# Estimation of the Impact of Caffeine on Skin Cancer Prevention:

# A Meta-Analysis

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**Abstract**

Purpose: *In vivo* and *in vitro* studies demonstrate a protective effect of caffeine on skin cancer. However, epidemiologic data on both nonmelanoma skin cancer (NMSC) and melanoma are conflicting. We aimed to clarify this association in addition to using these data to estimate the number of skin cancers prevented and cost saved annually in the United States.

Methods: A literature review and meta-analysis of observational studies published until June 30th, 2019 that examined the association between coffee or tea intake and NMSC or melanoma risk was performed. The DerSimonian and Laird method of the random effects model was used to calculate summary relative risk (SRR) and 95% confidence intervals (95% CI).

Results: We summarized 22 papers with 47,593 cases of NMSC and melanoma. An inverse association was found between caffeinated beverage intake and skin cancer with an overall SRR (95% CI) of 0.82 (0.76-0.88). Caffeinated coffee had the largest effect with an SRR of 0.78 (0.68-0.87), where decaffeinated coffee did not show an effect (0.98 (0.91-1.06)). Tea had less pronounced effect (0.85 (0.77-0.93)). The skin cancer-type SRRs were 0.88 (0.81-0.95) for basal cell carcinoma (BCC), 0.81 (0.69-0.93) for melanoma, 0.77(0.59-0.94) for squamous cell carcinoma (SCC), and 0.77 (0.59-0.95) for NMSC. The SRR for all coffee was 0.79 (0.72-0.87) which we used to calculate that 196,344 skin cancers are prevented annually, and 289 million dollars are saved annually by consuming coffee.

Conclusions*:* This meta-analysis suggests that caffeine lessens the burden of skin cancer. However, additional studies are needed to further clarify the dose needed for prevention and to examine whether caffeine should be an ingredient in sunscreen.

**Introduction**

Skin cancer is the most common malignancy in the United States, and the number of cases annually surpasses all other malignancies combined. The incidence of nonmelanoma skin cancer (NMSC) was estimated to be 5.4 million cases in the U.S. population in 2012 and doubled over ten years.[1] NMSC has two main types: basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Melanoma incidence was 66,000 in 2011, and that rate doubled since 1982.[2] In addition to increasing incidence, the costs of treating skin cancer have also risen. The average annual cost of treating skin cancer in 2011 was $8.1 billion and increased by $4.5 billion over the course of nine years.[3] Average annual cost per person went from $1,044 to $1,643 in the same time period. With projections of increasing cost and incidence, there is a need for new prevention approaches and treatments for skin cancer.

A well-documented risk factor for NMSC and melanoma is exposure to ultraviolet radiation (UVR), specifically UVB (280-315 nm). However, studies have recently discovered a potential connection between caffeine and skin cancer. Early *in vivo* studies demonstrated inhibition of UVB-induced carcinogenesis, including formation of thymine dimers, by pre-treating mouse models with topical caffeine prior to irradiation with UVB.[4,5] Oral administration of green and black tea was also shown to inhibit UVB-induced carcinogenesis in SKH-1 hairless mice, whereas the decaffeinated versions did not.[6] However, adding caffeine back into the decaffeinated tea re-established its anti-carcinogenic effects. SKH-1 mice that were pretreated with oral green tea or caffeine had increased p53-positive cells, p21-positive cells, and apoptotic sunburn cells after UVB irradiation.[7] Mice administered coffee exhibited the same effect, and these treatments had no effect without irradiation.[8]

Caffeine is known to target multiple enzymes including the ataxia-telangiectasia and Rad3-related (ATR) kinase, a pivotal kinase that senses UV-induced DNA damage. Caffeine-treated human keratinocytes have decreased ATR-mediated induction of phosphorylated Chk1 (Ser345) and increased apoptosis with UVB irradiation.[9] When inhibiting ATR with siRNA, apoptosis was augmented, but not any further with addition of caffeine, indicating that the primary mechanism in which caffeine amplifies UVB-induced apoptosis is through inhibition of the ATR pathway. Transgenic mice with decreased ATR function had 69% fewer tumors with chronic UVB treatment.[10]

Several epidemiological studies have shown a decreased risk of melanoma and NMSC with caffeinated beverage consumption.[11-25] A large cross-sectional study with nearly 94,000 women found a 5% decreased risk of NMSC with each daily cup of caffeinated coffee, but no significant change in risk with decaffeinated coffee or tea.[11] Other studies on caffeinated coffee replicated this result leading to the conclusion that the caffeine, but not alternative components of coffee, exerts protective effects. Conversely, there have been epidemiologic studies that demonstrate no effect of caffeine on skin cancer.[26-32] Furthermore, it is unknown whether caffeine in coffee and/or tea demonstrates a decreased risk in both types of NMSC as well as melanoma. Thus, we summarized previous data and used these to estimate how many skin cancers are prevented annually in the U.S., in addition to how much cost could be saved annually by drinking coffee or tea. This information could potentially answer the previously posed question: should caffeine be an ingredient in sunscreen?

Prior systematic reviews and meta-analyses show a decreased risk of skin cancer with caffeine consumption: two reviews on NMSC and five on melanoma.[33-39] Majority of these

summarized data from less than ten articles. To our knowledge, the present study is the first meta-analysis that contains data about NMSC and melanoma, in addition to coffee and tea, with 22 original articles.

## Methods

### Databases and Search Strategy

A comprehensive search of PubMed, Scopus, and EMBASE was performed. Search terms contained: (1) caffeine OR coffee OR tea AND (2) intake OR consumption OR drinking AND (3) melanoma OR non-melanoma skin cancer OR basal cell carcinoma OR squamous cell carcinoma OR skin cancer AND (4) risk OR incidence OR prevalence (Table 1). Articles were included up to the date June 30$^{th}$, 2019 without a specified start date. Filters for English language and human studies were applied. This strategy was discussed and reviewed with a health sciences librarian. The search was extended to the references of selected articles. Results were uploaded to Covidence to detect duplications and aid in the selection process.[40] The PRISMA chart (Figure 1) displays the search and elimination process.

**Table 1:** Search Strategy

| | |
|---|---|
| PubMed | ((("caffeine"[MeSH Terms] OR ("coffee"[MeSH Terms]) OR ("tea"[MeSH Terms]) AND (intake[All Fields]) OR ("consumption"[All Fields]) OR ("drinking"[MeSH Terms]) AND (("melanoma"[MeSH Terms]) OR ("skin neoplasms"[MeSH Terms]) OR ("skin cancer"[All Fields]) OR ("carcinoma, basal cell"[MeSH Terms]) OR ("carcinoma, squamous cell"[MeSH Terms]) OR (non-melanoma[All Fields] AND ("skin neoplasms"[MeSH Terms]) AND (("prevalence"[MeSH Terms]) OR ("incidence"[MeSH Terms]) OR ("risk"[MeSH Terms]) AND ("humans"[MeSH Terms] AND English[lang]) |

| | |
|---|---|
| Embase | ('caffeine'/exp OR 'caffeine' OR 'coffee'/exp OR 'coffee' OR 'tea'/exp OR 'tea') AND ('drinking'/exp OR 'drinking' OR 'consumption'/exp OR 'consumption' OR 'intake') AND ('melanoma'/exp OR 'melanoma' OR 'skin cancer'/exp OR 'skin cancer' OR 'non melanoma skin cancer'/exp OR 'non melanoma skin cancer' OR 'basal cell carcinoma'/exp OR 'basal cell carcinoma' OR 'squamous cell carcinoma'/exp OR 'squamous cell carcinoma') AND ('prevalence' OR 'risk' OR 'incidence') AND 'human'/de AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) AND [english]/lim |
| Scopus | ( ( *"caffeine"* OR *"coffee"* OR *"tea"* ) AND ( *"drinking"* OR *"consumption"* OR *"intake"* ) ) AND ( ( *"melanoma"* OR *"non-melanoma skin cancer"* OR *"skin cancer"* OR *"basal cell carcinoma"* OR *"squamous cell carcinoma"* ) AND ( *"prevalence"* OR *"risk"* OR *"incidence"* ) ) AND NOT INDEX ( *medline* ) AND ( LIMIT TO ( EXACTKEYWORD , *"Human"* ) ) AND ( LIMIT TO ( LANGUAGE , *"English"* )) |

**Inclusion and Exclusion Criteria**

Epidemiologic studies were included if the exposure was caffeine and the outcome was skin cancer. They also needed to include a measure of relative risk (RR) (including odds ratio, risk ratio, or hazard ratio) with 95% confidence intervals (CIs). Studies were excluded if they used other forms of caffeine such as chocolate or soda under the assumption that the majority of caffeine consumed comes from coffee or tea. Abstracts and review articles were also excluded.

**Data Abstraction**

Studies were initially selected according to their titles and abstracts, then assessed for eligibility after a full text review. Due to the fact that studies differed in the amount of coffee or tea they compared, the RR was extracted that compared the highest intake to the lowest intake of caffeine including coffee, tea, and/or decaffeinated coffee, as well as the RR with the greatest degree of adjustment. If studies had overlapping study populations, only the most recent article was included. Other data extracted include: first author name, location of study,

years of study, and year of publication, study design, study size, comparison of beverage intake, skin cancer type, and beverage type.

**Assessment of Bias**

Quality of the studies was measured using the Newcastle-Ottawa Scale (NOS).[41] Age, sex, and risk factors for skin cancer such as UV exposure or skin type were considered as important confounders to be adjusted for. Articles that received a score less than 5 were considered to have a high risk of bias and not included in the meta-analysis. The Egger test, Begg test, and trim-and-fill method were used to assess for publication bias.[42-44]

**Statistical Analysis**

The odds ratios were approximated as relative risks due to the low incidence of skin cancer. The summary relative risk (SRR) was calculated using the DerSimonian and Laird random effects model. The SRR was also calculated for the subgroups of skin cancer type (BCC, SCC, NMSC, and melanoma) as well as for beverage type (caffeinated coffee, decaffeinated coffee, all coffee, and tea). Heterogeneity was assessed using the $I^2$ statistic. $I^2$ is in-between 0% and 100%, and $I^2$ values of 25, 50 and 75% represent low, moderate and high heterogeneity, respectively.[45] All analyses were calculated using STATA software (StataCorp LLC).[46]

**Results**

A comprehensive search of PubMed, Scopus, and EMBASE returned 1,219 results, of which 458 were excluded as duplicates. 760 titles and abstracts were reviewed, and 704 were deemed irrelevant. The full text of 56 papers was examined, and 28 were excluded for failing to

adhere to the inclusion criteria. Four studies had overlapping patient populations, thus the two that were published most recently were included. After the quality assessment, six additional studies were excluded due to a high risk of bias as assessed by the Newcastle-Ottawa Scale. This resulted in 22 total studies to be analyzed.[11-32] Figure 1 illustrates the literature review strategy.

**Figure 1:** Flow diagram of the literature search (conducted on June 30th, 2019) and study selection process.

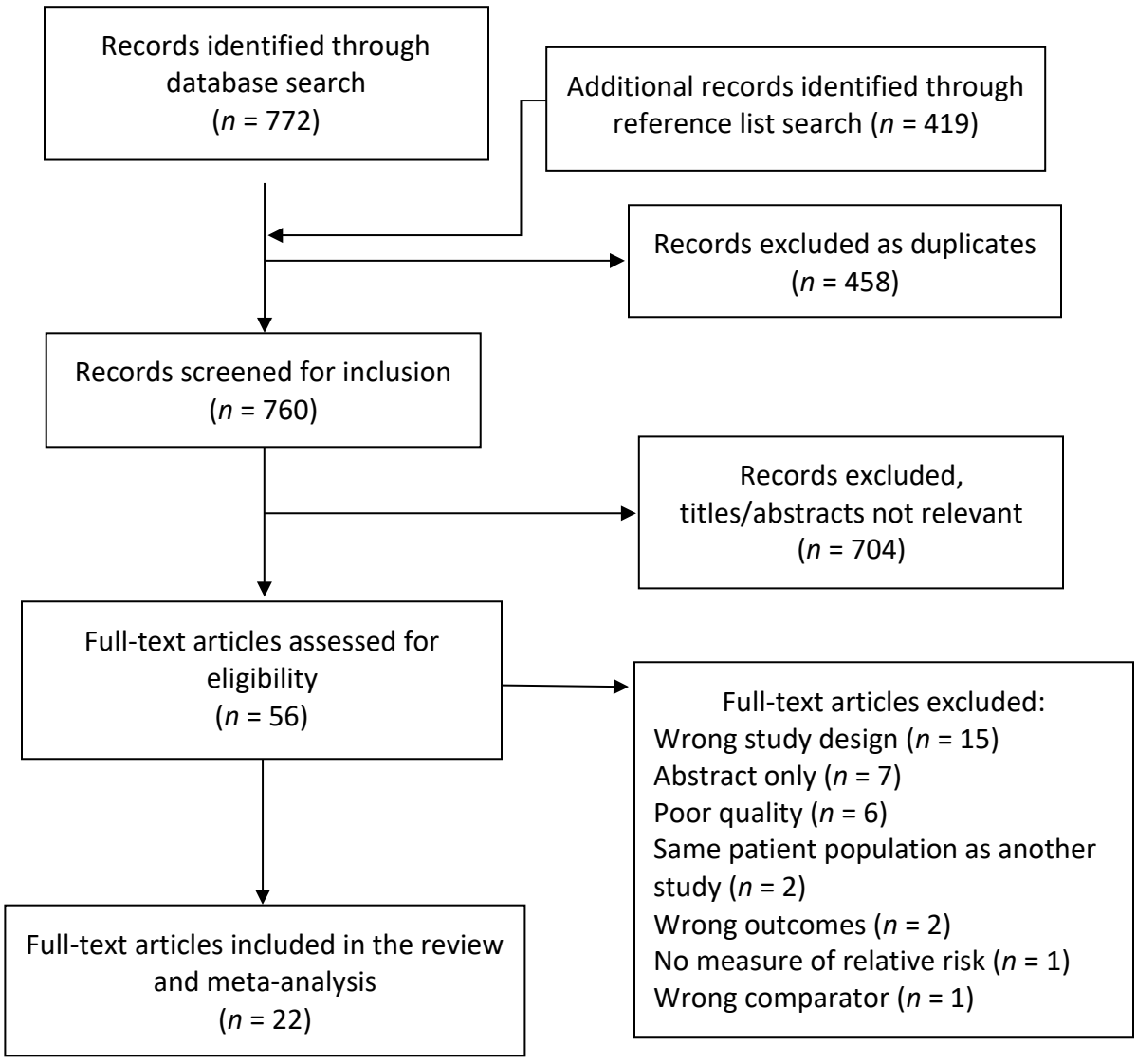


**Table 1A:** Characteristics of Studies Meeting Inclusion Criteria on Caffeinated Coffee

| REFERENCES | COUNTRY | STUDY YEAR | STUDY TYPE AND POPULATION | SKIN CANCER TYPE | COMPARISON | RR | 95% CI | ADJUSTED FOR AGE AND SEX | ADJUSTED FOR A SKIN CANCER RISK FACTOR[A] | NEWCASTLE-OTTAWA SCORE |
|---|---|---|---|---|---|---|---|---|---|---|
| **CAFFEINATED COFFEE** | | | | | | | | | | |
| **Abel et al.**[11] **2007** | USA | 1993-1998 | Cross-sectional Cases: 7482 | NMSC | ≥6 cups/day vs. none | 0.7 | 0.6-0.88 | ✓ | ✓ | 6 |
| **Caini et al.**[12] **2017** **Men** | Europe | 1992–2000 | Cohort Cases: 2712 Cohort: 476160 | Melanoma | Highest quartile vs. non-drinkers | 0.29 | 0.12-0.69 | ✓ | ✓ | 7 |
| **Caini et al.**[12] **2017** **Women** | Europe | 1992–2000 | Cohort Cases: 2712 Cohort: 476160 | Melanoma | Highest quartile vs. non-drinkers | 0.93 | 0.60-1.43 | ✓ | ✓ | 7 |
| **Ferrucci et al.**[13] **2013** | USA | 2006-2010 | Case control Cases: 377 Controls: 390 | BCC | ≥2 cups/day vs. none | 0.70 | 0.47–1.06 | ✓ | ✓ | 7 |
| **Loftfield et al.** [14] **2015** | USA | 1995-1996 | Cohort Cases: 2904 Cohort: 447357 | Melanoma | ≥4 cups/day vs. none | 0.75 | 0.64-0.89 | ✓ | ✓ | 7 |
| **Miura et al. 2014**[26] | Australia | 1992-1996 | Cohort Cases: 493 Cohort: 1325 | BCC | ≥2 cups/day vs. none | 0.92 | 0.67-1.28 | ✓ | ✓ | 6 |
| **Miura et al. 2014**[26] | Australia | 1992-1996 | Cohort Cases: 493 Cohort: 1325 | SCC | ≥2 cups/day vs. none | 1.17 | 0.71-1.91 | ✓ | ✓ | 6 |
| **Naldi et al.**[24] **2004** | Italy | 1992-1994 | Case control Cases: 542 Controls: 538 | Melanoma | ≥4 vs. <1 cup/day | 1.15 | 0.68-1.92 | ✓ | ✓ | 7 |
| **Song et al.**[15] **2012** **Men** | USA | 1984-2006 | Cohort Cases: 25480 Cohort: 112897 | BCC | >3 cups/day vs <1 cup/month | 0.90 | 0.80-1.01 | ✓ | ✓ | 5 |
| **Song et al.**[15] **2012** **Women** | USA | 1986-2006 | Cohort Cases: 25480 Cohort: 112897 | BCC | >3 cups/day vs <1 cup/month | 0.79 | 0.74-0.85 | ✓ | ✓ | 5 |

[A] Region of residence, recreational physical activity, freckles on face, actinic keratoses, family history of skin cancer, skin phototype, indoor tanning, etc.

**Table 1B:** Characteristics of Studies Meeting Inclusion Criteria on All Coffee

| REFERENCES | COUNTRY | STUDY YEAR | STUDY TYPE | SKIN CANCER TYPE | COMPARISON | RR | 95% CI | ADJUSTED FOR AGE AND SEX | ADJUSTED FOR A SKIN CANCER RISK FACTOR[A] | NEWCASTLE-OTTAWA SCORE |
|---|---|---|---|---|---|---|---|---|---|---|
| **ALL COFFEE** | | | | | | | | | | |
| **Corona et al.[22] 2001** | Italy | 1995-1997 | Case control Cases: 166 Controls: 158 | BCC | Drinker vs. non-drinker | 1.8 | 0.8-4.0 | ✓ | | 5 |
| **Fortes et al.[16] 2013** | Italy | 2001-2003 | Case Control Cases: 304 Controls: 305 | Melanoma | >once daily vs. ≤7 times weekly | 0.46 | 0.31-0.68 | ✓ | ✓ | 6 |
| **Jacobsen et al.[17] 1986** | Norway | 1964-1969 | Cohort Cases: 357 Cohort: 16555 | NMSC | ≥7 vs. ≤2 cups/day | 0.56 | 0.36–0.87 | ✓ | | 5 |
| **Jacobsen et al.[17] 1986** | Norway | 1964-1969 | Cohort Cases: 357 Cohort: 16555 | Melanoma | ≥7 vs. ≤2 cups/day | 2.63 | 0.52-4.45 | ✓ | | 5 |
| **Lukic et al.[18] 2016** | Norway | 1991-1992, 1996-1997, and 2003-2004 | Cohort Cases: 762 Cohort: 104,080 | Melanoma | >5 cups vs. ≤1 cup/day | 0.88 | 0.67-1.14 | | ✓ | 5 |
| **Nilsson et al.[28] 2010** | Sweden | 1992-2007 | Cohort Cases: 108 Cohort: 64603 | Melanoma | ≥4 vs. <1 occasions/day | 0.97 | 0.50-1.89 | ✓ | | 5 |
| **Oh et al.[19] 2019** | Singapore | 1993-1998 | Cohort Cases: 609 Cohort: 63257 | BCC | ≥3 cups/day vs. <weekly | 0.54 | 0.31-0.93 | ✓ | | 6 |
| **Oh et al.[19] 2019** | Singapore | 1993-1998 | Cohort Cases: 609 Cohort: 63257 | SCC | ≥3 cups/day vs. <weekly | 0.33 | 0.13-0.85 | ✓ | | 6 |
| **Østerlind et al.[20] 1998** | Denmark | 1982-1985 | Case control Cases: 474 Controls: 926 | Melanoma | High vs. low consumption level | 0.7 | 0.5-1.0 | ✓ | ✓ | 7 |
| **Veirerød et al.[21] 1997 Men** | Norway | 1977–1983 | Cohort Cases: 108 Cohort: 50757 | Melanoma | ≥7 vs. ≤2 cups/day | 1.5 | 0.5-4.6 | ✓ | | 6 |
| **Veirerød et al.[21] 1997 Women** | Norway | 1977–1983 | Cohort Cases: 108 Cohort: 50757 | Melanoma | ≥7 vs. ≤2 cups/day | 0.4 | 0.2-0.9 | ✓ | | 6 |

[A] Region of residence, recreational physical activity, freckles on face, actinic keratoses, family history of skin cancer, skin phototype, indoor tanning, etc.

**Table 1C:** Characteristics of Studies Meeting Inclusion Criteria on Decaffeinated Coffee

| REFERENCES | COUNTRY | STUDY YEAR | STUDY TYPE | SKIN CANCER TYPE | COMPARISON | RR | 95% CI | ADJUSTED FOR AGE AND SEX | ADJUSTED FOR A SKIN CANCER RISK FACTOR[A] | NEWCASTLE-OTTAWA SCORE |
|---|---|---|---|---|---|---|---|---|---|---|
| **DECAFFEINATED COFFEE** | | | | | | | | | | |
| **Abel et al.**[11] **2007** | USA | 1993-1998 | Cross-sectional Cases: 7482 | NMSC | ≥6 cups/day vs. none | 1.08 | 0.80-1.46 | ✓ | ✓ | 6 |
| **Caini et al.**[12] **2017 Men** | Europe | 1992–2000 | Cohort Cases: 2712 Cohort: 476160 | Melanoma | Highest quartile vs. non-drinkers | 0.84 | 0.35-2.05 | ✓ | ✓ | 7 |
| **Caini et al.**[12] **2017 Women** | Europe | 1992–2000 | Cohort Cases: 2712 Cohort: 476160 | Melanoma | Highest quartile vs. non-drinkers | 1.05 | 0.63-1.74 | ✓ | ✓ | 7 |
| **Loftfield et al.**[14] **2015** | USA | 1995-1996 | Cohort Cases: 2904 Cohort: 447357 | Melanoma | ≥4 cups/day vs. none | 0.95 | 0.76-1.18 | ✓ | ✓ | 7 |
| **Miura et al. 2014**[26] | Australia | 1992-1996 | Cohort Cases: 493 Cohort: 1325 | BCC | ≥2 cups/day vs. none | 1.05 | 0.73-1.52 | ✓ | ✓ | 6 |
| **Miura et al. 2014**[26] | Australia | 1992-1996 | Cohort Cases: 493 Cohort: 1325 | SCC | ≥2 cups/day vs. none | 1.15 | 0.69-1.92 | ✓ | ✓ | 6 |
| **Naldi et al.**[24] **2004** | Italy | 1992-1994 | Case control Cases: 542 Controls: 538 | Melanoma | Drinker vs. non-drinker | 0.84 | 0.60-1.18 | ✓ | ✓ | 7 |
| **Song et al.**[15] **2012 Men** | USA | 1984-2006 | Cohort Cases: 25480 Cohort: 112897 | BCC | >3 cups/day vs. <1 cup/month | 1.0 | 0.87-1.15 | ✓ | ✓ | 5 |
| **Song et al.**[15] **2012 Women** | USA | 1986-2006 | Cohort Cases: 25480 Cohort: 112897 | BCC | >3 cups/day vs. <1 cup/month | 0.98 | 0.87-1.10 | ✓ | ✓ | 5 |

[A] Region of residence, recreational physical activity, freckles on face, actinic keratoses, family history of skin cancer, skin phototype, indoor tanning, etc.

**Table 1D:** Characteristics of Studies Meeting Inclusion Criteria on Tea

| REFERENCES | COUNTRY | STUDY YEAR | STUDY TYPE | SKIN CANCER TYPE | COMPARISON | RR | 95% CI | ADJUSTED FOR AGE AND SEX | ADJUSTED FOR A SKIN CANCER RISK FACTOR[A] | NEWCASTLE-OTTAWA SCORE |
|---|---|---|---|---|---|---|---|---|---|---|
| **TEA** | | | | | | | | | | |
| **Abel et al. [11] 2007** | USA | 1993-1998 | Cross-sectional Cases: 7482 | NMSC | ≥6 cups/day vs. none | 0.84 | 0.61-1.17 | ✓ | ✓ | 6 |
| **Asgari et al. [29] 2011** | USA | 2004 | Case Control Cases: 415 Control: 415 | SCC | >1 cup/day vs. none | 0.98 | 0.55-1.73 | | ✓ | 5 |
| **Caini et al. [12] 2017 Men** | Europe | 1992–2000 | Cohort Cases: 2712 Cohort: 476,160 | Melanoma | Highest quartile vs. non-drinkers | 1.18 | 0.72-1.94 | ✓ | ✓ | 7 |
| **Caini et al. [12] 2017 Women** | Europe | 1992–2000 | Cohort Cases: 2712 Cohort: 476160 | Melanoma | Highest quartile vs. non-drinkers | 0.82 | 0.56-1.21 | ✓ | ✓ | 7 |
| **Corona et al.[22] 2001** | Italy | 1995-1997 | Case control Cases: 166 Controls: 158 | BCC | Drinker vs. non-drinker | 0.7 | 0.3-1.4 | ✓ | | 5 |
| **de Vries et al.[30] 2012** | Europe | | Case control Cases: 1371 Controls: 1550 | BCC | ≥3 vs. <3 times/week | 0.98 | 0.72-1.34 | ✓ | ✓ | 5 |
| **de Vries et al.[30] 2012** | Europe | | Case control Cases: 1371 Controls: 1550 | SCC | ≥3 vs. <3 times/week | 0.95 | 0.63-1.43 | ✓ | ✓ | 5 |
| **de Vries et al.[30] 2012** | Europe | | Case control Cases: 1371 Controls: 1550 | Melanoma | ≥3 vs. <3 times/week | 1.22 | 0.86-1.74 | ✓ | ✓ | 5 |
| **Ferrucci et al.[13] 2013** | USA | 2006-2010 | Case control Cases: 377 Controls: 390 | BCC | >0.43 versus ≤0.43 cups/day | 0.88 | 0.60-1.29 | ✓ | ✓ | 7 |
| **Fortes et al.[16] 2013** | Italy | 2001-2003 | Case Control Cases: 304 Controls: 305 | Melanoma | >once daily vs. ≤7 times weekly | 0.63 | 0.34-1.19 | ✓ | ✓ | 6 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Hakim et al.**[23] **2001** | USA | 1994–1996 | Case Control Cases: 234 | SCC | ≥1 cup/week vs. none | 0.60 | 0.30-1.23 | ✓ | ✓ | 7 |
| **Hughes et al.** [31] **2006** | Australia | 1992-2002 | Cohort Cases: 235 Cohort: 1056 | SCC | Highest versus lowest quantity | 0.82 | 0.45-1.51 | ✓ | ✓ | 7 |
| **Miura et al.** [32] **2015** | Australia | 1992-2007 | Cohort Cases: 493 Cohort: 1325 | SCC | ≥4 cups/day vs. none | 1.25 | 0.71-2.19 | ✓ | ✓ | 6 |
| **Miura et al.** [32] **2015** | Australia | 1992-2007 | Cohort Cases: 493 Cohort: 1325 | BCC | ≥4 cups/day vs. none | 1.03 | 0.70-1.53 | ✓ | ✓ | 6 |
| **Naldi et al.** [24] **2004** | Italy | 1992-1994 | Case control Cases: 542 Controls: 538 | Melanoma | Drinker vs. non-drinker | 0.79 | 0.61-1.03 | ✓ | ✓ | 7 |
| **Oh et al.**[19] **2019** | Singapore | 1993-1998 | Cohort Cases: 609 Cohort: 63,257 | BCC | Daily versus <monthly | 0.74 | 0.52-1.04 | ✓ | | 6 |
| **Oh et al.**[19] **2019** | Singapore | 1993-1998 | Cohort Cases: 609 Cohort: 63,257 | SCC | Daily versus <monthly | 0.62 | 0.36-1.08 | ✓ | | 6 |
| **Østerlind et al.**[20] **1998** | Denmark | 1982-2985 | Case Control Cases: 474 Controls: 926 | Melanoma | High vs. low consumption level | 1.5 | 1.1-2.2 | ✓ | ✓ | 7 |
| **Rees et al.** [25] **2007** | USA | 1993-2000 | Case control Cases: 770 Controls: 715 | BCC | ≥2 cups/day vs. none | 0.98 | 0.74-1.31 | ✓ | ✓ | 6 |
| **Rees et al.** [25] **2007** | USA | 1993-2000 | Case control Cases: 770 Controls: 715 | SCC | ≥2 cups/day vs. none | 0.65 | 0.44-0.96 | ✓ | ✓ | 6 |
| **van der Pols et al.** [27] **2011** | Australia | 1992-2002 | Cohort Cases: 501 Cohort: 1056 | BCC | Highest vs. lowest quantity | 0.9 | 0.6-1.41 | ✓ | ✓ | 7 |

[A] Region of residence, recreational physical activity, freckles on face, actinic keratoses, family history of skin cancer, skin phototype, indoor tanning, etc.

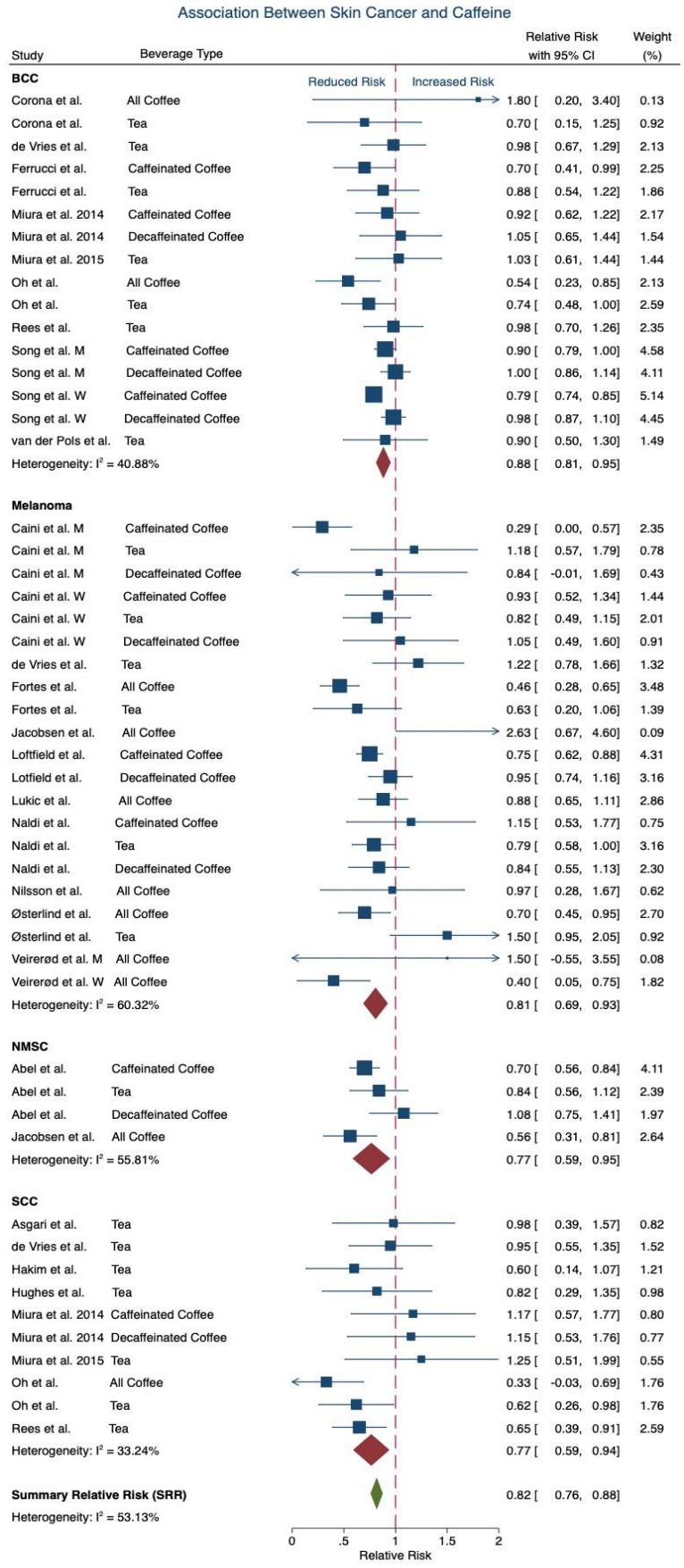
**Table 2:** Characteristics of 22 Studies

| Characteristic | Number (%) |
|---|---|
| Study Type | |
| Cross-sectional | 1 (4) |
| Case Control | 9 (41) |
| Cohort | 12 (55) |
| Skin Cancer Type | |
| Melanoma | 8 (36) |
| BCC | 3 (14) |
| SCC | 3 (14) |
| NMSC | 5 (22) |
| NMSC and melanoma | 3 (14) |
| Beverage Type | |
| Caffeinated Coffee | 7 (32) |
| Decaffeinated Coffee | 6 (27) |
| All Coffee | 8 (36) |
| Tea | 15 (68) |

**Study Characteristics**

The 22 studies included 9 case control studies, 12 cohort studies, and 1 cross-sectional study. Study publication dates ranged from 1986 to 2019. Among the studies, 8 examined melanoma, 3 BCC, 3 SCC, 5 NMSC, and 3 on both melanoma and NMSC. Studies were divided reasonably even between beverage types with 8 pertaining to coffee and tea, 7 to coffee only, and 7 to tea only. These studies included 47,953 cases of NMSC and melanoma. Some studies (8) did not separate caffeinated coffee and decaffeinated coffee, thus these were placed in an "all coffee" category. Due to UV light being a risk factor for both types of skin cancer, we recorded whether studies had adjusted for a skin cancer risk factor such as UV exposure, as well as age and sex. 15 of the 22 studies adjusted for all 3 of these factors, 5 adjusted for age and sex only, and 2 adjusted for a measure of UV exposure or skin cancer risk factor only. Some of the

**Figure 2:** Forest plot for the studies on the association of caffeine with NMSC and melanoma.



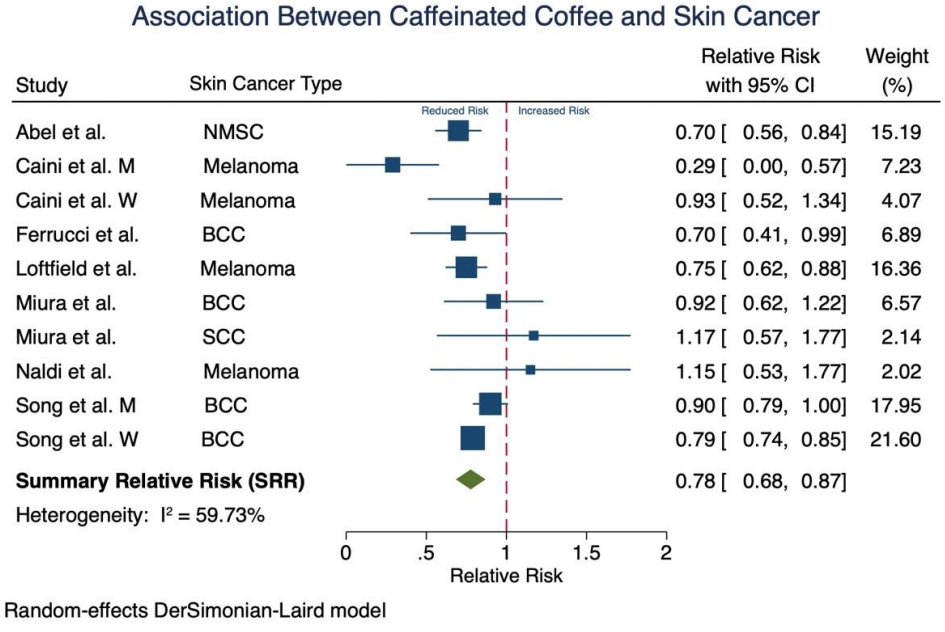

**adjustments included: region of residence, recreational physical activity, freckles on face or back, solar lentigines on arm, actinic keratoses, family** history of skin cancer, skin phototype, skin reaction after prolonged exposure to sunlight, indoor tanning, elastosis of neck, number of sunburns per year, number of moles greater than 5 mm, and original hair color. The majority of the studies (21) comprised of populations from Europe or the United States. The additional study examined NMSC in 63,257 men and women from Singapore.[19] In terms of comparison of caffeine intake, studies compared lower limits anywhere from less than 1 cup daily to less than 3 cups weekly, and higher limits anywhere from greater

than 1 cup daily to greater than 7 cups daily. One study measured in occasions per day instead of cups per day.[28] Several studies divided their participants into quartiles of intake or compared drinkers versus non-drinkers.[12 20 22 24 31 27]

**Study Quality**

The Newcastle-Ottawa scale for non-randomized studies was used to assess the quality of the papers. The case control, cohort, and cross-sectional versions were utilized, and the comparability section was adapted to this study by using age, sex, and risk factors for skin cancer as the adjustment criteria. More than half of the studies received two stars in this category for all 3 adjustments, the remaining studies only received 1 star for adjusting for either age and sex, or a skin cancer risk factor. Scores ranged from 5 to 7 with a mean of 6. Several studies (6) had a score of 4 and were excluded due to a high risk of bias.

**Figure 3**: Forest plot for the studies on the association of caffeinated coffee with NMSC and melanoma.




The squares and horizontal lines correspond to the study-specific relative risks (RRs) and 95% CIs, respectively. The diamond represents the summary relative risk (SRR) and 95% CI of the overall population. The vertical dashed line indicates the line of no effect at 1. NMSC, nonmelanoma skin cancer; BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

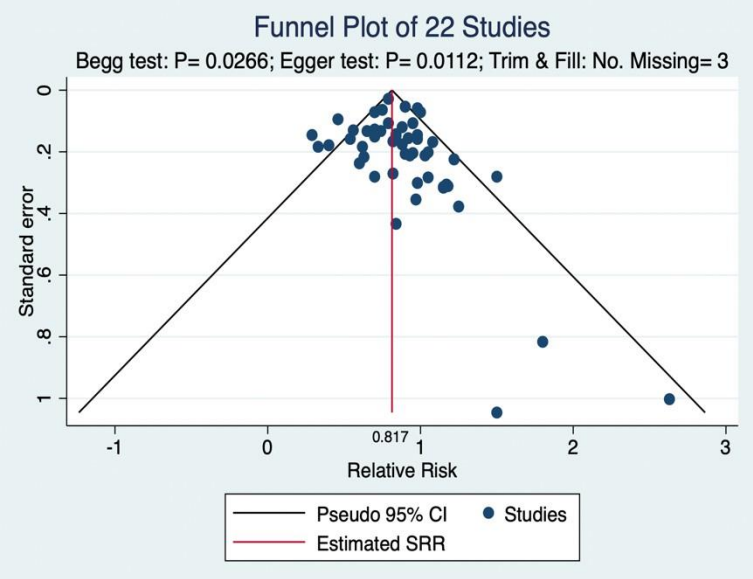
**Publication Bias**

The Begg and Egger tests were both statistically significant, suggesting that publication bias is present ($P$ = 0.0266 and $P$ = 0.0112, respectively). However, when the trim-and-fill method was applied (3 datasets were filled in), the corrected SRR was similar to the original (0.817 vs. 0.814), indicating that the publication bias impact is minor. Figure 4 illustrates the funnel plot in addition to the analysis results.

**Meta-Analysis**

In the pooled analysis, caffeine intake and skin cancer exhibited an inverse association with an overall SRR of 0.82 (95% CI 0.76-0.88, $I^2$ = 53.13%). In the sub-group analysis of skin cancer type BCC had an SRR of 0.88 (95% CI 0.81-0.95, $I^2$ = 40.88%), the melanoma SRR was 0.81 (95% CI 0.69-0.93, $I^2$ = 60.32%), the NMSC SRR was 0.77 (95% CI 0.59-0.95, $I^2$ = 55.81%), and the SCC SRR was 0.77 (95% CI 0.59-0.94, $I^2$ = 33.24%). These data are shown in Figure 2 in addition to the overall SRR. The caffeinated coffee subgroup had an SRR of 0.78 (95% CI 0.68-0.87, $I^2$ = 59.73%) (Figure 3), whereas the decaffeinated coffee SRR was 0.98 (95% CI 0.91-1.06, $I^2$ = 0%). Tea also showed an inverse association with an SRR of 0.85 (95% CI 0.77-0.93, $I^2$ = 1.76%). Finally, an analysis was run on caffeinated coffee, decaffeinated coffee, and the all coffee categories, resulting in an SRR of 0.79 (95% CI 0.72-0.87, $I^2$ = 65.99%).

**Figure 4:** Funnel plot for studies on the association between skin cancer and caffeine.




Using this SRR, we calculated the number of skin cancers prevented annually in the U.S. Since this SRR compares the highest intake to the lowest intake, we input data on the percentage of Americans who drink more than 3 cups per day, which is 17%.[47] Based on these data and the estimated annual incidence of 5,434,193 NMSC[1] and 65,647 melanoma[2], we calculated that 196,344 skin cancers are prevented annually. We also calculated annual savings of 289 million dollars, using the 8.1 billion dollar estimate of skin cancer treatment.[3]

**Discussion**

To our knowledge, this is the first systematic review and meta-analysis to summarize data about the association between the three most common types of skin cancer (BCC, SCC, and melanoma) and caffeinated beverage (coffee or tea). This meta-analysis comprised the largest number of studies compared to prior meta-analyses. The main finding was a 22% decreased risk of all three types of skin cancer with caffeinated coffee intake. This association was not present with decaffeinated coffee. Other meta-analyses have found no significant association between tea and skin cancer, but according to our results, tea had a 15% decreased risk of skin cancer. This result is plausible due to the relative caffeine content of tea being

approximately half that of coffee. The reduced risks of BCC, SCC, NMSC, and melanoma with total caffeine intake were 12%, 23%, 23%, and 19%, respectively. Using these data, we also found the number of skin cancers prevented and the cost savings annually to be significant. A moderate amount of heterogeneity is present among the studies ($I^2$ = 53.13%), which contributes some imprecision to the results.

Majority of the epidemiological studies examining caffeine and skin cancer found an inverse association; some found this effect in a dose-dependent manner.[11] There are also convincing data on the pro-apoptotic effect of caffeine in keratinocytes after UVB irradiation in *in vivo* and *in vitro* studies.[4-10] Evidence from biological and epidemiological studies, including the present study, combines to suggest that the apparent beneficial effect of caffeine on skin cancer prevention is likely due to the biologic effect of caffeine, possibly through inhibition of the ATR pathway. Caffeine has also shown a protective effect with several other cancer types including hepatocellular, endometrial, and colorectal cancer.[48] Contrarily, a positive association with caffeine has been demonstrated in lung, gastric, and bladder cancer.[49-51]

The main strength of this study is that it parallels the previous research completed on this subject and adds evidence to the hypothesis of the inverse association between skin cancer and caffeine. In addition to this, the present meta-analysis had a greater amount of studies and datasets compared to earlier analyses. This study has several limitations. First, each included study measured the amount of caffeine intake differently, which contributes to the overall heterogeneity. There were a variety of countries included, and participants could brew coffee or tea differently or use a variety of coffee beans, resulting in different caffeine contents. This study did not take into account the various individual types of teas and incorporated studies

that assessed more than one type of tea. A majority of the papers used questionnaires to obtain caffeine intake information which is subject to recall bias. The potential confounders that were adjusted for were different in each study. Due to some studies not adjusting for UV light exposure, the present study may have residual confounding from UV exposure, which is the greatest risk factor for developing skin cancer. Because the majority of studies assessed predominantly Caucasian populations, it is unknown whether our findings apply to non-Caucasian populations.

In conclusion, we found a beneficial effect of caffeinated coffee and tea on skin cancer but did not find cancer-preventive effect with decaffeinated coffee. This study does not directly answer the question of whether we need to add caffeine to sunscreen; however, the growing evidence of the inverse relationship between skin cancer and caffeine indicates a need for randomized controlled trials. Additional prospective cohort studies are also vital to examine a more accurate amount of caffeine that is considered protective. Although UV exposure continues to be the main risk factor and avoiding the sun is crucial to skin cancer prevention, these findings suggest that caffeine intake can lessen the skin cancer disease burden as well as the increasing costs of skin cancer treatment.

**References**


1. Rogers HW, Weinstock MA, Feldman SR, Coldiron BM. Incidence Estimate of Nonmelanoma Skin Cancer (Keratinocyte Carcinomas) in the U.S. Population, 2012. *JAMA Dermatol.* 2015;151(10):1081-1086.
2. Guy GP, Jr., Thomas CC, Thompson T, Watson M, Massetti GM, Richardson LC. Vital signs: melanoma incidence and mortality trends and projections - United States, 1982-2030. *MMWR Morb Mortal Wkly Rep.* 2015;64(21):591-596.
3. Guy GP, Jr., Machlin SR, Ekwueme DU, Yabroff KR. Prevalence and costs of skin cancer treatment in the U.S., 2002-2006 and 2007-2011. *Am J Prev Med.* 2015;48(2):183-187.
4. Zajdela F, Latarjet R. Inhibition of skin carcinogenesis in vivo by caffeine and other agents. *National Cancer Institute monograph.* 1978(50):133-140.
5. Lu YP, Lou YR, Xie JG, et al. Caffeine and caffeine sodium benzoate have a sunscreen effect, enhance UVB-induced apoptosis, and inhibit UVB-induced skin carcinogenesis in SKH-1 mice. *Carcinogenesis.* 2007;28(1):199-206.
6. Huang MT, Xie JG, Wang ZY, et al. Effects of tea, decaffeinated tea, and caffeine on UVB light-induced complete carcinogenesis in SKH-1 mice: Demonstration of caffeine as a biologically important constituent of tea. *Cancer Research.* 1997;57(13):2623-2629.
7. Lu YP, Lou YR, Li XH, et al. Stimulatory effect of oral administration of green tea or caffeine on ultraviolet light-induced increases in epidermal wild-type p53, p21(WAF1/CIP1), and apoptotic sunburn cells in SKH-1 mice. *Cancer Research.* 2000;60(17):4785-4791.
8. Conney AH, Zhou S, Lee MJ, et al. Stimulatory effect of oral administration of tea, coffee or caffeine on UVB-induced apoptosis in the epidermis of SKH-1 mice. *Toxicol Appl Pharmacol.* 2007;224(3):209-213.
9. Heffernan TP, Kawasumi M, Blasina A, Anderes K, Conney AH, Nghiem P. ATR-Chk1 pathway inhibition promotes apoptosis after UV treatment in primary human keratinocytes: potential basis for the UV protective effects of caffeine. *J Invest Dermatol.* 2009;129(7):1805-1815.
10. Kawasumi M, Lemos B, Bradner JE, et al. Protection from UV-induced skin carcinogenesis by genetic inhibition of the ataxia telangiectasia and Rad3-related (ATR) kinase. *Proceedings of the National Academy of Sciences of the United States of America.* 2011;108(33):13716-13721.
11. Abel EL, Hendrix SO, McNeeleya SG, et al. Daily coffee consumption and prevalence of nonmelanoma skin cancer in Caucasian women. *European Journal of Cancer Prevention.* 2007;16(5):446-452.
12. Caini S, Masala G, Saieva C, et al. Coffee, tea and melanoma risk: findings from the European Prospective Investigation into Cancer and Nutrition. *International Journal of Cancer.* 2017;140(10):2246-2255.
13. Ferrucci LM, Cartmel B, Molinaro AM, Leffell DJ, Bale AE, Mayne ST. Tea, coffee, and caffeine and early-onset basal cell carcinoma in a case-control study. *European Journal of Cancer Prevention.* 2014;23(4):296-302.

14. Loftfield E, Freedman ND, Graubard BI, et al. Coffee Drinking and Cutaneous Melanoma Risk in the NIH-AARP Diet and Health Study. *Jnci-Journal of the National Cancer Institute.* 2015;107(2).
15. Song F, Qureshi AA, Han J. Increased Caffeine Intake Is Associated with Reduced Risk of Basal Cell Carcinoma of the Skin. *Cancer Research.* 2012;72(13):3282-3289.
16. Fortes C, Mastroeni S, Boffetta P, et al. The protective effect of coffee consumption on cutaneous melanoma risk and the role of GSTM1 and GSTT1 polymorphisms. *Cancer Causes & Control.* 2013;24(10):1779-1787.
17. Jacobsen BK, Bjelke E, Kvale G, Heuch I. COFFEE-DRINKING, MORTALITY, AND CANCER INCIDENCE - RESULTS FROM A NORWEGIAN PROSPECTIVE-STUDY. *Journal of the National Cancer Institute.* 1986;76(5):823-831.
18. Lukic M, Jareid M, Weiderpass E, Braaten T. Coffee consumption and the risk of malignant melanoma in the Norwegian Women and Cancer (NOWAC) Study. *Bmc Cancer.* 2016;16.
19. Oh CC, Jin A, Yuan JM, Koh WP. Coffee, tea, caffeine, and risk of nonmelanoma skin cancer in a Chinese population: The Singapore Chinese Health Study. *J Am Acad Dermatol.* 2019;81(2):395-402.
20. Osterlind A, Tucker MA, Stone BJ, Jensen OM. THE DANISH CASE-CONTROL STUDY OF CUTANEOUS MALIGNANT-MELANOMA .4. NO ASSOCIATION WITH NUTRITIONAL FACTORS, ALCOHOL, SMOKING OR HAIR-DYES. *International Journal of Cancer.* 1988;42(6):825-828.
21. Veierod MB, Thelle DS, Laake P. Diet and risk of cutaneous malignant melanoma: A prospective study of 50,757 Norwegian men and women. *International Journal of Cancer.* 1997;71(4):600-604.
22. Corona R, Dogliotti E, D'Errico M, et al. Risk factors for basal cell carcinoma in a Mediterranean population - Role of recreational suit exposure early in life. *Archives of Dermatology.* 2001;137(9):1162-1168.
23. Hakim IA, Harris RB. Joint effects of citrus peel use and black tea intake on the risk of squamous cell carcinoma of the skin. *BMC dermatology.* 2001;1:3-3.
24. Naldi L, Gallus S, Tavani A, Imberti GL, La Vecchia C, Italian Grp Epidemiologic Res D. Risk of melanoma and vitamin A, coffee and alcohol: a case-control study from Italy. *European Journal of Cancer Prevention.* 2004;13(6):503-508.
25. Rees JR, Stukel TA, Perry AE, Zens MS, Spencer SK, Karagas MR. Tea consumption and basal cell and squamous cell skin cancer: Results of a case-control study. *Journal of the American Academy of Dermatology.* 2007;56(5):781-785.
26. Miura K, Hughes MCB, Green AC, van der Pols JC. Caffeine intake and risk of basal cell and squamous cell carcinomas of the skin in an 11-year prospective study. *European Journal of Nutrition.* 2014;53(2):511-520.
27. van der Pols JC, Hughes MCB, Ibiebele TI, Marks GC, Green AC. Food intake and risk of basal cell carcinoma in an 11-year prospective study of Australian adults. *European Journal of Clinical Nutrition.* 2011;65(1):39-46.
28. Nilsson LM, Johansson I, Lenner P, Lindahl B, Van Guelpen B. Consumption of filtered and boiled coffee and the risk of incident cancer: a prospective cohort study. *Cancer Causes & Control.* 2010;21(10):1533-1544.

29. Asgari MM, White E, Warton EM, Hararah MK, Friedman GD, Chren M-M. Association of Tea Consumption and Cutaneous Squamous Cell Carcinoma. *Nutrition and Cancer-an International Journal.* 2011;63(2):314-318.
30. de Vries E, Trakatelli M, Kalabalikis D, et al. Known and potential new risk factors for skin cancer in European populations: a multicentre case-control study. *British Journal of Dermatology.* 2012;167:1-13.
31. Hughes MC, van der Pols JC, Marks GC, Green AC. Food intake and risk of squamous cell carcinoma of the skin in a community: The Nambour skin cancer cohort study. *International Journal of Cancer.* 2006;119(8):1953-1960.
32. Miura K, Hughes MCB, Arovah NI, van der Pols JC, Green AC. Black Tea Consumption and Risk of Skin Cancer: An 11-Year Prospective Study. *Nutrition and Cancer-an International Journal.* 2015;67(7):1049-1055.
33. Wang J, Li X, Zhang D. Coffee consumption and the risk of cutaneous melanoma: a meta-analysis. *European Journal of Nutrition.* 2016;55(4):1317-1329.
34. Vaseghi G, Haghjoo-Javanmard S, Naderi J, Eshraghi A, Mahdavi M, Mansourian M. Coffee consumption and risk of nonmelanoma skin cancer: a dose-response meta-analysis. *Eur J Cancer Prev.* 2018;27(2):164-170.
35. Yew YW, Lai YC, Schwartz RA. Coffee Consumption and Melanoma: A Systematic Review and Meta-Analysis of Observational Studies. *American Journal of Clinical Dermatology.* 2016;17(2):113-123.
36. Micek A, Godos J, Lafranconi A, Marranzano M, Pajak A. Caffeinated and decaffeinated coffee consumption and melanoma risk: a dose-response meta-analysis of prospective cohort studies. *Int J Food Sci Nutr.* 2018;69(4):417-426.
37. Liu J, Shen B, Shi M, Cai J. Higher Caffeinated Coffee Intake Is Associated with Reduced Malignant Melanoma Risk: A Meta-Analysis Study. *Plos One.* 2016;11(1).
38. Grosso G, Godos J, Galvano F, Giovannucci EL. Coffee, Caffeine, and Health Outcomes: An Umbrella Review. In: Stover PJ, Balling R, eds. *Annual Review of Nutrition, Vol 37.* Vol 37.2017:131-156.
39. Caini S, Cattaruzza S, Bendinelli B, et al. Coffee, tea and caffeine intake and the risk of non-melanoma skin cancer: a review of the literature and meta-analysis. *European Journal of Nutrition.* 2017;56(1):1-12.
40. Covidence systematic review software. In. Melbourne, Australia: Veritas Health Innovation.
41. GA W, B S, D OC, J P, V W, M L. The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. . In. Ottawa, Canada. : The Ottawa Health Research Institute; 2005:http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm .
42. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics.* 2000;56(2):455-463.
43. Begg CB, Mazumdar M. OPERATING CHARACTERISTICS OF A BANK CORRELATION TEST FOR PUBLICATION BIAS. *Biometrics.* 1994;50(4):1088-1101.
44. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *Bmj.* 1997;315(7109):629-634.

*45.* Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med.* 2002;21(11):1539-1558.
46. *Stata Statistical Software: Release 16* [computer program]. College Station, TX: StataCorp LLC; 2019.
47. Loftfield E, Freedman ND, Dodd KW, et al. Coffee Drinking Is Widespread in the United States, but Usual Intake Varies by Key Demographic and Lifestyle Factors. *J Nutr.* 2016;146(9):1762-1768.
48. Arab L. Epidemiologic evidence on coffee and cancer. *Nutr Cancer.* 2010;62(3):271-283.
49. Wu W, Tong Y, Zhao Q, Yu G, Wei X, Lu Q. Coffee consumption and bladder cancer: a meta-analysis of observational studies. *Sci Rep.* 2015;5:9051.
50. Xie Y, Qin J, Nan G, Huang S, Wang Z, Su Y. Coffee consumption and the risk of lung cancer: an updated meta-analysis of epidemiological studies. *Eur J Clin Nutr.* 2016;70(2):199-206.
51. Liu H, Hua Y, Zheng X, et al. Effect of coffee consumption on the risk of gastric cancer: a systematic review and meta-analysis of prospective cohort studies. *PLoS One.* 2015;10(5):e0128501.