| 0.71                | 0.59–0.86    | 0.002 a            |
| CCL7/MCP-3| 1.02                | 0.76–1.36    | 0.58 d             |
| CCL8/MCP-2| 0.86                | 0.69–1.06    | 0.30 a             |
| C-peptide  | 0.87                | 0.68–1.10    | 0.46 a             |
| CRP        | 1.46                | 1.12–1.90    | 0.019 a            |
| CXCL1/GRO  | 0.97                | 0.81–1.17    | 0.84 a             |
| CXCL10/IP-10| 0.93                | 0.77–1.11   | 0.34 a             |
| CXCL11/I-TAC| 1.27                | 1.02–1.57   | 0.12 a             |
| CXCL12/SDF-1α| 1.11                | 0.90–1.38   | 0.35 a             |
| CXCL5/ENA-78| 1.02                | 0.83–1.26   | 0.62 a             |
| CXCL6/GCP2| 1.01                | 0.82–1.24   | 1.00 a             |
| CXCL9/MIG| 1.22                | 0.98–1.52    | 0.10 a             |
| EGF        | 0.90                | 0.75–1.07    | 0.56 a             |
| Eotaxin    | 0.97                | 0.80–1.18    | 0.78 a             |
| Eotaxin-2  | 0.82                | 0.66–1.02    | 0.14 a             |
| FGF-2      | 0.73                | 0.58–0.92    | 0.003 c            |
| Fractalkine| 0.88                | 0.64–1.20    | 0.34 d             |
| G-CSF      | 0.97                | 0.79–1.19    | 0.31 c             |
| GIP        | 0.85                | 0.67–1.07    | 0.31 a             |
| GLP-1      | 1.03                | 0.74–1.43    | 0.63 d             |
| Glucagon   | 0.83                | 0.59–1.16    | 0.49 d             |
| GM-CSF     | 0.78                | 0.63–0.97    | 0.022 c            |
| IFN-α2     | 0.93                | 0.68–1.28    | 0.55 d             |
| IFN-γ      | 0.75                | 0.61–0.92    | 0.004 c            |
| IFN-γ/IL-29| 0.91                | 0.65–1.28    | 0.28 d             |
| IL-10      | 1.13                | 0.90–1.42    | 0.25 c             |
| IL-11      | 0.67                | 0.51–0.87    | 0.005 d            |
| IL-12 (p40)| 1.07                | 0.83–1.36    | 0.79 d             |
| IL-12 (p70)| 0.78                | 0.56–1.07    | 0.11 d             |
| IL-15      | 1.16                | 0.91–1.49    | 0.24 d             |
| IL-16      | 0.91                | 0.74–1.12    | 0.53 b             |
| IL-17      | 0.91                | 0.75–1.10    | 0.26 b             |
| IL-1α      | 1.06                | 0.82–1.36    | 0.92 d             |
| IL-1Ra     | 0.98                | 0.77–1.25    | 0.79 d             |
| IL-1β      | 1.10                | 0.88–1.37    | 0.47 c             |
| IL-2       | 1.08                | 0.86–1.36    | 0.58 d             |
| IL-33      | 0.86                | 0.65–1.14    | 0.41 d             |
| IL-4       | 1.15                | 0.89–1.48    | 0.28 d             |
| IL-5       | 0.93                | 0.69–1.25    | 0.67 d             |
| IL-6       | 1.03                | 0.83–1.28    | 0.83 c             |

Abbreviation: CI, confidence interval; sCD40L, soluble CD40 ligand; SCF, stem cell factor; sEGFR, soluble EGFR; sGPN10, soluble GPN10; sILR, soluble ILR; sTNFR, soluble TNFR; sVEGFR, soluble VEGF receptor; TRAIL, TNF-related apoptosis-inducing ligand.

¹OR per tertile where median values were 204, 493, and 811 watt-h/m² could be the difference between UVR in Washington DC on a typical day in July (monthly median of 709 watt-h/m²) and September (614 watt-h/m²). Adjusted for 5-year age group, sex, involvement of case-control status, body mass index (<18.5, ≥25–<30 and ≥30 vs. ≥18.5–<25 kg/m²), coffee consumption (0.25–<25 and ≥25 vs. 0.25–<25 cups per day vs. nondrinkers), and time of blood draw (afternoon vs. morning).

²P-values for solar UVR were based on trend tests using continuous solar UVR with bold indicating significant 5% false discovery rate-corrected P-value.

³a: comparing highest quartile versus lowest quartile, b: comparing tertile versus undetectable, c: comparing above median for detected versus undetectable, and d: comparing detectable versus undetectable; to the proportion below the lowest limit of detection with ambient UVR exposure. Estimated with weighted logistic regression that yielded ORs of markers with ambient UVR exposure.
### Supplementary Table S2. OR and 95% CI of High Versus Low Marker Level and Same-Day Ambient UVR Tertiles Using Bootstrap Method with 1,000 Replicates

| Markers         | OR† Per UVR Tertile | 95% CI        | P-Trend‡ Category§ |
|-----------------|---------------------|---------------|---------------------|
| Amylin          | 0.83                | 0.63–1.08     | 0.25                | b                   |
| BCA-1           | 0.96                | 0.77–1.20     | 0.45                | a                   |
| CCL13/MCP-4     | 0.95                | 0.76–1.20     | 0.33                | a                   |
| CCL15/MIP-1d    | 0.83                | 0.65–1.03     | 0.17                | a                   |
| CCL17/TARC      | 1.18                | 0.94–1.47     | 0.14                | a                   |
| CCL19/MIP-3b    | 0.92                | 0.75–1.13     | 0.40                | a                   |
| CCL2/MCP-1      | 1.15                | 0.94–1.36     | 0.21                | a                   |
| CCL20/MIP-3a    | 0.89                | 0.72–1.11     | 0.31                | b                   |
| CCL21/CKINE     | 0.87                | 0.69–1.10     | 0.11                | a                   |
| CCL22/MDC       | 0.92                | 0.74–1.12     | 0.29                | a                   |
| CCL27/TACK      | 0.76                | 0.62–0.94     | <0.001              | a                   |
| CCL3/MIP-1a     | 0.86                | 0.62–1.17     | 0.30                | d                   |
| CCL4/MIP-1b     | 0.71                | 0.58–0.85     | 0.002               | a                   |
| CCL7/MCP-3      | 1.02                | 0.74–1.35     | 0.43                | d                   |
| CCL8/MCP-2      | 0.85                | 0.67–1.07     | 0.25                | a                   |
| C-peptide       | 0.88                | 0.68–1.11     | 0.38                | a                   |
| CRP             | 1.48                | 1.13–1.95     | 0.017               | a                   |
| CXCL1/GRO       | 0.98                | 0.81–1.16     | 0.47                | a                   |
| CXCL10/IP-10    | 0.93                | 0.75–1.12     | 0.30                | a                   |
| CXCL11/TAC      | 1.27                | 1.00–1.57     | 0.11                | a                   |
| CXCL12/SDF-1a   | 1.11                | 0.88–1.38     | 0.32                | a                   |
| CXCL5/ENA-78    | 1.02                | 0.81–1.29     | 0.41                | a                   |
| CXCL6/GCP2      | 1.00                | 0.79–1.25     | 0.50                | a                   |
| CXCL9/MIG       | 1.23                | 0.97–1.56     | 0.10                | a                   |
| EGF             | 0.90                | 0.75–1.08     | 0.41                | a                   |
| Eotaxin         | 0.97                | 0.79–1.18     | 0.47                | a                   |
| Eotaxin-2       | 0.82                | 0.66–1.02     | 0.11                | a                   |
| FGFR2           | 0.73                | 0.58–0.92     | 0.002               | c                   |
| Fractalkine     | 0.88                | 0.63–1.19     | 0.31                | d                   |
| G-CSF           | 0.97                | 0.78–1.19     | 0.27                | c                   |
| Gp              | 0.85                | 0.67–1.08     | 0.29                | a                   |
| GLP-1           | 1.04                | 0.73–1.42     | 0.45                | d                   |
| Glucagon        | 0.82                | 0.58–1.12     | 0.39                | d                   |
| GM-CSF          | 0.79                | 0.62–1.00     | 0.023               | c                   |
| IFN-α2          | 0.93                | 0.67–1.24     | 0.41                | d                   |
| IFN-γ           | 0.75                | 0.61–0.92     | 0.003               | c                   |
| IFN-γ/IL-29     | 0.92                | 0.63–1.26     | 0.26                | d                   |
| IL-10           | 1.14                | 0.89–1.41     | 0.24                | c                   |
| IL-11           | 0.66                | 0.49–0.86     | 0.004               | d                   |
| IL-12 (p40)     | 1.06                | 0.80–1.35     | 0.47                | d                   |
| IL-12 (p70)     | 0.79                | 0.56–1.08     | 0.11                | d                   |
| IL-15           | 1.17                | 0.91–1.51     | 0.21                | d                   |
| IL-16           | 0.92                | 0.73–1.14     | 0.40                | b                   |
| IL-17           | 0.91                | 0.74–1.09     | 0.25                | b                   |
| IL-1a           | 1.06                | 0.81–1.36     | 0.50                | d                   |
| IL-1Ra          | 0.98                | 0.77–1.22     | 0.48                | d                   |
| IL-1β           | 1.10                | 0.87–1.36     | 0.38                | c                   |
| IL-2            | 1.09                | 0.85–1.36     | 0.44                | d                   |
| IL-33           | 0.86                | 0.63–1.12     | 0.35                | d                   |
| IL-4            | 1.15                | 0.88–1.47     | 0.28                | d                   |
| IL-5            | 0.93                | 0.67–1.25     | 0.46                | d                   |
| IL-6            | 1.03                | 0.82–1.27     | 0.53                | c                   |
| IL-7            | 0.67                | 0.48–0.88     | 0.024               | d                   |
| IL-8            | 0.99                | 0.81–1.21     | 0.45                | a                   |
| Insulin         | 0.81                | 0.62–1.05     | 0.19                | a                   |

(continued)
### Supplementary Table S3. Description of Three Case-Control Studies Nested within the Prostate, Lung, Colorectal and Ovarian Cancer Screening Study

| Characteristics                                      | Lung Cancer | Non-Hodgkin's Lymphoma | Ovarian Cancer |
|------------------------------------------------------|-------------|------------------------|----------------|
| Cases (n)                                            | 526         | 301                    | 150            |
| Controls (n)                                         | 592         | 301                    | 149            |
| Median time from blood draw to cancer diagnosis      | 2.9 years   | 8 years                | 7.9 years      |
| Inclusion criteria                                   |             |                        |                |
| Screening arm                                        |             |                        |                |
| Baseline questionnaire                               |             |                        |                |
| Follow-up                                            |             |                        |                |
| Biochemical consent                                  |             |                        |                |
| Valid smoking history                                |             |                        |                |
| Prior history of cancer                              |             |                        |                |
| Serum specimens available at baseline                |             |                        |                |
| Matching criteria                                    | Age at randomization (5-year) | Age at randomization (5-year) | Age at randomization (5-year) |
| Year of randomization                                |             | Sex                    | Race           |
| Smoking history                                      |             | Study center           | Year of blood draw |
| Years since quitting smoking                         |             | Time of blood draw (am/pm) | Time of blood draw (am/pm) |
| Panels tested                                        |             | Cytokine panel 1a (22-plex) | Cytokine panel 1a (22-plex) |
| Cytokine panel 1b (15-plex)                          |             | Cytokine panel 1b (15-plex) | Cytokine panel 1b (15-plex) |
| Cytokine panel II (17-plex)                          |             | Cytokine panel II (17-plex) |                |
| Cytokine panel III (7-plex)                          |             | Cytokine panel III (7-plex) |                |
| Cardiovascular disease panel (3-plex)                |             |                        | CRP only       |
| Soluble receptor panel (13-plex)                     |             | Soluble receptor panel (13-plex) | Soluble receptor panel (13-plex) |
| Metabolic hormone panel (9-plex)                     | Metabolic hormone panel (9-plex) |                |
| Total number of circulating markers                  | 77          | 60                     | 83             |
| Included in this study (n)<sup>2</sup>              | 998         | 572                    | 249            |

<sup>1</sup>See Supplementary Table S4 for a list of markers included in each panel.

<sup>2</sup>We excluded 152 participants who did not report being non-Hispanic white, 31 participants with a personal history of cancer before randomization, 6 participants with duplicate records in two of the three case-control studies, and 11 participants with incomplete data on smoking or solar ultraviolet radiation.
| Cytokine Panel 1a | Cytokine Panel 1b | Cytokine Panel 2 | Cytokine Panel 3 | Metabolic Disease Panel | Soluble Receptor Panel | Cardiovascular Disease Panel 2 |
|------------------|------------------|------------------|------------------|------------------------|------------------------|-----------------------------|
| EGF              | GM-CSF           | CCL13/BCA-1      | CCL19/MIP-3b     | Insulin                | sCD30\(^1\)            | CRP                         |
| CCL11/Eotaxin    | IL-10            | CCL21/CKINE      | CCL20/MIP-3a     | Leptin                 | sEGFR                  | SAA                         |
| FGF-basic        | IL-12 (p70)      | CCL27/CTACK      | CXCL11/L-TAC     | GIP (total)            | sGP130                 | SAP                         |
| FLT-3 ligand     | IL-15            | CCL5/ENA-78      | CXCL6/GCP2       | Polypeptide            | sIL-1R\(^1\)           |                             |
| CX3CL1/Fractalkine| IL-17            | CCL11/Eotaxin    | CXCL9/MIG        | PYY (total)            | sIL-4R                 |                             |
| G-CSF            | IL-1b            | IL-16\(^1\)      | IL-11            | GLP-1 (active)         | sIL-6R                 |                             |
| CXCL1/GRO        | IL-1Ra           | IL-33            | IL-29/IFN-g1     | Amylin (total)         | sIL-1R\(^1\)           |                             |
| IFN-a2           | IL-2             | LIF\(^1\)        | C-peptide        |                         | sRAGE\(^1\)            |                             |
| IFN-\(\gamma\)  | IL-3\(^1\)       | CCL8/MCP-2       | Glucagon         |                         | sTNFR-I                |                             |
| IL-12 (p40)      | IL-4             | CCL14/MCP-4      | sTNFR-II         |                         |                       |                             |
| IL-1a            | IL-5             | CCL15/MIP-1d     | sVEGFR\(^1\)     |                         |                       |                             |
| IL-8             | IL-6             | SCF              | sVEGFR2          |                         |                       |                             |
| CXCL10/IP-10     | IL-7             | CXCL12/SDF-1a/b  | sVEGFR3          |                         |                       |                             |
| CCL2/MCP-1       | TGF\(\alpha\)   | CCL17/TARC       | sIL2RA\(^1\)    |                       |                       |                             |
| CCL7/MCP-3       | TGF\(\beta\)    | TPO              | sVEGFR           |                         |                       |                             |
| CCL22/MDC        |                 | TRAIL            |                  |                         |                       |                             |
| CCL3/MIP-1a      |                 | TSLP             |                  |                         |                       |                             |
| CCL4/MIP-1b      |                 |                  |                  |                         |                       |                             |
| sCD40L           |                 |                  |                  |                         |                       |                             |
| sIL2RA\(^1\)    |                 |                  |                  |                         |                       |                             |
| TNF\(\alpha\)   |                 |                  |                  |                         |                       |                             |
| VEGF             |                 |                  |                  |                         |                       |                             |

Abbreviation: sCD40L, soluble CD40 ligand; SCF, stem cell factor; sEGFR, soluble EGFR; sGP130, soluble GP130; sIL soluble IL; sTNFR, soluble TNFR; sVEGFR, soluble VEGF receptor; TRAIL, TNF-related apoptosis-inducing ligand.

\(^1\)Excluded from the analysis because of poor performance (>90% below the lower limit of detection).