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Supplemental Material

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

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Figure S2. Funnel plot for ambient UVR exposure. The outer dashed lines indicate the triangular region within which 95% of studies are expected to lie in the absence of bias. The solid black line corresponds to the summary effect estimate. The black dots correspond to studies included in this analysis (Edvardsen et al. 2011, Engel et al., 2011, Anderson et al. 2011, John et al. 1999, Millen et al. 2009, Zamoiski et al. 2016, Lin et al. 2012).

References

Search strategies

Database(s): **Ovid MEDLINE(R), Ovid MEDLINE(R) Daily and Epub Ahead of Print, In-Process & Other Non-Indexed Citations** 1946 to Present

Search Strategy:

Searches

- 1 sunlight.mp
- 2 (sun adj4 (exposure or exposed)).mp.
- 3 ultraviolet radiation.mp
- 4 ultraviolet rays.mp.
- 5 UV rays.mp.
- 6 UVB.mp.
- 7 sunbathing.mp.
- 8 sun bathing.mp.
- 9 tanning.mp.
- 10 ultraviolet light.mp.
- 11 sunlight/ or ultraviolet rays/
- 12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
- 13 Breast Neoplasms/
- 14 breast cancer.mp.
- 15 13 or 14
- 16 12 and 15
- 17 limit 16 to (editorial or "review")
- 18 16 not 17

Database(s): **Embase Classic+Embase** 1947 to 2019 April 03

Search Strategy:

Searches

- 1 sunlight.mp.
- 2 (sun adj4 (exposure or exposed)).mp.
- 3 ultraviolet radiation.mp.
- 4 ultraviolet rays.mp.
- 5 UV rays.mp.
- 6 UVB.mp.
- 7 sunbathing.mp.
- 8 sun bathing.mp.

- 9 tanning.mp.
- 10 sun exposure/
- 11 sunlight/
- 12 ultraviolet radiation/ or ultraviolet b radiation/
- 13 ultraviolet light.mp.
- 14 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
- 15 breast cancer.mp.
- 16 breast cancer/
- 17 15 or 16
- 18 14 and 17
- 19 limit 18 to conference abstract
- 20 18 not 19
- 21 limit 20 to (editorial or "review")
- 22 20 not 21

Web of Science:

- 1 **TOPIC:** (sunlight) *OR* **TOPIC:** ((sun NEAR/3 (exposed or exposure))) *OR* **TOPIC:** (tanning) *OR* **TOPIC:** (sun bathing) *OR* **TOPIC:** (sunbathing) *OR* **TOPIC:**(ultraviolet radiation) *OR* **TOPIC:** (ultraviolet light) *OR* **TOPIC:** (ultraviolet rays) *OR* **TOPIC:** (UV rays) *OR* **TOPIC:** (UVB)
- 2 **TOPIC:** (breast cancer)
- 3 2 AND 1
- 4 2 AND 1

Refined by: DOCUMENT TYPES: (ARTICLE)

Newcastle – Ottawa Quality Assessment Scale Case Control Studies

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

- 1) Is the case definition adequate?
 - a) yes, with independent validation *
 - b) yes, eg record linkage or based on self-reports
 - c) no description
- 2) Representativeness of the cases
 - a) consecutive or obviously representative series of cases *
 - b) potential for selection biases or not stated

- 3) Selection of Controls
 - a) community controls *
 - b) hospital controls
 - c) no description
- 4) Definition of Controls
 - a) no history of disease (endpoint) *
 - b) no description of source

Comparability

- 1) Comparability of cases and controls on the basis of the design or analysis
 - a) study controls for _____ (Select the most important factor.) *
 - b) study controls for any additional factor * (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

- 1) Ascertainment of exposure
 - a) secure record (eg surgical records) *
 - b) structured interview where blind to case/control status *
 - c) interview not blinded to case/control status
 - d) written self-report or medical record only
 - e) no description
- 2) Same method of ascertainment for cases and controls
 - a) yes *
 - b) no
- 3) Non-Response rate
 - a) same rate for both groups *
 - b) non respondents described
 - c) rate different and no designation

Newcastle – Ottawa Quality Assessment Scale Cohort Studies

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

- 1) Representativeness of the exposed cohort
 - a) truly representative of the average _____ (describe) in the community *
 - b) somewhat representative of the average _____ in the community *
 - c) selected group of users eg nurses, volunteers
 - d) no description of the derivation of the cohort
- 2) Selection of the non-exposed cohort
 - a) drawn from the same community as the exposed cohort *
 - b) drawn from a different source
 - c) no description of the derivation of the non-exposed cohort

3) Ascertainment of exposure

- a) secure record (eg surgical records) *
- b) structured interview *
- c) written self-report
- d) no description

4) Demonstration that outcome of interest was not present at start of study

- a) yes *
- b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis

- a) study controls for _____ (select the most important factor) *
- b) study controls for any additional factor * (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome

- a) independent blind assessment *
- b) record linkage *
- c) self-report
- d) no description

2) Was follow-up long enough for outcomes to occur

- a) yes (select an adequate follow up period for outcome of interest) *
- b) no

3) Adequacy of follow up of cohorts

- a) complete follow up - all subjects accounted for *
- b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) *
- c) follow up rate < ____ % (select an adequate %) and no description of those lost
- d) no statement

Newcastle – Ottawa Quality Assessment Scale Summary Categorization

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor):

Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

Table S1. Evaluation of study quality and risk of bias for case control studies included in the meta-analyses

Author	Analysis	Case	Representativeness	Controls	Definition	Control for confounding ^a	Exposure	Method	Non-response	Score ^b	Overall Quality ^c
Cauchi et al. 2016	Time spent in the sun	1	0	1	1	0	0	1	0	4	Poor
Bidgoli & Azarshab 2014	Time spent in the sun	1	0	1	1	0	0	1	0	4	Poor
Anderson et al. 2011	Time spent in the sun, Ambient	1	1	1	1	2	0	1	1	8	Good
Knight et al. 2007	Time spent in the sun	1	1	1	1	1	0	1	1	7	Good
John et al. 2007	Time spent in the sun	1	1	1	1	2	0	1	1	8	Good

*All categories were scored based on the Newcastle Ottawa Scale (NOS) with the exception of the category “Control for confounding”, see Supplemental Materials, Newcastle Ottawa Scale Assessment Score Case Control Studies

^aConfounding: adequate control for confounding (adjusted for age, reproductive factors, exogenous hormone use, body mass index, physical activity, alcohol consumption, smoking, and fruit and vegetable consumption; score = 2), moderate (failed to adjust for physical activity or reproductive factors; score = 1), and insufficient (failed to adjust for multiple established and suspected confounders; score = 0). Variables were considered adjusted for if eliminated from the final model through backwards elimination, stepwise selection, or change-in-estimate approaches.

^bThe summary score for each study was calculated by summing the scores from each category

^cStudies were categorized for overall study quality based on the Newcastle Ottawa Scale categorization, see Supplemental Materials, Newcastle Ottawa Scale Summary Categorization

Table S2. Evaluation of study quality and risk of bias for cohort studies included in the meta-analyses

Author	Analysis	Representative	Non-exposed	Exposure	Outcome not present	Control for confounding ^a	Outcome	Follow up	Adequate follow up	Score ^b	Overall Quality ^c
Zamoiski et al. 2016	Time spent in the sun, Ambient	0	1	0	1	2	1	1	1	7	Fair
Engel et al. 2014	Ambient	0	1	0	1	1	1	1	1	6	Fair
Lin et al. 2012	Ambient	0	1	0	0	1	1	1	1	5	Poor
Engel et al. 2011	Ambient	0	1	1	1	2	1	1	1	8	Good
Edvardsen et al. 2010	Ambient	1	1	0	0	1	1	1	1	6	Fair
Millen et al. 2009	Time spent in the sun, Ambient	1	1	0	1	2	1	1	1	8	Good
John et al. 1999	Time spent in the sun, Ambient	1	1	1	1	2	0	1	1	8	Good

*All categories were scored based on the Newcastle Ottawa Scale (NOS) with the exception of the category “Control for confounding”, see Supplemental Materials, Newcastle Ottawa Scale Assessment Score Cohort Studies

^aConfounding: adequate control for confounding (adjusted for age, reproductive factors, exogenous hormone use, body mass index, physical activity, alcohol consumption, smoking, and fruit and vegetable consumption; score = 2), moderate (failed to adjust for physical activity or reproductive factors; score = 1), and insufficient (failed to adjust for multiple established and suspected confounders; score = 0). Variables were considered adjusted for if eliminated from the final model through backwards elimination, stepwise selection, or change-in-estimate approaches.

^bThe summary score for each study was calculated by summing the scores from each category

^cStudies were categorized for overall study quality based on the Newcastle Ottawa Scale categorization, see Supplemental Materials, Newcastle Ottawa Scale Summary Categorization

Table S3. Sensitivity analyses investigating the effects of assumptions made in time spent in the sun analyses.

	Estimates (n)	Relative Risk (95% CI)	I ²
<u>≥ 1 hour/day vs. < 1 hour/day</u>			
Overall	9	0.84 (0.77, 0.91)	73.6%
Excluding John et al. 1999	8	0.86 (0.79, 0.93)	68.6%
Excluding studies with referent group other than < 1hr/day*	4	0.89 (0.84,0.94)	0.0%
<u>1 to < 2 hours/day vs. < 1 hour/day</u>			
Overall	7	0.83 (0.78, 0.89)	8.3%
Excluding John et al. 1999	6	0.84 (0.79, 0.90)	3.6%
Excluding studies with referent group other than < 1hr/day*	3	0.83 (0.73, 0.93)	0.0%
<u>≥2 hours/day vs. < 1 hour/day</u>			
Overall	7	0.83 (0.75, 0.93)	71.9%
Excluding John et al. 1999	6	0.84 (0.76, 0.94)	74.8%
Excluding studies with referent group other than < 1hr/day*	3	0.83 (0.75, 0.94)	53.0%

*Anderson et al. 2011, Cauchi et al. 2016, Engel et al. 2014, Zamoiski et al. 2016
 Relative risk estimates for each subgroup were estimated with DerSimonian and Laird random-effect models.
 Heterogeneity was determined by I^2 statistic.

Table S4. Studies included in each of the analyses of time spent in the sun stratified by exposure window.

Subgroup	Estimates (n)	Studies
<u>≥ 1 hour/day vs. < 1 hour/day</u>		
Adolescence	3	Knight et al. 2007, Anderson et al. 2011, Zamoiski et al. 2016
Later in life (≥ 45 years of age)	3	Knight et al. 2007, Anderson et al. 2011, Zamoiski et al. 2016
<u>Dose-response</u>		
Adolescence		
1 to < 2 hour/day vs. < 1 hour/day	3	Knight et al. 2007, Anderson et al. 2011, Zamoiski et al. 2016
≥ 2 hours/day vs. < 1 hour/day	3	Knight et al. 2007, Anderson et al. 2011, Zamoiski et al. 2016
Later in life (≥ 45 years of age)		
1 to < 2 hour/day vs. < 1 hour/day	3	Knight et al. 2007, Anderson et al. 2011, Zamoiski et al. 2016
≥ 2 hours/day vs. < 1 hour/day	3	Knight et al. 2007, Anderson et al. 2011, Zamoiski et al. 2016
<u>Ambient UVR (high exposure vs. low exposure)</u>		
Adolescence	4	John et al. 1999, Millen et al. 2009, Anderson et al. 2011, Zamoiski et al. 2016
Later in life (≥ 45 years of age)	2	Anderson et al. 2011, Zamoiski et al. 2016

Table S5. Studies included in the subgroup analyses by study quality factors

Subgroup	Estimates (n)	Studies
<u>≥ 1 hour/day vs. < 1 hour/day</u>		
Study Design		
Prospective cohort	4	John et al. 1999, Millen et al. 2009, Engel et al. 2014, Zamoiski et al. 2016
Case-control	5	Knight et al. 2007, John et al. 2007, Anderson et al. 2011, Bidgoli & Azarshab 2014, Cauchi et al. 2016
Control for confounding		
Adequate	5	John et al. 1999, John et al. 2007, Millen et al. 2009, Anderson et al. 2011, Zamoiski et al. 2016
Moderate	2	Knight et al. 2007, Engel et al. 2014
Insufficient	2	Bidgoli & Azarshab 2014, Cauchi et al. 2016
Newcastle-Ottawa scores		
Good	5	John et al. 1999, John et al. 2007, Knight et al. 2007, Millen et al. 2009, Anderson et al. 2011
Fair	2	Engel et al. 2014, Zamoiski et al. 2016
Poor	2	Bidgoli & Azarshab 2014, Cauchi et al. 2016
<u>1 to < 2 hours/day vs. < 1 hour/day</u>		
Study Design		
Prospective cohort	4	Zamoiski et al. 2016, Engel et al. 2014, John et al. 1999, Millen et al. 2009
Case-control	3	Anderson et al. 2011, John et al. 2007, Knight et al. 2007
Newcastle-Ottawa scores		
Good	5	Anderson et al. 2011, Knight et al. 2007, John et al. 1999, John et al. 2007, Millen et al. 2009
Fair	2	Zamoiski et al. 2016, Engel et al. 2014

Control for confounding

Adequate	5	Zamoiski et al. 2016, John et al. 1999, John et al. 2007, Millen et al. 2009, Anderson et al. 2011
Moderate	2	Knight, et al. 2007, Engel et al. 2014
Insufficient	0	NA

≥ 2 hours/day < 1 hour/day

Study Design

Prospective cohort	4	Zamoiski et al. 2016, Engel et al. 2014, John et al. 1999, Millen et al. 2009
Case-control	3	Anderson et al. 2011, John et al. 2007, Knight et al. 2007

Control for confounding

Adequate	5	Zamoiski et al. 2016, John et al. 1999, John et al. 2007, Millen et al. 2009, Anderson et al. 2011
Moderate	2	Knight et al. 2007, Engel et al. 2014
Insufficient	0	NA

Newcastle-Ottawa scores

Good	5	Anderson et al. 2011, Knight et al. 2007, John et al. 1999, John et al. 2007, Millen et al. 2009
Fair	2	Zamoiski et al. 2016, Engel et al. 2014
Poor	0	NA

Ambient UVR (high exposure vs. low exposure)

Study Design

Prospective cohort	6	Zamoiski et al. 2016, Lin et al. 2011, Edvardsen et al. 2011, Engel et al. 2011, John et al. 1999, Millen et al. 2009
Case-control	1	Anderson et al. 2011

Control for confounding

Adequate	5	Zamoiski et al. 2016, Anderson et al. 2011, Engel et al. 2011, John et al. 1999, Millen et al. 2009
Moderate	2	Lin et al. 2012, Edvardsen et al. 2011
Insufficient	0	NA

Newcastle-Ottawa scores

Good	4	Millen et al. 2009, Anderson et al. 2011, Engel et al. 2011, John et al. 1999
Fair	2	Zamoiski et al. 2016, Edvardsen et al. 2011
Poor	1	Lin et al. 2012

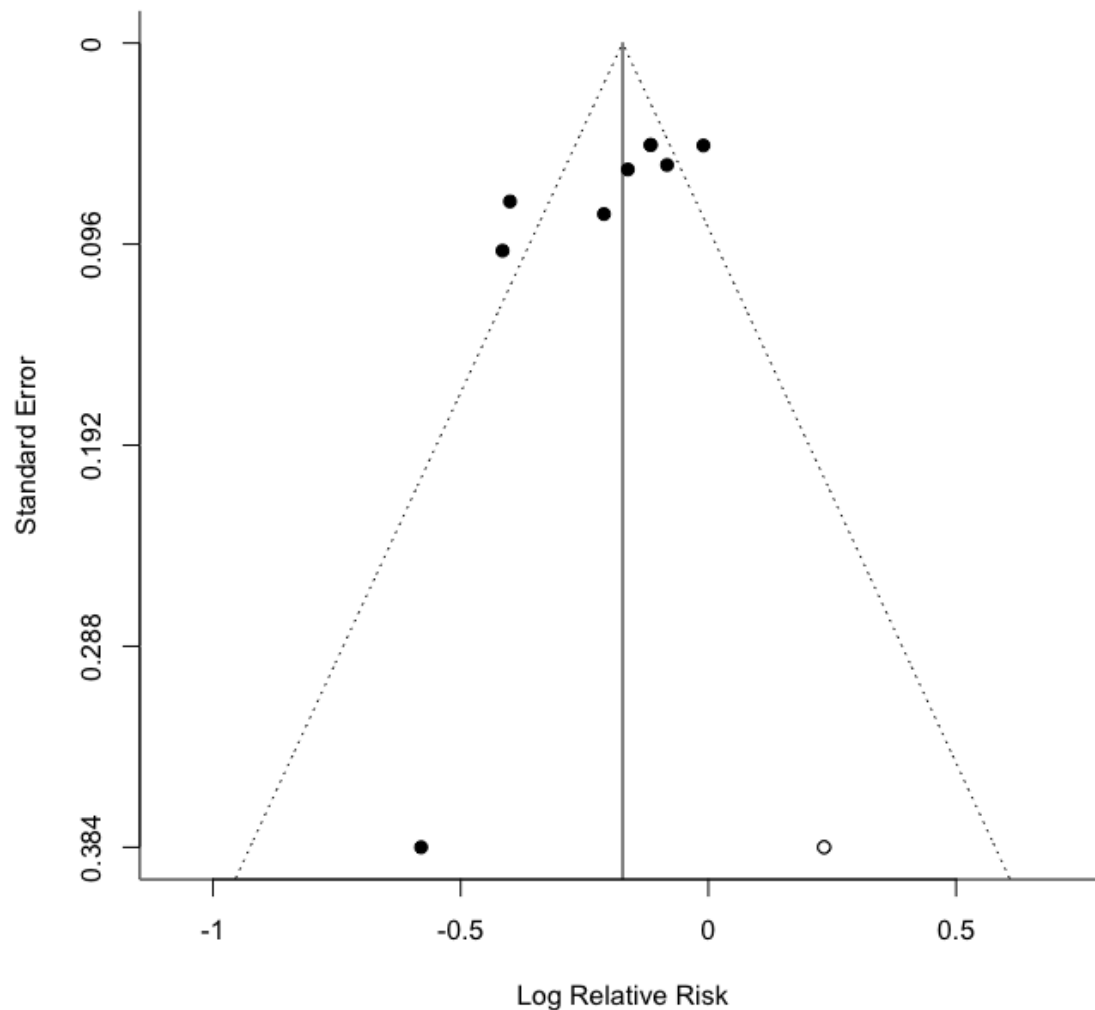


Figure S1. Funnel plot for lifetime < 1 vs ≥ 1 hour spent in the sun per day.

The outer dashed lines indicate the triangular region within which 95% of studies are expected to lie in the absence of bias. The solid black line corresponds to the summary effect estimate. The black dots correspond to studies included in this analysis (Knight et al. 2007, Anderson et al. 2011, John et al. 1999, John et al. 2007, Millen et al. 2009, Engel et al. 2014, Bidgoli & Azarshab 2014, Cauchi et al. 2016, Zamoiski et al. 2016). The white dot corresponds to one unpublished study suggested by the trim and fill method.

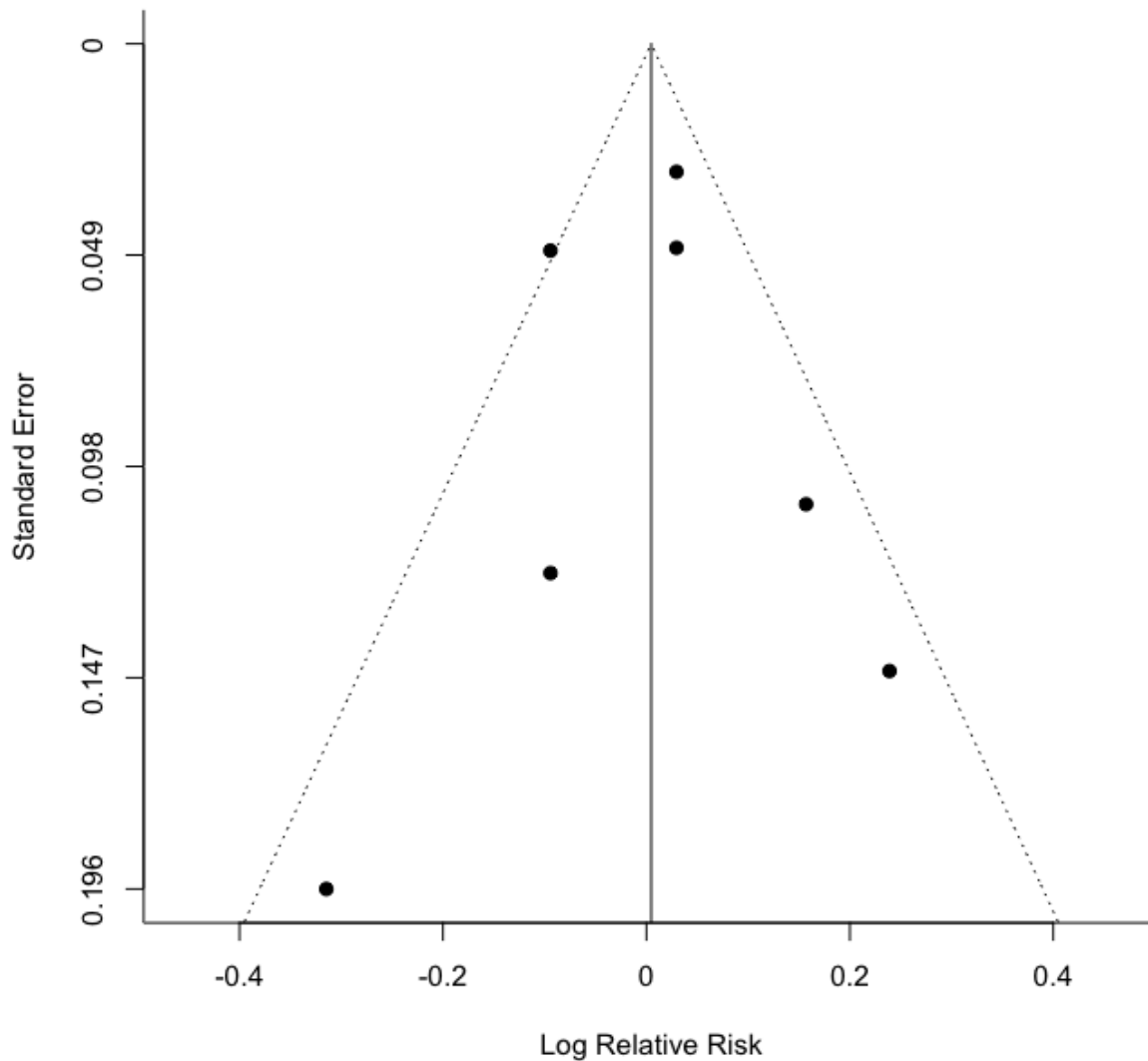


Figure S2. Funnel plot for ambient UVR exposure.

The outer dashed lines indicate the triangular region within which 95% of studies are expected to lie in the absence of bias. The solid black line corresponds to the summary effect estimate. The black dots correspond to studies included in this analysis (Edvardsen et al. 2011, Engel et al.,

2011, Anderson et al. 2011, John et al. 1999, Millen et al. 2009, Zamoiski et al. 2016, Lin et al. 2012).

References

- Anderson, L. N., Cotterchio, M., Kirsh, V. A., & Knight, J. A. (2011). Ultraviolet Sunlight Exposure During Adolescence and Adulthood and Breast Cancer Risk: A Population-based Case-Control Study Among Ontario Women. *American Journal of Epidemiology*, *174*(3), 293–304. <https://doi.org/10.1093/aje/kwr091>
- Bidgoli, S. A., & Azarshab, H. (2014). Role of Vitamin D Deficiency and Lack of Sun Exposure in the Incidence of Premenopausal Breast Cancer: a Case Control Study in Sabzevar, Iran. *Asian Pacific Journal of Cancer Prevention*, *15*(8), 3391–3396. <https://doi.org/10.7314/APJCP.2014.15.8.3391>
- Cauchi, J. P., Camilleri, L., & Scerri, C. (2016). Environmental and lifestyle risk factors of breast cancer in Malta—a retrospective case-control study. *The EPMA Journal*, *7*(1), 20. <https://doi.org/10.1186/s13167-016-0069-z>
- Edvardsen, K., Veierd, M. B., Brustad, M., Braaten, T., Engelsen, O., & Lund, E. (2011). Vitamin D-effective solar UV radiation, dietary vitamin D and breast cancer risk. *International Journal of Cancer*, *128*(6), 1425–1433. <https://doi.org/10.1002/ijc.25463>
- Engel, L. S., Satagopan, J., Sima, C. S., Orlow, I., Mujumdar, U., Coble, J., ... Alavanja, M. C. (2014). Sun exposure, vitamin D receptor genetic variants, and risk of breast cancer in the agricultural health study. *Environmental Health Perspectives*, *122*, 165. Retrieved from <http://link.galegroup.com/apps/doc/A362064434/AONE?u=queensulaw&sid=AONE&xid=>

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- Engel, P., Fagherazzi, G., Mesrine, S., Boutron-Ruault, M., & Clavel-Chapelon, F. (2011). Joint Effects of Dietary Vitamin D and Sun Exposure on Breast Cancer Risk: Results from the French E3N Cohort. *Cancer Epidemiol Biomarkers Prev*, 20(1), 187. Retrieved from <http://cebp.aacrjournals.org/content/20/1/187.abstract>
- John, E. M., Schwartz, G. G., Dreon, D. M., & Koo, J. (1999). Vitamin D and Breast Cancer Risk: The NHANES I Epidemiologic Follow-up Study, 1971–1975 to 1992. *Cancer Epidemiol Biomarkers Prev*, 8(5), 399. Retrieved from <http://cebp.aacrjournals.org/content/8/5/399.abstract>
- John, E. M., Schwartz, G. G., Koo, J., Wang, W., & Ingles, S. A. (2007). Sun Exposure, Vitamin D Receptor Gene Polymorphisms, and Breast Cancer Risk in a Multiethnic Population. *American Journal of Epidemiology*, 166(12), 1409–1419. Retrieved from <http://dx.doi.org/10.1093/aje/kwm259>
- Knight, J. A., Lesosky, M., Barnett, H., Raboud, J. M., & Vieth, R. (2007). Vitamin D and Reduced Risk of Breast Cancer: A Population-Based Case-Control Study. *Cancer Epidemiol Biomarkers Prev*, 16(3), 422. Retrieved from <http://cebp.aacrjournals.org/content/16/3/422.abstract>
- Lin, S.-W., Wheeler, D. C., Park, Y., Cahoon, E. K., Hollenbeck, A. R., Freedman, D. M., & Abnet, C. C. (2012). Prospective study of ultraviolet radiation exposure and risk of cancer in the United States. *International Journal of Cancer*, 131(6), E1023. <https://doi.org/10.1002/ijc.27619>
- Millen, A. E., Pettinger, M., Freudenheim, J. L., Langer, R. D., Rosenberg, C. A., Mossavar-Rahmani, Y., ... Wactawski-Wende, J. (2009). Incident Invasive Breast Cancer, Geographic

Location of Residence, and Reported Average Time Spent Outside. *Cancer Epidemiol Biomarkers Prev*, 18(2), 495. Retrieved from

<http://cebp.aacrjournals.org/content/18/2/495.abstract>

Zamoiski, R. D., Freedman, D. M., Linet, M. S., Kitahara, C. M., Liu, W., & Cahoon, E. K.

(2016). Prospective study of ultraviolet radiation exposure and risk of breast cancer in the United States. *Environmental Research*.

<https://doi.org/10.1016/j.envres.2016.08.013>