A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP4861.

Solar Ultraviolet Radiation and Breast Cancer Risk: A Systematic Review and Meta-Analysis

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Background: A protective relationship has been hypothesized between exposure to solar ultraviolet radiation (UVR) and the development of breast cancer.

Objective: The objective of this study was to conduct a systematic literature review and meta-analysis of studies examining the association of exposure to solar UVR and breast cancer risk.

Methods: We searched Medline, EMBASE, and Web of Science for all studies investigating exposure to solar UVR and breast cancer risk. Separate analyses were performed using estimates of time spent in the sun, and ambient UVR. Associations were estimated using DerSimonian and Laird random-effect models. Heterogeneity was investigated through subgroup analyses and I^2 statistics.

Results: Fourteen studies were included in the review and 13 in the meta-analysis, with the majority ($n = 8$) conducted in North America. We observed a decreased risk of breast cancer for individuals spending ≥1 h/d in the sun during summer months over a lifetime or usual adulthood compared with <1 h/d [pooled relative risk (RR) = 0.84; 95% CI: 0.77, 0.91]. Spending ≥2 h/d in the sun had a similar protective effect as 1 to <2 h/d when compared with <1 h/d (RR = 0.83; 95% CI: 0.75, 0.93 vs. 0.83; 95% CI: 0.78, 0.89). Exposure during adolescence was suggestive of a lower risk of breast cancer than exposure later in life (≥45 years of age) (RR = 0.83; 95% CI: 0.71, 0.98 vs. 0.97; 95% CI: 0.85, 1.11). Ambient UVR was not associated with the risk of breast cancer (RR = 1.00; 95% CI: 0.93, 1.09).

Discussion: To our knowledge, this was the first meta-analysis to estimate the risk of developing breast cancer associated with time spent in the sun. The results suggest that obtaining greater than an hour a day in the sun during the summer months could decrease the risk of developing breast cancer. https://doi.org/10.1289/EHP4861

Introduction

Breast cancer is the most common cancer (excluding nonmelanoma skin cancer) diagnosed among females worldwide, being responsible for 25% of incident cases (WHO 2016). Rates of breast cancer differ more than 5-fold between regions of the world, owing to differences in the prevalence of risk factors (WHO 2016). Established risk factors for breast cancer include increasing age, Caucasian ethnicity, having a family history of breast cancer, germ-line genetic mutations in key tumor suppressor genes (*BRCA1*, *BRCA2*, *CHEK2*, and *PALB2*), reproductive history (including early age at menarche, late age at menopause, nulliparity, and late age at first birth), exogenous hormone use (long-term use of oral contraceptives and hormone replacement therapy), and lifestyle factors (high alcohol intake, obesity, adult weight gain, physical inactivity, poor diet, and smoking) (Sun et al. 2017). Despite what is known about risk factors for breast cancer, further research is merited to identify additional risk factors. For example, within the Nurses' Health Study, Tamimi et al. (2016) reported that established modifiable and nonmodifiable risk factors accounted for approximately 70% of postmenopausal breast cancer cases, whereas modifiable risk factors accounted for 34%.

Solar ultraviolet radiation (UVR) is an omnipresent exposure with confirmed detrimental and potential protective effects on cancer risk. Although a causal relationship between UVR and cutaneous malignancies has been established (IARC 1992), a certain amount of ultraviolet B (UVB) radiation—wavelength of 290–315 nm—from the sun may be protective for some noncutaneous malignancies, including breast cancer (van der Rhee et al. 2013). The potential biological mechanisms underlying a protective relationship between moderate UVR exposure and noncutaneous malignancies are based on the antiproliferative and apoptotic properties of vitamin D (Webb and Holick 1988) as well as increases in nocturnal melatonin concentrations, which have also been shown to have antiproliferative effects (Stevens 2005).

Several ecologic studies have examined the relationship between breast cancer incidence and latitude or measures of ambient UVR (Bilinski et al. 2014; Boscoe and Schymura 2006; Gorham et al. 1990; Grant 2012, 2013; Mandal et al. 2009; Mohr et al. 2008). These ecologic studies, despite their limitations, in general support the hypothesis that greater levels of solar UVR exposure may reduce an individual's risk of breast cancer. In addition, the most recent meta-analysis (Estébanez et al. 2018) and pooled analysis (McDonnell et al. 2018) on circulating vitamin D and breast cancer risk have found a reduced risk with increasing levels of vitamin D. A body of literature exists pertaining to the relationship between solar UVR exposure and breast cancer risk, including a systematic review of case–control and cohort studies (van der Rhee et al. 2013). Two primary measures of solar UVR exposure exist: ambient UVR radiation—an ecologic measure—often measured in kilojoules per squared meter (kJ/m^2) or Watts (W) (for use in large studies, where individual measurements have not been collected or are not practical), and time spent in the sun—usually denoted as the number of hours an individual spends outdoors on an average summer weekday/weekend. Among this body of literature, study results have been inconsistent (van der Rhee et al. 2013). Differences in geographic location, study design, confounders adjusted for, and exposure measures exist, which may explain the current heterogeneity of results. Existing literature has demonstrated differences in the risk factor profiles for breast cancers based on menopausal and

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Supplemental Material is available online (https://doi.org/10.1289/EHP4861).

The authors declare they have no actual or potential competing financial interests.

Received 10 December 2018; Revised 29 November 2019; Accepted 2 December 2019; Published 6 January 2020.

hormone receptor subgroups (Blackmore et al. 2008). In addition, there is some evidence that UVR exposure during periods of development and hormonal changes—such as adolescence—may have a distinct relationship with the incidence of breast cancer (Colston and Hansen 2002; Setiawan et al. 2009). The published literature has yet to be synthesized through the generation of summary effect estimates.

The first objective of this study was to identify all relevant cohort and case–control studies that investigated the risk of breast cancer associated with varying levels of exposure to UVR. The second objective was to qualitatively synthesize the literature on this topic and to assess overall study quality. The third objective was to estimate the risk of breast cancer associated with different levels of time spent in the sun and ambient UVR exposure (strength of the sun or latitude as a proxy) during lifetime or usual adult exposure. The fourth objective was to perform analyses by different exposure windows (adolescence and later in life) to determine whether particular life periods are most important. The fifth objective was to determine whether different subtypes of breast cancer were differentially associated with exposure to UVR. The final objective was to explore sources of heterogeneity, including study design, control for important confounders, and overall study quality.

Methods

Literature Search and Study Inclusion Criteria

A Populations of interest, Exposures, Comparators, and Outcomes (PECO) statement was developed to identify cohort and case–control studies relevant to breast cancer risk and exposure to solar UVR. The population of interest was adult women over 18 years of age at the time of exposure and outcome assessment. Relevant exposures included self-reported time spent in the sun and sunbathing via self-administered questionnaires and strength of the sun at residence, which was measured via satellite (absolute ambient UVR) or latitude (proxy for ambient UVR, given that it is the strongest determining factor). The primary exposure time window is lifetime exposure or usual adulthood exposure. Exposure during other life periods are also of interest including exposure during adolescence and later in life. Comparators were the lowest amount of time spent in the sun, lowest sunbathing activities or the lowest ambient UVR (by satellite or by highest latitude). Outcomes included a diagnosis of breast cancer or self-report of diagnosis in a follow-up survey.

A systematic review was conducted using the reporting guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). The literature search was conducted using Medline, EMBASE, and Web of Science, with all studies published on breast cancer risk and its relationship to solar UVR exposure up to April 2019 included. The in-depth search strategy was developed by T.H. and D.E.O. (see "Search strategies" in the Supplemental Material). Secondary sources, including the reference lists of included manuscripts, studies included in a previous systematic review (van der Rhee et al. 2013) on this topic, and studies that cited this previous review were also examined for additional articles.

During the literature search process, articles were included for full-text review whether the subjects were adult humans, the outcomes included incident breast cancer cases, and included an assessment of UVR exposure. Studies using mortality as the outcome were excluded owing to the relatively high survival rate for breast cancer and the potential role for UVR exposure to influence cancer survival. If two studies reported on the same or overlapping population, only the study with the largest sample size was included; if the studies included distinct and relevant exposure or stratified analysis (ER/PR status), then both studies were included. Reviews, meta-analyses, and cross-sectional and ecologic studies were excluded from this review, and we made no restrictions of the language of studies to be included. The screening of studies for inclusion/exclusion was conducted by T.H. and D.E.O.

Data Extraction and Qualitative Synthesis

T.H. extracted information on author, year of publication, geographic location, study design, sample size, age of participants, measures of UVR (e.g., ambient, time spent in the sun) exposure measured, and confounders included in models for each study. The referent category, effect estimates and confidence intervals were extracted for each exposure category of time spent in the sun and ambient UVR (strength of sun or latitude category). If a study reported results for different exposure periods (years of age) the same information as above was extracted for each of these periods. If any stratified analyses were conducted, such as by hormone receptor status, effect estimates for these analyses were also extracted. All of the extracted information was stored in an excel file and was checked for accuracy by D.E.O.

Study Quality Assessment

Study quality and risk of bias were evaluated using a modified version of the Newcastle-Ottawa Scale (NOS) for case–control and cohort studies. The NOS is a study quality scale for nonrandomized trials, where studies are judged on three broad perspectives: *a*) the selection of study groups, *b*) the comparability of the groups, and *c*) the ascertainment of exposure and outcome of interest (Wells et al. 2009). The criteria and questions of the scale vary by study design (case–control and cohort) (see "Newcastle–Ottawa Scale Case Control Studies" and "Newcastle–Ottawa Scale Cohort Studies" in the Supplemental Material). The only modification to the original scale was pertaining to control for confounding. Control for important confounders was considered by grouping studies into three strata: *a*) adequate control for confounding [adjusted for age, reproductive factors, exogenous hormone use, body mass index (BMI), physical activity, alcohol consumption, smoking, and fruit and vegetable consumption] that was assigned a score of 2; *b*) moderate (failed to adjust for physical activity or reproductive factors) that was assigned a score of 1; and *c*) insufficient (failed to adjust for multiple established and suspected confounders) that received a score of 0. Variables were considered adjusted for if eliminated from the final model through backwards elimination, stepwise selection, or change-in-estimate approaches. Studies were categorized for overall quality based on NOS categorization (poor, fair, and good; see "Newcastle–Ottawa Quality Assessment Scale Summary Categorization" in the Supplemental Material).

Meta-Analysis

To determine the risk of breast cancer associated with $\geq$1 h/d spent in the sun during adulthood compared with <1 h/d (either lifetime exposure or exposure between 20 and 65 years of age, depending on the study), a relative risk (RR) estimate for this comparison was extracted from each study. In studies where multiple levels of exposure $\geq$1 h/d were presented in comparison with the <1 h/d, the RR estimate was obtained by pooling RRs for exposure categories with inverse variance weighting. The standard error for this estimate was computed using reported contingency table counts to adjust for the degree of covariance among the category estimates. If a study had a referent category that was not <1 h/d we used the risk estimate that was compared with the lowest exposure category and assumed that it represented a similar effect to the comparison of $\geq$1 h/d with <1 h/d. We tested the influence of this assumption on the results by conducting sensitivity analyses where these studies were removed.

To determine the association between varying amounts of time spent in the sun and breast cancer risk, we conducted analyses

comparing 1 to <2 h/d and ≥2 h/d to <1 h/d. When combining multiple categories for either of these analyses, we used the same method as described above for the primary analysis. For studies examining the association between ambient UVR and breast cancer risk, there was heterogeneity in how the studies categorized exposure. Studies categorized ambient UVR in quartiles, quintiles, or by region (North vs. South). To pool estimates across studies, we took the effect estimate for the highest exposure versus the lowest exposure.

For the purposes of this study, hazard ratios and odds ratios were treated as estimates of RR. DerSimonian and Laird random-effect models were used in all analyses (DerSimonian and Laird 1986). The main analysis assessed the risk of breast cancer according to time spent in the sun during lifetime or usual adult exposure. Heterogeneity was quantified using the Q-test and the I^2 statistics. Meta-regression was utilized to assess statistical differences in our subgroup analyses. Publication bias was assessed by examining funnel plots and through both Egger's weighted linear regression and Begg's rank correlation tests. In the presence of statistical evidence of publication bias, the trim and fill approach was performed to adjust for potential publication bias. All analyses were performed using the R computing framework (version 13.4.0; R Development Core Team) and the metafor package.

Exposure Window and Breast Cancer Subtype Analyses

To determine whether exposure to UVR during particular life periods have differential effects on breast cancer risk, we conducted analyses by different exposure windows (adolescence vs. exposure later in life). For a study to be included in this analysis, it needed to report risk estimates for different age periods. For the later life period we used the estimate from the oldest age period in each study, which corresponded to exposure after 45 years of age. To determine whether different subtypes of breast cancer were differentially associated with exposure to UVR, we conducted an analysis of risk estimates stratified by estrogen receptor (ER) status. If a study presents results for ER^+PR^+, ER^+PR^-, and ER^-PR^-, we pooled results of the ER^+ to obtain results by just ER status.

Study Quality Subgroup Analyses

To determine whether factors related to study quality influenced the results of the meta-analysis, we conducted subgroup analyses by study design (prospective cohort vs. case–control) for investigation of the potential for recall bias, adjustment for confounding, and overall study quality determined by the NOS.

Results

Study Inclusion and Characteristics of Included Studies

The literature search returned 1,818 unique articles (Figure 1). Fourteen reports on 13 different study populations were included in this review. Three additional studies on this relationship were identified during database searching but were excluded due to having study populations overlapping with those of studies that were already included (Anderson et al. 2011a; Fuhrman et al. 2013; Kuper et al. 2009). Characteristics of studies assessing the relationship of UVR and breast cancer risk are presented in Table 1. Of the studies included in a meta-analysis, eight were conducted in North America (Anderson et al. 2011b; Engel et al. 2014; John et al. 1999, 2007; Knight et al. 2007; Lin et al. 2012; Millen et al. 2009; Zamoiski et al. 2016), four were conducted in Europe (Edvardsen et al. 2011; Engel et al. 2011; Yang et al. 2011; Cauchi et al. 2016), and one in Iran (Bidgoli and Azarshab 2014). The studies included were mainly conducted on Caucasian women with the following exceptions: Two studies did not specify the ethnic makeup of their study populations (Bidgoli and Azarshab 2014; Cauchi et al. 2016), and another study had equal proportions of Caucasian, Hispanic, and black women (John et al. 2007). The majority of studies consisted of general populations that included both pre- and postmenopausal female subjects and did not make restrictions on family history of breast cancer. One study each were conducted on premenopausal women (Bidgoli and Azarshab 2014) and women without a family history of breast cancer only (Cauchi et al. 2016). In this body of literature, the majority of studies were prospective cohort designs ($n = 8$) (Edvardsen et al. 2011; LS Engel et al. 2014; P Engel et al. 2011; John et al. 1999; Lin et al. 2012; Millen et al. 2009; Zamoiski et al. 2016; Yang et al. 2011). In terms of UVR measurement, five (two cohort, three case–control) measured only time spent in the sun (Bidgoli and Azarshab 2014; Cauchi et al. 2016; Engel et al. 2014; Knight et al. 2007; Yang et al. 2011), three (all cohort) measured only ambient UVR (Edvardsen et al. 2011; Engel et al. 2011; Lin et al. 2012), whereas five studies (three cohort, two case–control) measured both (Anderson et al. 2011b; John et al. 1999, 2007; Millen et al. 2009; Zamoiski et al. 2016), but only one study constructed a combined measurement (Zamoiski et al. 2016). One study (Yang et al. 2011) examined the association of sunbathing with the risk of developing breast cancer. In terms of breast cancer outcomes, two studies stratified analyses by ER status (Blackmore et al. 2008; Engel et al. 2014) and another study stratified by localized versus advanced stage breast cancer (John et al. 2007), while the remaining studies assessed breast cancer as a homogeneous disease.

Risk of Bias among Included Studies

For the risk of bias of included studies, we restricted selection to studies that were included in a main analysis and on a novel study population. Yang et al. (2011) was not assessed for risk of bias because it was not included in a meta-analysis, and Blackmore et al. (2008) was not included because it was a reanalysis of the study population reported by Knight et al. (2007). After application of the NOS, study quality was appraised as follows: Three studies each were rated as poor (Cauchi et al. 2016; Bidgoli and Azarshab 2014; Lin et al. 2012) and fair (Zamoiski et al. 2016; Engel et al. 2014; Edvardsen et al. 2011), respectively, and the remaining six were classified as good (Anderson et al. 2011b; Knight et al. 2007; John et al. 2007, 1999; Engel et al. 2011; Millen et al. 2009) (see Tables S1 and S2). For time spent in the sun ≥1 h/d compared with <1 h/d, five studies had good study quality, whereas two studies had fair quality and two had poor quality. For the dose–response analyses, five studies had good study quality and two studies had fair quality. Finally, among the ambient UVR studies, four were of good quality, two were of fair quality, and one was of poor quality.

Studies classified as poor had inadequate consideration/description of several factors included in the NOS. For example, one study (Lin et al. 2012) had a cohort that was not representative of the general population, did not clarify the method used to remove participants who had a cancer at the time of enrollment, used an inadequate method for gathering exposure information, and did not adjust for reproductive factors. Studies of fair quality had similar shortcomings to those classified as poor; however, the number of inadequacies was less [e.g., nonrepresentative study population, self-reported exposure measures, and adequate/moderate control for confounding (Zamoiski et al. 2016; Engel et al. 2014)]. In contrast, the good-quality studies lost minimal points, with no study losing more than 1 point in any of the domains considered.

Time in the Sun and Breast Cancer Risk

The association between spending ≥1 h in the sun per day compared with spending <1 h and the risk of developing breast cancer

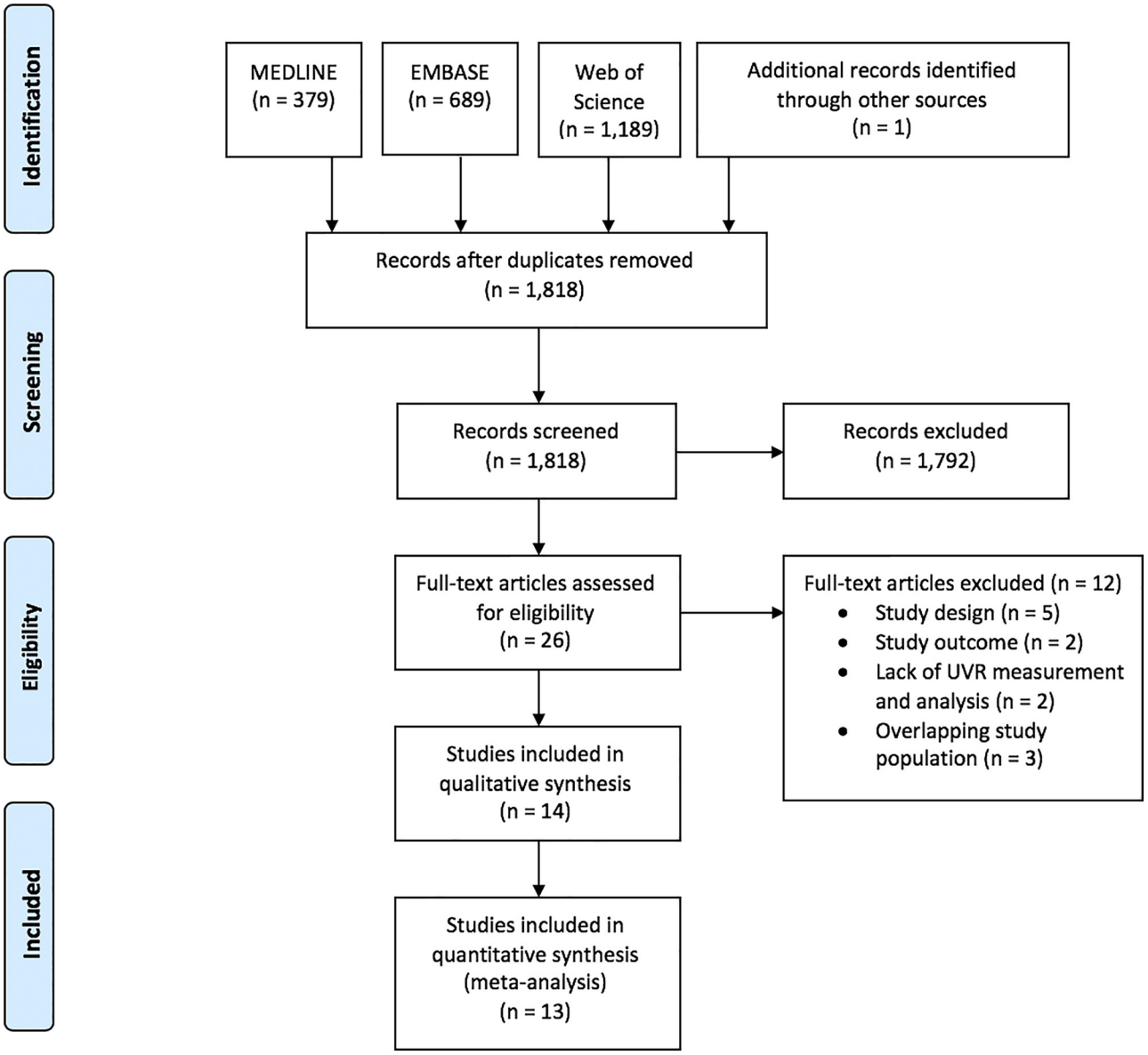

Figure 1. Flow diagram of the selection procedure of studies assessing the relationship of exposure to solar UVR with the risk of breast cancer. A PRISMA flow diagram that details the inclusion and exclusion of studies considered for this systematic review. Note: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; UVR, ultraviolet radiation.

is graphically displayed in Figure 2. We observed a lower risk of breast cancer for individuals with ≥1 h of time spent in the sun per day during summer months compared with individuals that had <1 h [pooled RR = 0.84; 95% confidence interval (CI): 0.77, 0.91; $p < 0.001$]. There was a high degree of heterogeneity among the risk estimates ($I^2 = 73.6\%$), and there was some evidence of publication bias (Begg's test: $p = 0.05$; Egger's test: $p = 0.02$). The trim and fill method suggested one unpublished study (see Figure S1) and did not change the summary effect estimate or confidence interval.

After determining the risk of breast cancer associated with ≥1 h/d compared with <1 h/d in the sun, we next sought to determine whether increasing time spent in the sun further protected against breast cancer or whether there was a threshold where no further protective effect was conferred. For 1 to <2 h/d in the sun during the summer compared with <1 h/d, the pooled RR = 0.83 (95% CI: 0.78, 0.89; $p < 0.001$; Figure 3). For ≥2 h/d in the sun compared with <1 h/d, the pooled RR of breast cancer was the same as that of 1 to <2 h compared with <1 h/d (pooled RR = 0.83; 95% CI: 0.75, 0.93; $p < 0.001$; Figure 3). Among the studies included in this analysis, there was little heterogeneity in risk estimates for 1 to <2 h/d spent in the sun ($I^2 = 8.3\%$), but there was high heterogeneity for estimates of breast cancer risk associated with ≥2 h/d in the sun ($I^2 = 71.9\%$).

Sensitivity analyses were conducted excluding one study that categorized time spent in the sun as rare/never, occasional, and frequent (John et al. 1999) and excluding the studies that did not use <1 h in the sun per day as their referent group (Anderson et al. 2011b; Cauchi et al. 2016; Engel et al. 2014; Zamoiski et al. 2016); neither of these exclusions changed the RRs considerably for the comparison of <1 h/d versus ≥1 h/d, or the dose–response analysis (see Table S3).

Ambient UVR and Breast Cancer Risk

Given that several studies assessed the association of ambient UVR with the risk of breast cancer, we sought to determine the

Table 1. Characteristics of all studies investigating the association of solar UVR with the risk of breast cancer ($n = 14$).

Reference	Country	Study design	Sample size [case/controls (n/n)]	Age (y)	Exposures	Exposure window[a]	Subgroup analyses	Confounders
Zamoiski et al. 2016	USA	Cohort	716/36,009	40–70	Ambient, time spent in the sun, combined UVR	0–12, 13–19, 20–39, 40–64, >65	None	Age, race, BMI, ever given birth, exercise, age at first birth, age at menarche, HRT, family history, menopause, number of births, OC use, alcohol consumption, ionizing radiation to the breast
Cauchi et al. 2016	Malta	Case–control	200/403	20–80	Time spent in the sun	lifetime	None	Diet, OC use, menopausal status, history of myocardial infarction, height, family history of breast cancer
Engel et al. 2014	USA (IA and NC)	Cohort	578/32,127	18–86	Time spent in the sun	Enrollment, 10 y before enrollment	ER/PR status, menopausal status	Age, race, menopause, combined parity and age at first birth, family history of breast cancer
Bidgoli and Azarshab 2014	Iran	Case–control	60/116	20–40	Amount of time spent outdoors, coverage of body from sunlight	Lifetime	None	Not specified
Lin et al. 2012	USA (CA, FL, LA, NJ, NC, PA, GA, MI)	Cohort	8,681/178,138	50–75	Ambient UVR	Baseline to end of follow-up	None	Age, BMI, caloric intake, intake of fruit and vegetables, red and white meat, alcohol consumption, tobacco smoking, education, physical activity, and median household income
Yang et al. 2011[b]	Sweden	Cohort	2,303/49,261	50–60	Number of weeks spent on sunbathing vacations, solarium use	10–19, 20–29, 30–39	None	Education, smoking, alcohol, BMI, physical activity, parity, age at first birth, age at menarche, OC use, breast feeding, family history of breast cancer
Engel et al. 2011	France	Cohort	2,871/67,721	42–72	Ambient, place of residence	Baseline to end of follow-up	Menopausal status	Menopausal status, BMI, PA, age at menopause, age at menarche, OC use, use of HRT, calcium intake, use of calcium supplement, alcohol, total energy intake–alcohol, university degree, family history, sunburn resistance, skin complexion
Anderson et al. 2011b	Canada (ON)	Case–control	3,101/3,420	Mean age = 56	Time spent in the sun, ambient UVR, solar vitamin D score	Teen years, 20s–30s, 40s–50s, 60s–75	None	Age, marital status, education, ethnicity, BMI, smoking status and pack-years, breastfeeding, lactation, age at menarche, OC use, OC duration, parity, age at first live birth, age at last menstruation, duration of HRT use, history of benign breast disease, family history of breast cancer, screening mammogram, alcohol intake, fat intake, calorie intake, physical activity, phytoestrogen intake, vitamin D and calcium intake
Edvardsen et al. 2011	Norway	Cohort	948/41,181	50–60	Ambient (VD dose), sun-seeking	Lifetime	None	Age, BMI, alcohol, parity, OC use, menopausal status, hormone therapy, age

Table 1. (*Continued.*)

Reference	Country	Study design	Sample size [case/controls (*n*/*n*)]	Age (y)	Exposures	Exposure window[a]	Subgroup analyses	Confounders
					holidays, solarium use			at first birth, mammography frequency
Millen et al. 2009	USA (23 states and DC)	Cohort	2,535/71,662	50–80	Region of residence over life periods, reported time spent in the sun	Study follow-up from 1993–1998 to 2006	ER/PR status for ambient	Age, race, education, weight, family history, age at menarche, age at menopause, parity, age at first birth, HRT, alcohol, physical activity
Blackmore et al. 2008	Canada (ON)	Case–control	759/1,135	Mean age = 54	Time spent outdoors	10–19, 20–29, 45–54	ER/PR status	Age, ethnicity, family history, ever breastfed, education, age menarche, age at first birth
John et al. 2007	USA (San Francisco Bay)	Case–control	2,054/2,129	35–80	Self-reported lifetime outdoor activity	Lifetime	Localized vs. advanced	Age, race, education, family history, personal history of benign breast disease, number of full-term pregnancies, breastfeeding, height, alcohol consumption, BMI, menopausal status, HRT
Knight et al. 2007	Canada (ON)	Case–control	972/1,135	40–65	Time spent outdoors	10–19, 20–29, 45–54	None	Age, ethnicity, family history, ever breastfed, education, age menarche, age at first birth
John et al. 1999	USA	Cohort	190/5,009	25–74 at baseline	Recreational, occupational time spent in the sun, combined recreational and occupational UVR exposure, ambient UVR	Follow-up from 1971–1975 to 1992	None	Age, education, age at menarche, age at menopause, BMI, frequency of alcohol consumption, physical activity

Note: BMI, body mass index; CA, California; DC, District of Columbia; FL, Florida; GA, Georgia; HRT, hormone replacement therapy; IA, Iowa; LA, Louisiana; MI, Michigan; NC, North Carolina; NJ, New Jersey; OC, oral contraceptives; ON, Ontario; PA, Pennsylvania; USA, United States of America; UVR, ultraviolet radiation; VD, vitamin D.
[a]Number ranges correspond to years of age.
[b]Study was not included in quantitative meta-analysis because the exposures did not match those within the current study.

relationship by defined categories of high ambient UVR at residence and the risk of breast cancer. A random effects meta-analysis of seven studies yielded a pooled RR = 1.00 (95% CI: 0.93, 1.09; $p = 0.91$; Figure 4) comparing the highest ambient UVR category to the lowest ambient UVR category in each study. There was moderate heterogeneity among the included studies ($I^2 = 54.2\%$) and no evidence of publication bias among this body of literature (Begg's test: $p = 1.0$; Egger's test: $p = 0.90$; Figure S2).

Exposure Window and Breast Cancer Subtype Analyses

Subgroup analyses by different exposure windows are presented in Table 2. The studies included in each of the exposure windows are presented in Table S4. Among studies that measured time in the sun over different life periods, exposure during adolescence was associated with a lower risk of breast cancer than exposure later in life (≥45 years of age) when comparing ≥1 h/d in the sun to <1 h/d (pooled RR = 0.83; 95% CI: 0.71, 0.98 vs. 0.97; 95% CI: 0.85, 1.11) (Table 2). In subgroup analyses of exposure windows, 1 to <2 h/d and ≥2 h/d spent in the sun compared with <1 h/d spent in the sun was associated with a lower risk of breast cancer during adolescence (pooled RR = 0.88; 95% CI: 0.79, 0.99 and 0.72; 95% CI: 0.65, 0.80), whereas 1 to <2 h and ≥2 h compared with <1 h/d later in life (≥45 years of age) was not associated with a lower risk in breast cancer (pooled RR = 1.00; 95% CI: 0.86, 1.16 and 0.94; 95% CI: 0.85, 1.04) (Table 2). Among the four studies that measured ambient exposure during adolescence, the pooled RR of breast cancer was 0.99 (95% CI: 0.84, 1.17; $p = 0.93$, whereas the risk associated with exposure later in life (≥45 years of age) was 1.07 (95% CI: 0.77, 1.48) comparing highest and lowest ambient UVR categories.

Two studies (Blackmore et al. 2008; Engel et al. 2014) assessed the relationship of ≥1 h/d spent in the sun compared with <1 h and breast cancer risk stratified by ER status. When pooling results from these two studies, there was a significantly lower risk of breast cancer for ER^+ tumors (pooled RR = 0.70; 95% CI: 0.60, 0.81), but not for ER^- tumors (pooled RR = 0.82; 95% CI: 0.64, 1.05), associated with lifetime or usual adulthood time spent in the sun ≥1 h/d compared with <1 h/d.

Study Quality Subgroup Analyses

Subgroup analyses by study quality, control for confounding, and study design are presented in Table 3. The studies included in each of the subgroup analyses are presented in Table S5. Study quality—according to the NOS—was not a significant source of heterogeneity among studies included in the main analysis (≥1 h/d vs. <1 h/d, meta-regression $p = 0.74$, Table 3). In addition, RRs for ≥1 h/d compared with <1 h per day were similar among different study designs, whereas studies with adequate control for confounding had RRs closer to the null compared with those studies with moderate or insufficient control for confounding (≥1 h/d vs. <1 h/d; Table 3).

In subgroup analyses based on NOS scores, study quality was not a significant source of heterogeneity for studies with estimates for 1 to <2 h or ≥2 h spent in the sun per day (meta-

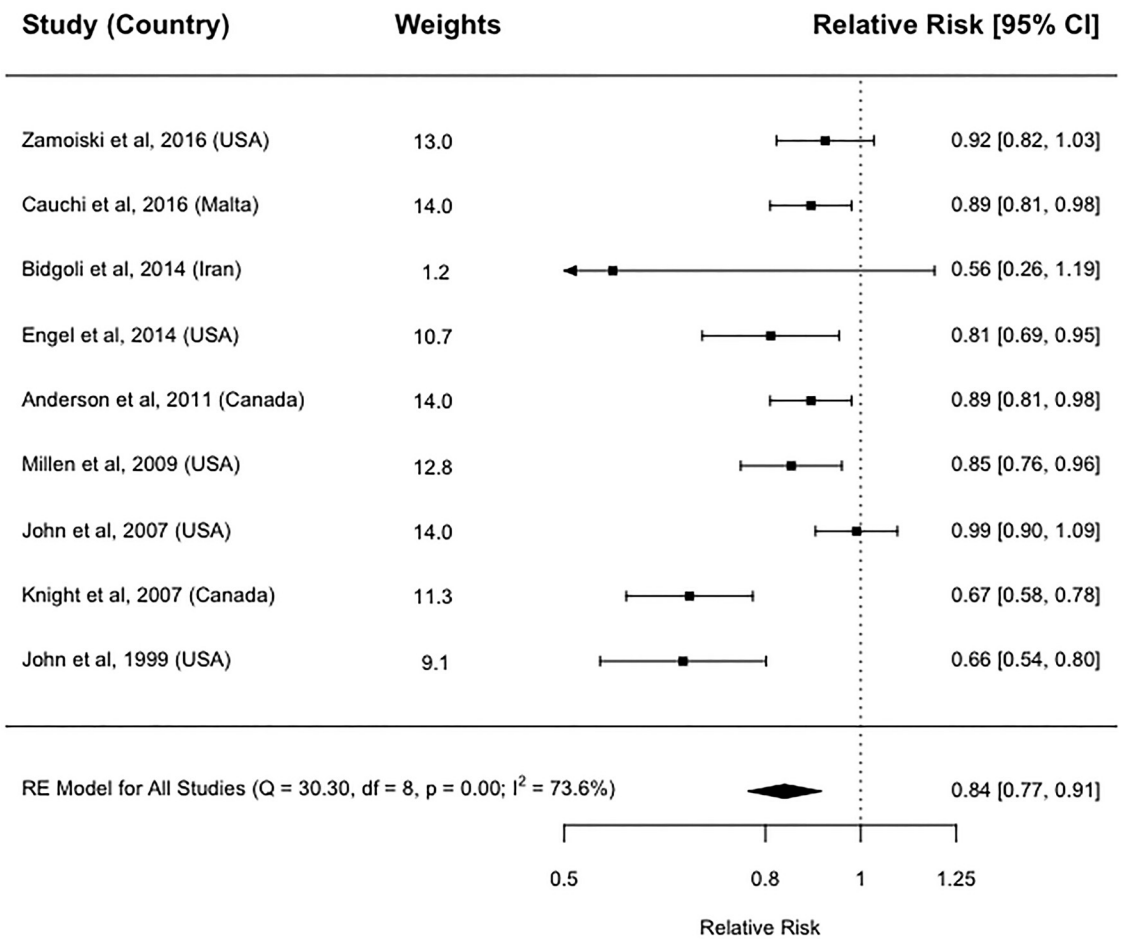

Figure 2. Forest plot and random effects pooled relative risk of breast cancer comparing women that spend ≥1 h in the sun per day during summer months to women that spend less than an hour in the sun per day during lifetime or usual adulthood. The black squares represent the effect estimates for each study and the whiskers represent the 95% CIs around these estimates for each study. The black diamond represents the summary effect estimate around 95% CI, with the center being the estimate and the ends being the confidence intervals. The vertical line represents a relative risk of 1. Note: CI, confidence interval; RE, random effects.

regression $p = 0.81$ and 0.60) (Table 3). Study design was not a significant source of heterogeneity among the studies included in the dose–response analysis [meta-regression $p = 0.79$ (1 to <2 h) and 0.89 (≥2 h)]; however, there was evidence that the risk estimates for cohort studies were more consistent than for case–control studies (Table 3). For all of the dose–response comparisons, studies that had adequate control for confounding observed smaller protective effects compared with studies with moderate control for confounding (Table 3).

Among studies examining the association of ambient UVR and breast cancer risk, study quality was a source of heterogeneity (meta-regression $p = 0.06$; Table 3) with studies of higher quality observing a protective effect that approached statistical significance (RR = 0.94; 95% CI: 0.85, 1.04). Neither study design or control for confounding were significant sources of heterogeneity among these studies (meta-regression $p = 0.47$ and $p = 0.29$; Table 3).

Discussion

In this study, we conducted a meta-analysis examining the relationship of self-reported measures of solar UVR exposure, such as time spent in the sun, as well as ambient UVR with the risk of developing breast cancer. Women spending ≥1 h/d in the sun had a significantly reduced risk of breast cancer when compared with those spending less than 1 h in the sun per day; indicating that sun exposure may be protective against breast cancer. This relationship was evident for lifetime or usual adult exposure as well as exposure during adolescence. There is potential that when open-ended exposure categories (≥1 h and ≥2 h/d) were used in the evaluation of time spent in the sun and breast cancer risk that different exposure distributions existed within the category, resulting in high heterogeneity. In a comparison of varying levels of time spent in the sun, we found that compared with <1 h/d, 1 to <2 h/d in the sun were associated with a lower risk of breast cancer, while ≥2 h/d did not afford any additional benefit. Both levels of exposure showed null results for exposure later in life (≥45 years of age). Finally, living in an area with high relative ambient UVR was not associated with the risk of breast cancer during any life periods. It is possible that the relationship between sun exposure and breast cancer risk differs based on menopausal status and/or hormone receptor status subtypes; however, there is a paucity of studies that have explored these potential differences.

The current study demonstrates an apparent reduction in breast cancer risk afforded to women with at least 1 h of time spent in the sun per day, with a potential increase in benefit for greater than 2 h of exposure per day during adolescence, but not adulthood. One explanation for this difference is that higher amounts of time spent in the sun—and presumably circulating vitamin D—may have greater importance during breast tissue development than during adulthood (Lopes et al. 2012). Overall, this effect can most likely be credited to the potency of UVB radiation for producing vitamin

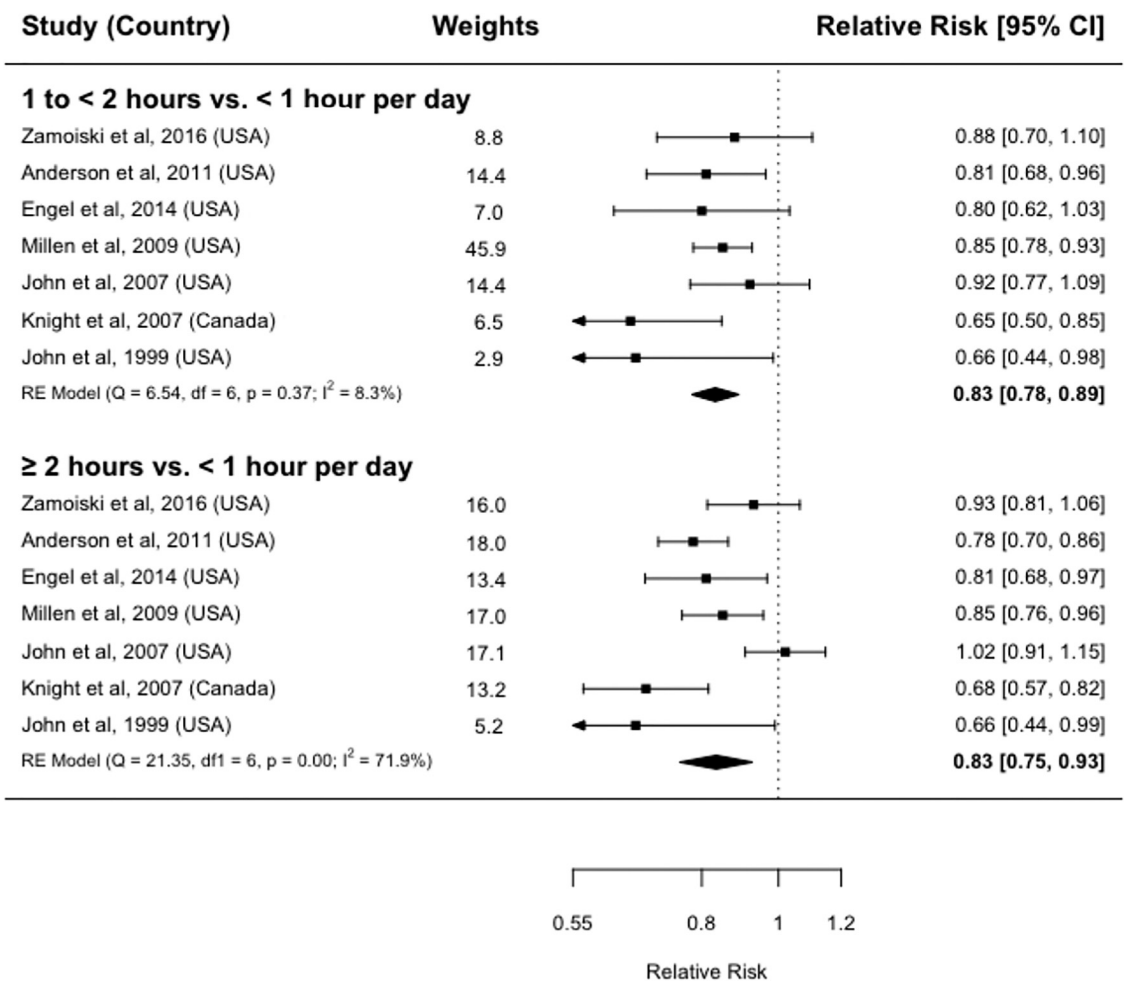

Figure 3. Forest plot and random effects pooled relative risk of breast cancer comparing women that spend less than an hour in the sun per day during summer months to women that spend 1 to <2 h/d and ≥2 h/d during lifetime or usual adulthood. The black squares represent the effect estimates for each study and the whiskers represent the 95% CIs around these estimates for each study. The black diamond represents the summary effect estimate around 95% CI, with the center being the estimate and the ends being the confidence intervals. The vertical line represents a relative risk of 1. Note: CI, confidence interval; RE, random effects.

D in the skin. Exposure of one-fourth of the skin surface to 1 standard erythemal dose ($100\,J/m^2$) is equivalent to approximately 1,000 IU of vitamin D supplementation (Engelsen 2010). The amount of time spent in the sun shown to be beneficial may be such that sufficient amounts of vitamin D are created for storage and release during the winter, when temperatures and low UVB radiation availability make vitamin D production impossible—such as at northern latitudes. Previous research has shown vitamin D produced as a result of solar UVR exposure can be stored in adipose tissue and released during times of vitamin D insufficiency (Martinaityte et al. 2017). The lack of a greater protective effect with higher sun exposure may also be influenced by a sublinear relationship between sun exposure and dermal synthesis of vitamin D (Nair-Shalliker et al. 2014). Additional protective effects from higher hours of sun per day may also be small and therefore difficult to detect given exposure misclassification.

Few studies considered effect modification in relation to factors influencing biologic response to UVR exposure, such as skin type and sunscreen use. Studies reporting on effect modification by skin type did not observe different effects for time spent in the sun (Millen et al. 2009) or ambient UVR (Edvardsen et al. 2011; Engel et al. 2011). Only one study examined effect modification by sunscreen use and observed no effect modification of the relationship between time spent in the sun and breast cancer risk (Engel et al. 2014). The use of sun protection may modify this relationship; however, further research is needed before conclusions can be drawn.

Our findings regarding time spent in the sun during different life periods have important implications for understanding the etiology of this relationship. In this study, we found a lower breast cancer risk for women with ≥1 h of time spent in the sun per day during the summer months during adolescence compared with women with <1 h. In addition to this early exposure window, a protective effect of >1 h/d per day of time spent in the sun during adulthood was observed, this finding could be attributed to the action of vitamin D during adolescence, as well as during the reproductive cycle (Lopes et al. 2012). In mice models, vitamin D receptor (VDR)-knockout mice had improper breast development and reduced apoptosis after cessation of breast feeding (Lopes et al. 2012). In contrast, exposure later in life (≥45 years of age) was not protective against breast cancer. The lack of a relationship observed during this period may be indicative of vitamin D not playing a significant role in slowing tumorigenesis (Lopes et al. 2012).

Despite the lack of studies separating breast cancer cases based on hormone receptor status (two studies), our pooled analysis of these studies revealed an apparent lower risk of ER^+ breast cancer for >1 h spent in the sun per day during adulthood, but not for ER^- breast cancer. A recent systematic review of circulating vitamin D and breast cancer reported no clear relationship for any subtype

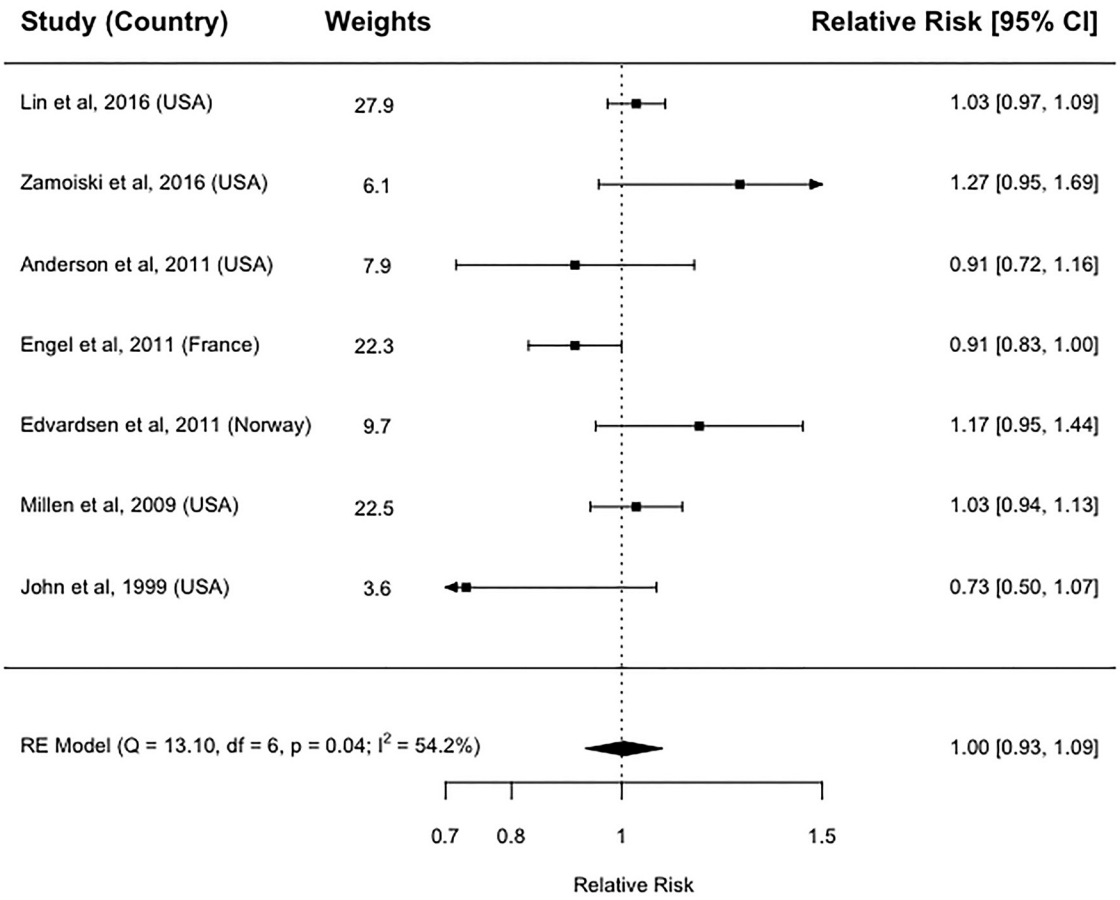

Figure 4. Forest plot and random effects pooled relative risk of developing breast cancer comparing highest and lowest exposure categories of ambient UVR exposure during lifetime or usual adulthood. Ambient UVR is the strength of the sun at a person's place of residence. The black squares represent the effect estimates for each study and the whiskers represent the 95% CIs around these estimates for each study. The black diamond represents the summary effect estimate around 95% CI, with the center being the estimate and the ends being the confidence intervals. The vertical line represents a relative risk of 1. Note: CI, confidence interval; RE, random effects; UVR, ultraviolet radiation.

other than triple-negative breast cancer (Tommie et al. 2018). Clearly, further research is warranted on time spent in the sun, subsequent circulating vitamin D levels, and the risk of different subtypes of breast cancer.

This study suggests that ambient UVR, whether measured in units representing the strength of the sun or based on geographical area, is not associated with breast cancer risk. Ambient UVR is an ecologic measure of the strength of the sun but does not incorporate any element of behavior; therefore, without knowledge of an individual's sun behavior, classifying solar UVR exposure based solely on ambient UVR could misrepresent the exposure. Research from Canada has shown that women are more likely to practice sun safety behaviors when living in an area with higher levels of ambient UVR (Pinault and Fioletov 2017). This finding is important because these individuals would be assigned the highest values of ambient UVR but may be misrepresented in terms of true solar UVR exposure. The potential of ambient UVR in terms of estimating true solar UVR exposure is in combination with time spent in the sun in order to estimate the vitamin D production potential of an individuals' exposure. This combination of ambient exposure and time in the sun has previously only been presented in a single study (Zamoiski et al. 2016), and further evidence is required on this exposure.

In terms of both ambient UVR exposure and time spent in the sun, papers use different units or categories for analysis, which makes combining and collapsing categories difficult. As a result, at times the categories being combined are not identical, but they are similar enough to ensure our confidence in the estimates reported herein. In addition, although the adjustment for confounders in the papers reviewed are generally strong, there is variation among studies that could have resulted in our summary estimates being confounded by other factors. In particular, greater time spent in the sun is associated with higher levels of physical activity; therefore, our estimates could be subject to residual and uncontrolled confounding by physical activity—a strong protective factor for breast cancer. Pertaining to postmenopausal breast

Table 2. Subgroup analyses by different exposure windows for the association between solar UVR exposure and the risk of developing breast cancer.

Subgroup	Estimates (n)	Relative risk (95% CI)	I^2 (%)
≥1 h/d vs. <1 h/d			
Adolescence	3	0.83 (0.71, 0.98)	78.5
Later in life (≥45 years of age)	4	0.97 (0.85, 1.11)	55.2
Dose–response			
Adolescence			
1 to <2 h vs. <1 h	3	0.88 (0.79, 0.99)	0.0
≥2 h vs. <1 h	3	0.72 (0.65, 0.80)	0.0
Later in life (≥45 years of age)			
1 to <2 h vs. <1 h	4	1.00 (0.86, 1.16)	54.0
≥2 h vs. <1 h	4	0.94 (0.85, 1.04)	5.7
Ambient UVR (high exposure vs. low exposure)			
Adolescence	4	0.99 (0.84, 1.17)	54.8
Later in life (≥45 years of age)	2	1.07 (0.77, 1.48)	67.3

Note: Relative risk estimates for each subgroup were estimated with DerSimonian and Laird random-effect models. UVR, ultraviolet radiation.

Table 3. Subgroup analyses based on study quality factors for the association between solar UVR exposure and the risk of developing breast cancer.

Subgroup	Estimates (n)	Relative risk (95% CI)	I^2 (%)	Meta-regression (p-value)
≥1 h/d vs. <1 h/d				
Study design				0.65
Prospective cohort	4	0.82 (0.73, 0.92)	65.2	
Case–control	5	0.85 (0.75, 0.97)	80.3	
Newcastle-Ottawa scores				0.74
Good	5	0.81 (0.72, 0.92)	81.7	
Fair	2	0.92 (0.82, 1.03)	0.0	
Poor	2	0.83 (0.59, 1.15)	30.3	
Control for confounding				0.11
Adequate	5	0.89 (0.82, 0.97)	65.9	
Moderate	2	0.74 (0.61, 0.89)	66.1	
Insufficient	2	0.82 (0.57, 1.18)	73.3	
1 to <2 h/d vs. <1 h/d				
Study design				0.79
Prospective cohort	3	0.84 (0.78, 0.91)	0.0	
Case–control	4	0.80 (0.67, 0.96)	57.0	
Newcastle-Ottawa scores				0.81
Good	5	0.82 (0.74, 0.90)	35.8	
Fair	2	0.84 (0.71, 1.00)	0.0	
Poor	0	NA	NA	
Control for confounding				0.11
Adequate	5	0.85 (0.80, 0.91)	0.0	
Moderate	2	0.72 (0.59, 0.89)	18.1	
Insufficient	0	NA	NA	
≥2 h/d vs. <1 h/d				
Study design				0.89
Prospective cohort	3	0.86 (0.79, 0.93)	12.1	
Case–control	4	0.82 (0.66, 1.02)	88.8	
Newcastle-Ottawa scores				0.6
Good	5	0.81 (0.70, 0.94)	79.2	
Fair	2	0.88 (0.77, 1.00)	32.3	
Poor	0	NA	NA	
Control for confounding				0.17
Adequate	5	0.87 (0.77, 0.98)	72.2	
Moderate	2	0.74 (0.63, 0.88)	45.1	
Insufficient	0	NA	NA	
Ambient UVR (high exposure vs. low exposure)				
Study design				0.47
Prospective cohort	7	1.01 (0.93, 1.10)	59.7	
Case–control	1	0.91 (0.72, 1.16)	NA	
Newcastle-Ottawa scores				0.06
Good	4	0.94 (0.85, 1.04)	46.1	
Fair	2	1.20 (1.02, 1.43)	0.0	
Poor	1	1.03 (0.97, 1.09)	0.0	
Control for confounding				0.29
Adequate	5	0.97 (0.86, 1.09)	24.0	
Moderate	2	1.05 (0.96, 1.16)	58.2	
Insufficient	0	NA	NA	

Note: Relative risk estimates for each subgroup were estimated with DerSimonian and Laird random-effect models. Meta-regression was used to determine whether there were significant differences in the risk of breast cancer by exposure to UVR in different study quality subgroups. NA, not applicable; UVR, ultraviolet radiation.

cancer, an inverse relationship may exist between BMI and time spent in the sun; accordingly, it is possible that the sun exposure and breast cancer relationship in postmenopausal women specifically may be susceptible to residual or uncontrolled confounding by BMI. This meta-analysis is also limited in terms of the subgroup analyses that could be conducted. Previous studies examined different exposure windows; also, few studies have information on ER/PR status of cases. The pooled RRs for adolescence for both personal sun exposure analyses use effect estimates from only three previously published studies; therefore, in order to establish this relationship, more research is required for this exposure window. In addition, the effect of time spent in the sun on the risk of developing breast cancer may vary by latitude, but there was not enough variation to conduct subgroup analyses by latitude. The results of this study are primarily generalizable to women living at northern latitudes (such as North America and Europe). The relationship could be quite different at latitudes closer to the equator, where ambient UVR is much stronger.

Conclusion

To our knowledge, the current study is the first meta-analysis on solar UVR exposure and breast cancer risk. Using previously published literature, this study observed a protective effect of time spent in the sun on breast cancer risk for both exposure during usual adulthood and adolescence. These patterns of time spent in the sun are most likely of the greatest utility in northern countries where the only viable solar UVR exposure for creating vitamin D is present in the summer months. Based on this study, further research should be performed to investigate the competing risk reduction of breast cancer and increased risk of skin cancer conveyed by sun exposure.

Acknowledgments

T.H. is supported by an Empire Life Fellowship and an Ontario Graduate Scholarship. D.E.O. is supported by a Queen Elizabeth II Scholarship and an Empire Life Fellowship. D.R.B. holds a Canadian Cancer Society Cancer Prevention Capacity

Development Award (703917). The authors thank S. McKeown for her thoughtful feedback pertaining to the search strategy.

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