Abstract. Background: The epidemiological relationship between vitamin D levels and cancer has been thoroughly investigated. Published data from large studies appear to corroborate a significant relationship between higher serum vitamin D concentrations and improved survival. Mechanistic reviews on commonly-studied cancers – including breast cancer, colon cancer and melanoma – focus predominantly on data from older studies. In outlining avenues for future research, we believe there is utility in summarizing novel findings introduced to the literature. Materials and Methods: In this narrative review, we used MEDLINE, PUBMED and Cochrane databases to identify mechanistic studies published from January 1, 2015 onwards exploring this topic. Results: Twenty-five mechanistic studies were included in this review. It was found that vitamin D plays a critical role in both direct (i.e. tumor gene expression, proliferation, invasiveness, sensitivity to chemotherapy etc.) and indirect (i.e. effects on the tumor microenvironment and immunomodulation) tumor suppression mechanisms. Conclusion: These newly-identified pathways warrant further research, with the hopes that we may understand how and when vitamin D supplementation can be integrated into precision medicine therapeutics for cancers of the breast, colon and skin. Cancer care providers should consider recommendations to screen for vitamin D deficiency in this population.
relationship between vitamin D and cancer have focused heavily on older studies (9-13). In outlining new areas for future research, we believe there is utility in summarizing these novel molecular mechanisms and assessing how they fit into the context of existing models relating vitamin D to cancer.

Thus, in this review, we evaluate literature published over the last five years to explore the underlying molecular biology linking vitamin D to carcinogenesis, focusing on the most commonly reported cancer subtypes: breast cancer, colon cancer, and melanoma.

Materials and Methods

A literature search was conducted using PUBMED, MEDLINE and Cochrane databases to capture peer-reviewed research articles (including reviews and meta-analyses), published between January 1, 2015 and August 20, 2020. Articles in any language were included if an English translation existed.

The initial step of the search strategy involved combining the following MeSH terms with the boolean operator OR: “Vitamin D”, “Ergocalciferol”, “Cholecalciferol”, “Calcitriol”, “Calcifediol”, “Vitamin D Deficiency” as well as the keyword “hydroxyvitamin D”. This created the first search string. The MeSH term “Neoplasms” was then combined with the keyword “cancer” using the OR Boolean operator to create the second search string. Consequently, both search strings were combined. All collected abstracts were surveyed by two, independent researcher associates in order to confirm article relevancy to the proposed study topics. Data extraction was performed on the included articles that met our review objectives.

Results

A total of 1,197 articles were produced by the aforementioned search strategy. This was parsed down to 1,383 after selecting for articles that focused on breast cancer (BC), colorectal cancer (CRC) or melanoma (the three, most commonly reported malignancies). The authors chose to review mechanistic studies published in the last 5 years in order to harvest data that best represents contemporary knowledge. As a result, 25 were then eligible after excluding duplicated studies or lack of relatedness based on abstract summaries. Additionally, to show the breadth of epidemiological data published on this topic, we presented all 17 meta-analyses captured by our search in one summary table. The flow chart in Figure 1 presents the full inclusion schema of articles analyzed for this review.

A significant portion of the literature explored the mechanisms governing the association between vitamin D and tumorigenesis. These mechanisms can be broadly categorized into two main groups: those pertaining to a direct effect on cancer cells (e.g. tumor gene expression, proliferation, invasiveness, sensitivity to chemotherapy etc.) and those associated with indirect effects (e.g. effects on the tumor microenvironment and immunomodulation), as outlined in Figure 2.

Vitamin D as a modulator of tumor aggressiveness. We identified 11 major mechanisms describing the direct effects of vitamin D on tumor aggressiveness. These mechanisms are corroborated by clinical data revealing an association between reduced vitamin D levels and markers of poor prognosis, including: regional lymph node positivity, resistance to chemotherapy, and metastasis (14).

Vitamin D modulates a number of multifunctional transcriptional complexes. i) Mouse models with VDR gene knockouts exhibit increased expression of a helix-loop-helix transcription factor known as the “inhibitor of differentiation” (Id1) (8). This is associated with higher rates of BC tumor growth and metastasis. Id1 is also implicated in epithelial-to-mesenchymal transitioning (EMT), angiogenesis and tumor invasiveness (15). ii) In the MCF-7 BC cell line, calcitriol and its analog tacalcitol, also decrease the expression of MiR-125b (16); a member of a class of microRNAs that regulates post-transcriptional gene expression and is known to promote BC cell migration, invasiveness and chemosensitivity (16). iii) Vitamin D acts antagonistically toward retinoid-related orphan receptor (ROR) alpha and gamma; transcription factors expressed in all major skin populations that may be intimately involved in melanoma tumorigenesis (17). iv) Finally, vitamin D binds the beta-catenin transcriptional complex, reducing nuclear B-catenin content and upregulating Wnt inhibitor molecules (e.g. ROCK, p38 MAPK, and MSK1 kinases) (13). β-catenin signaling is
involved in malignant transformation, increased proliferation and migration of colorectal cells (13). Important to note is the potential distinction recently made between colitis-associated colon cancer and other sporadic or inherited colon cancers. Meeker et al. (2020) reported decreased colon tumor incidence and severity of colonic dysplasia in mouse models for colitis-associated colon cancer (CAC) fed with vitamin D-null diets, likely due to higher epithelial cell proliferation associated with vitamin D deficiency that is more optimal for healthy homeostasis of inflamed mucosa. v) In malignant melanoma, vitamin D has also been related to mitogen-activated protein kinase (MAPK) signaling, which is known to affect phosphorylation and regulation of transcription factors, co-regulatory proteins and chromatin proteins (18). Vitamin D modulates cellular proliferation through checkpoint regulators. vi) Vitamin D may cause cell-cycle arrest in G1 via decreased expression of the cyclin D1 (19). This mechanism initiates apoptosis when cancer cells detach from the extracellular matrix (ECM), thereby limiting the metastatic potential of malignant cells. vii) Vitamin D can also influence checkpoint regulation through induction of cyclin-dependent kinase inhibitors (CDKIs), specifically p21 and p27 (13, 19). This finding is corroborated by an RCT investigating calcium and vitamin D supplementation over a 6-month period in patients with sporadic colorectal adenomas. Increased expression of p21 (a marker of differentiation) and bax (a marker of apoptosis) was noted (20). Vitamin D also modulates cellular migration. viii) Calcitriol-treated BC cells demonstrate decreased expression of stress fibers (cytoskeletal structures composed of actin), impairing cellular migration and invasiveness (21). ix) Calcitriol has also been shown to positively regulate the expression of adhesion molecules (e.g., E-cadherin, occludin, claudin, plectin, and filamin A), which contributes to an increased stability of epithelial barriers and cell-to-cell adhesion (13). This may be mediated through vitamin D-related inhibition of Sprouty-2, a protein which deregulates E-cadherin. One surprising pathway was identified by Anisiewicz et al. (2018), showing a x) net pro-metastatic effect of vitamin D on mouse models for basal-like breast cancer tumor expression of osteopontin (OPN) (22). No other studies identified such an unfavorable impact on metastatic capacity.
Finally, vitamin D may also modulate responsiveness of cancer cells to therapy. xi) Vitamin D3 has been shown to enhance breast cancer stem cell responsiveness to conventional chemotherapeutic agents through downregulating expression of the enzyme aldehyde dehydrogenase-1 (ALDH1) (23). This has been described more thoroughly in Section 3.3: Vitamin D and Clinical Practice.

Vitamin D and the tumor microenvironment. A cancerous mass consists of not only malignant cells but also adjacent resident or infiltrating host cells, secreted factors and the surrounding ECM. This is known as the tumor microenvironment. With the advent of immunotherapy and other forms of precision medicine, cancer research has expanded its focus to include analysis of the tumor microenvironment. We identified 14 major mechanisms related to the indirect effects of vitamin D on tumorigenesis.

Vitamin D signaling modulates numerous immune mediators. i) Vitamin D concentrations are significantly associated with DNA methylation (a form of epigenetic modulation) of CpG regions of immune function-related genes in BC patients, effectively silencing their expression (24). Pawlik et al. (2018) noted that calcitriol and its analogs contribute to tumor-conductive changes in tumor-bearing mice (25). Specifically, she noted a ii) decrease in NK CD335+ cells in model spleen and lymph nodes after supplementation with vitamin D. iii) In triple negative breast cancer (TNBC) cell lines, calcitriol exerts an anti-proliferative effect through the production of cytokines IL-1B and TNF-α (26). This is in contrast to the two prior studies that highlighted potential immune suppression.

Vitamin D also modulates hormonal or metabolic cascades implicated in cancer. Estrogen is a known driving force behind BC growth, particularly in postmenopausal or obese women (8). iv) Vitamin D blocks estrogenic signaling at multiple steps: it inhibits estrogen synthesis (through downregulation of CYP19A1, which encodes for the aromatase, among other mechanisms) and also downregulates estrogen receptor signaling (27). v) Vitamin D also restores the adipokine profile (decreased leptin signaling and increased adiponectin signaling) dysregulated by obesity. In a trial of 29 BC patients, Going et al. (2018) noted that vi) high-dose (10,000 IU/day) supplementation of vitamin D decreased circulating 27-hydroxycholesterol (27HC) levels compared to supplementation of low-dose vitamin D (400 IU/day) (28). This is associated with inhibition of CYP27A1, the enzyme that normally synthesizes 27HC. The 27HC protein is an endogenous selective estrogen receptor modulator (SERM) which accelerates the growth of ER receptor positive BC.

Adipose tissue is also implicated in CRC tumorigenesis. vii) Vitamin D might play a role in epigenetic modification of visceral adipose tissue (VAT) genes through DNA-methyltransferase. Adipose tissue DNMT3A mRNA is both negatively associated with serum vitamin D levels and positively associated with adipose tissue VDR and NFκB1 methylation (29). This VAT microenvironment is associated with chronic, obesity-associated low-grade inflammation, insulin resistance and angiogenesis (29). viii) Moreover, with respect to inflammation, vitamin D has been shown to block nucleotide-binding oligomerization domain-containing protein 2 (NOD2), which is implicated in inflammatory bowel disease (30), and to decrease expression of the inflammatory cytokine interleukin-6 (IL-6), independent of NOD2 (31).

Finally, vitamin D modulates homeostatic processes of surrounding tissue. Tumor-associated fibroblasts alter the extracellular matrix and facilitate the migration of carcinoma cells (13). ix) VDR is found on these fibroblasts and elevated VDR in these cells is associated with longer overall survival in CRC (32). x) Vitamin D facilitates calcium and phosphate absorption in the gut. Higher serum calcium levels can bind bile acids and fatty acids, thereby reducing oxidative DNA damage (20) that may indirectly contribute to tumorigenesis. In breast cell lines, oxidative stress is prevented via transcriptional downregulation of pyruvate carboxylase upon treatment with vitamin D (33). xi) VDR activation also up-regulates CYP3A4, and this was shown to favor an anti-tumorigenic microenvironment by catabolism of toxic lithocholic acid (34). xii) In melanoma, the active form of vitamin D reduces AMP hydrolysis and adenosine production, likely through ecto-5’-nucleotidase/CD73 activity (35). Adenosine is one of the primary immunosuppressive metabolites in the tumor microenvironment (36), possibly contributing to increased tumor cell viability. Resident gut microbiota has also been implicated in the carcinogenesis of CRC (37). xiii) Calcitriol supplementation to CYP27B1 knockout mice may modulate this through reduced Helicobacter titers and severity of inflammation in colitis. xiv) Fernandez-Barral reported vitamin D-related expression of stemness-related genes, which is hypothesized to contribute to the homeostasis of healthy colonic mucosa in regeneration upon injury (38).

Vitamin D and clinical practice. At the time of this review, the National Cancer Institute reported the inclusion of cholecalciferol in 8 clinical trials. This includes a randomized phase IIa trial, examining the preventative effects of vitamin D supplementation, for lung cancer, in chronic obstructive pulmonary disease patients (COPD), as well as a partially randomized early phase I trial examining vitamin D in colon cancer patients with liver metastasis. Furthermore, many investigators have identified avenues for future consideration of vitamin D supplementation in the clinical setting.

Hypercalcemia is a toxic effect of vitamin D supplementation that limits the extent of its applicability in the clinical setting. Multiple studies have investigated means to avoid this. Ferronato et al. (2019) proposes the use of...
calcitriol analogs, such as ML-344 (which has an amide and carboxyl group in its side chain) that display anti-tumor, but not hypercalcemic, effects (21). Wang et al. also notes that vitamin D signaling mediated by specific cytochrome P450 enzymes (CYP11A1 and CYP3A4) is noncalcemic and antiproliferative, identifying potential new targets for therapy (39). Finally, Nicolas et al. (2018) explores new mechanisms of delivery, such as polymeric nanocapsules as drug carriers for calcitriol, that are efficacious but nontoxic (40).

A number of preclinical studies have investigated the potential utility of vitamin D, combined with traditional chemotherapy regimens, in order to enhance the anti-tumorigenic effects of these treatments while minimizing side effects. Lim et al. (2018) reported synergism between ruxolitinib and calcitriol in the treatment of an estrogen receptor-positive, human epidermal growth factor receptor 2-positive BC cell line (41). Pre-treatment with vitamin D analogues potentiates TNF-α cytotoxic effects through impaired cell viability as well as DNA fragmentation (26). Synergism has also been reported between vitamin D and tamoxifen (42), histone deacetylase inhibitors (43), paclitaxel (44), dacarbazine and cisplatin (45), 5-fluorouracil (5-FU) (46), bevacizumab (47), immune checkpoint inhibitors (48), and the nutraceutical S-adenosylmethionine (SAM).

Vitamin D may have utility in improving quality of life overall in cancer patients. Recent literature has described the relationship between vitamin D deficiency and immunosuppression, particularly as it relates to safety for patients with cancer during the COVID-19 pandemic (49). However, randomized controlled trials investigating the use of vitamin D for patients with COVID-19 pneumonia showed it was not significantly associated with changes in duration of hospital stay, rate of ICU admission or mechanical ventilation requirement (50). Vitamin D is also commonly prescribed, along with other pharmaceuticals, to prevent or minimize iatrogenic osteoporosis in patients receiving estrogen-depleting therapy for breast cancer (51). Deficiency may be related to medication-related osteonecrosis of the jaw, a rare complication of bisphosphonates that are often incorporated into care for these patients (52). Additionally, in a recent clinical trial, Keshavarzi et al. (2019) showed that vitamin D vaginal suppositories also improve vaginal atrophy in women with BC on tamoxifen (53).

**Epidemiological studies.** Large-scale epidemiological studies, evaluating the association between vitamin D and cancer incidence (54-61) or mortality (7, 62-70), have provided consistent results. Table I outlines a summary of the meta-analyses published over the last five years on this topic. The relationship between higher serum vitamin D levels and favorable outcomes in patients who already have cancer is more consistently corroborated than the hypothesis that deficiency may increase the risk of developing cancer.

**Discussion**

This review indicates that while there is strong evidence to show vitamin D levels may be related to morbidity and mortality outcomes in patients with cancer, our understanding of the molecular interplay between vitamin D and different neoplasms is still evolving.

Large epidemiological studies displayed consistency in these findings that serum vitamin D is not likely related to the risk of developing cancer, but is likely significantly related to cancer mortality, as outlined in Table I. Gaulao et al. (which did not yield a significant combined effect of vitamin D on mortality) included trials with short periods of follow-up (the longest trial exhibited a median follow-up of 6.2 years). These shorter follow-up intervals may not be of adequate length to capture relevant information in the context of BC survival (54). Meta-regressions in the study by Zhang et al. revealed that all-cause mortality was indeed significantly decreased in studies with longer follow-up periods (62), re-iterating the limited scope of the Gaulao et al. review, and its inconclusive results. The review by Keum et al. is limited in the diversity of included study populations, which were composed predominantly of white patients (63). This is a noteworthy limitation considering non-white individuals, particularly those of African and Middle Eastern descent, are more likely to suffer from vitamin D deficiency. Additionally, studies exploring the vitamin D effect in skin cancer also offered mixed results regarding whether vitamin D is protective or potentially deleterious (71). More work is thus needed to verify that the significant protective relationship is consistent across a diverse group of patients.

Interestingly, these significant results of preclinical studies, over the last five years, seem to corroborate the findings of meta-analyses suggesting that functional vitamin D pathways may play a role in improving cancer outcomes but not necessarily attenuating cancer risk. Studies investigating for an association between VDR and previously-established initiating pathways of malignancy did not yield significant results. Irving et al. (2018) showed no relationship between vitamin D and adenomatous polyposis coli (APC) gene functioning, one of the first tumor suppressors defective in the adenoma-carcinoma sequence, implicated in both sporadic and familial forms of colorectal cancer (72). Similarly, Kwan et al. (2019) failed to show a significant effect between vitamin D supplementation and colorectal mucosa expression of MSH2, known to be involved in the DNA mismatch repair mechanisms that are defective in Lynch syndrome (73). Figure 2 presents significant molecular findings relating vitamin D and tumorigenesis, published over the last five years, in a timeline. It shows that vitamin D deficiency may favor a microenvironment conducive to tumor growth and is also directly implicated in more aggressive, chemo-resistant disease. However, a paucity of
| Source               | Outcome(s)                  | Exposure               | # Included studies (Sample size) | Effect                        | p-Value |
|---------------------|-----------------------------|------------------------|---------------------------------|-------------------------------|---------|
| **Nonspecific**     |                             |                        |                                 |                               |         |
| Keum et al. (2019)  | Incidence                   | Supplementation        | 10 RCTs (83,353)                 | RR=0.98 (95% CI=0.83-1.09)    | 0.42    |
|                     | All-cause mortality         |                        | 5 RCTs (73,239)                 | RR=0.87 (95% CI=0.79-0.96)    | 0.005   |
| Zhang et al. (2019) | All-cause mortality         | Supplementation        | 42 RCTs using vitamin D3 (57,910)| RR=0.95 (95% CI=0.90-1.00)    | 0.06    |
|                     |                             |                        | 10 RCTs using vitamin D2 (17,554)| RR=0.98 (95% CI=0.95-1.02)    | 0.3     |
|                     | Cancer-related mortality    |                        |                                 |                               |         |
|                     | Cardiovascular mortality    |                        |                                 |                               |         |
|                     | Non-cancer, non-cardiovascular mortality |                  |                                 |                               |         |
| Goulão et al. (2018) | Incidence                   | Supplementation        | 24 RCTs (18,440)                 | RR=1.03 (95% CI=0.91-1.15)    | 0.911   |
|                     | Cancer-related mortality    |                        | 17 RCTs (15,893)                | RR=0.85 (95% CI=0.70-1.04)    | 0.679   |
| Gaksch et al. (2017)| All-cause mortality         | Serum vitamin D concentration of 40-49.99 nmol/l vs. 75-99.99 nmol/l | 8 cohort studies (26,916)            | HR=1.15 (95% CI=1-1.29)         | <0.05   |
|                     |                             | Serum vitamin D concentration of 30-39.99 nmol/l vs. 75-99.99 nmol/l |                         | HR=1.33 (95% CI=1.16-1.51)     | <0.05   |
|                     |                             | Serum vitamin D concentration of <30 nmol/l vs. 75-99.99 nmol/l |                         | HR=1.67 (95% CI=1.44-1.89)     | <0.05   |
| Vaughan-Shaw et al. (2017) | Overall survival Progression-free survival | Highest vs. lowest quartile serum vitamin D concentration | 38 studies - mixed design (24,013) | HR=0.74 (95% CI=0.66-0.82) | <0.05   |
|                     | Risk                        | Supplementation        | 23 studies - mixed design (14,307) | HR=0.84 (95% CI=0.77-0.91) | <0.05   |
| Bjelakovic et al. (2014) | All-cause mortality | Risk                  | Serum vitamin D concentration | 5 case-control studies (15,758) | OR=0.61 (95% CI=0.33-1.16) | >0.05   |
|                     |                             | Supplementation        | 2 cohort studies (62,412)       | OR=0.78 (95% CI=0.63-0.98)    | <0.05   |
|                     |                             |                        | 14 case-control studies (123,044) | RR=1.06 (95% CI=0.90-1.25)    | >0.05   |
|                     |                             |                        | 5 case-control studies (2796)   | RR=0.99 (95% CI=0.98-1.00)    | 0.17    |
| Estébanez et al. (2018) | Risk                        | Serum vitamin D concentration | 6 cohort studies (5984)          | HR=0.67 (95% CI=0.56-0.79)    | <0.001  |
| Hossain et al. (2018) | Risk                        | Serum vitamin D concentration | 24 case-control or cohort studies (31,867) | RR=0.92 (95% CI=0.83-1.02) | >0.05   |
| Hu et al. (2018)    | Overall survival            | Serum vitamin D concentration (highest versus lowest category) | 6 case-control or cohort studies (6092) | RR=0.61 (95% CI=0.48-0.79) | <0.05   |
| Kim et al. (2014)   | Risk                        | Serum vitamin D concentration (highest versus lowest category) | 6 case-control or cohort studies (4556) | RR=0.58 (95% CI=0.40-0.85) | <0.05   |
| Colorectal cancer   | Overall survival            | Serum vitamin D concentration (highest versus lowest category) | 11 cohort studies (7718)           | HR=0.68 (95% CI=0.55-0.85)    | <0.05   |
| Maalmi et al. (2018)| CRC-specific survival       | Serum vitamin D concentration (highest versus lowest category) | 8 cohort studies (6756)            | HR=0.67 (95% CI=0.57-0.78)    | <0.05   |

Table I. Continued
studies have reported a relationship to the function of tumor suppressor genes (such as BRCA, APC, TP53) or oncogenes (such as HER2 and BRAF) known to be primary genetic defects in many malignancies (74).

### Conclusion

This review sought to evaluate the most recently-identified molecular mechanisms governing the relationship between vitamin D and carcinogenesis, as well as the clinical impact of vitamin D deficiencies on cancer risk and prognosis. It was found that vitamin D plays a critical role in both direct and indirect tumor suppression mechanisms. Supporting the wealth of studies highlighting relevant biological pathways are also a number of meta-analyses identifying a significant association between normalized vitamin D levels and improved survival. However, the impact on cancer risk was not found to be significant. More work is needed to understand if the observed protective effects persist across the different analogs of vitamin D, different races, and different disease processes. While the USPSTF does not make recommendations to screen for vitamin D deficiency in asymptomatic individuals, it can be diagnosed through a simple blood test and is commonly performed in a wide variety of clinical contexts. Noting that this information may be readily available to their patients, cancer care providers should consider supplementation in cases of deficiency as a significant component of holistic care.

### Conflicts of Interest

The Authors declare no conflicts of interest.

### Authors’ Contributions

Conceptualization, N.B., L.E. and Z.N.; methodology, N.B., C.S and L.E.; writing-original draft preparation, N.B., C.S., L.E. and Z.N.; writing-review and editing, N.B., C.S., L.E., E.E., M.S., and Z.N.; supervision, Z.N.

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### Table I. Continued

| Source                  | Outcome(s)                              | Exposure                                      | # Included Studies (Sample Size) | Effect                        | p-Value       |
|-------------------------|-----------------------------------------|-----------------------------------------------|----------------------------------|-------------------------------|---------------|
| Xu et al. (2018) (68)   | Overall survival                        | Serum vitamin D (highest versus lowest category) | 11 cohort studies (7367)         | HR=0.67 (95% CI=0.55-0.80)    | <0.00001      |
|                         | Progression-free survival               | Serum vitamin D (highest versus lowest category) | 2 cohort studies (599)           | HR=0.74 (95% CI=0.61-0.90)    | 0.003         |
|                         | CRC-specific survival                   | Serum vitamin D (highest versus lowest category) | 5 cohort studies (4126)          | HR=0.74 (95% CI=0.61-0.90)    | 0.03          |
| Ekmekcioglu et al. (2017) (59) | Risk                                   | Serum vitamin D (highest versus lowest category) | 26 case-control or cohort studies (42,258) | RR=0.83 (95% CI=0.76-0.90)    | <0.05         |
| Garland et al. (2017) (60) | Risk                                   | Serum vitamin D (highest versus lowest category) | 15 case-control studies (175,127) | OR=0.67 (95% CI=0.59-0.76)    | <0.05         |
| Choi et al. (2015) (61) | Risk                                    | Serum vitamin D (highest versus lowest category) | 15 studies - mixed design (12,110) | OR=0.68 (95% CI=0.54-0.82)    | <0.05         |
| Ou et al. (2015) (69)   | All-cause mortality                     | Serum vitamin D (highest versus lowest category) | 5 cohort studies (3761)          | OR=0.80 (95% CI=0.67-0.95)    | <0.05         |
|                         | Cancer-related mortality                | Serum vitamin D (highest versus lowest category) | 6 cohort studies (241,893)       | RR=1.42 (95% CI=1.17-1.72)    | <0.05         |
| Melanoma                | Mahamat-Saleh et al. (2020) (74)        | Risk                                          |                                  |                               |               |
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