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Review

Vitamin D and Cancer: An Historical Overview of the Epidemiology and Mechanisms

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Abstract: This is a narrative review of the evidence supporting vitamin D's anticancer actions. The first section reviews the findings from ecological studies of cancer with respect to indices of solar radiation, which found a reduced risk of incidence and mortality for approximately 23 types of cancer. Meta-analyses of observational studies reported the inverse correlations of serum 25-hydroxyvitamin D [25(OH)D] with the incidence of 12 types of cancer. Case-control studies with a 25(OH)D concentration measured near the time of cancer diagnosis are stronger than nested case-control and cohort studies as long follow-up times reduce the correlations due to changes in 25(OH)D with time. There is no evidence that undiagnosed cancer reduces 25(OH)D concentrations unless the cancer is at a very advanced stage. Meta-analyses of cancer incidence with respect to dietary intake have had limited success due to the low amount of vitamin D in most diets. An analysis of 25(OH)D-cancer incidence rates suggests that achieving 80 ng/mL vs. 10 ng/mL would reduce cancer incidence rates by 70 ± 10%. Clinical trials have provided limited support for the UVB-vitamin D-cancer hypothesis due to poor design and execution. In recent decades, many experimental studies in cultured cells and animal models have described a wide range of anticancer effects of vitamin D compounds. This paper will review studies showing the inhibition of tumor cell proliferation, dedifferentiation, and invasion together with the sensitization to proapoptotic agents. Moreover, 1,25-$(OH)_2D_3$ and other vitamin D receptor agonists modulate the biology of several types of stromal cells such as fibroblasts, endothelial and immune cells in a way that interferes the apparition of metastases. In sum, the available mechanistic data support the global protective action of vitamin D against several important types of cancer.

Keywords: 25-hydroxyvitamin D; 1,25-$(OH)_2D_3$; antitumor action; breast cancer; case-control studies; colorectal cancer; cohort studies; ecological studies; epidemiological studies; randomized controlled trials; UVB; vitamin D

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1. Introduction

The role of vitamin D in reducing the risk of cancer incidence and death has been studied for years. A search of PubMed on 10 March 2022 searching for "cancer" and "vitamin D" or "vitamin D_3" in the title or abstract found 6732 publications starting in 1949. Of these, 523 were published prior to 2000; 1630 were published from 2000 through 2009; 1797 were published from 2010 through 2014; and 2782 were published in or after 2015. Publications with vitamin D and cancer in the title or abstract rose from 13 in 1990, 34 in 1995, 75 in 2000, 170 in 2005, 338 in 2010, 401 in 2012, and between 400 and 500 per year since then.

The earliest studies were ecological studies of cancer mortality rates with respect to indices of solar total or UVB radiation or laboratory studies of mechanisms of vitamin D metabolites on cancer cells. As time progressed, observational studies of cancer incidence with respect to serum 25-hydroxyvitamin D [25(OH)D] took place, and studies of the

mechanisms of vitamin on cancer incidence, progression, and metastasis were conducted. Later, randomized controlled trials (RCTs) of cancer risk with respect to vitamin D supplementation were conducted, and as more observational studies accrued, meta-analyses were conducted. Along the way, research approaches built on previous studies. However, since there are many sources of vitamin D, UVB exposure, diet, and supplements, and since 25(OH)D concentrations vary with time, both seasonally and over long periods, and since quantifying 25(OH)D concentrations can be uncertain and is not always conducted in studies, all such human studies of vitamin D and cancer are subject to error. There are also methodological issues, such as how to adjust for when 25(OH)D was measured. In addition, what was found in one group of people may not apply to other groups, such as those with different diets, geographical location, clothing, occupation, age, genetics, and BMI. Thus, all the epidemiological studies and RCTs have inherent limitations. However, by taking a comprehensive look at the findings from many types of studies and trying to identify those that are most reliable, a reasonable picture can emerge. What has emerged is that 25(OH)D concentrations play very important roles in the incidence, progression, and death for many types of cancer. While the roles of vitamin D in cancer are not fully understood, there is enough information for clinical and public health decisions to be made.

The epidemiology of vitamin D and cancer can be examined through the prisms of ecological studies, observational studies, and clinical trials. This review looks at findings from ecological studies of cancer risk with respect to indices of solar ultraviolet-B (UVB) doses, observational studies of cancer risk with respect to serum 25(OH)D concentration and oral vitamin D intake, and randomized controlled trials (RCTs) of cancer risk with respect to vitamin D supplementation.

Epidemiological data prompted the study of the putative anticancer action of vitamin D in the laboratory. Two important considerations in the study of the action of 1,25-$(OH)_2D_3$ and analogues in experimental cancer systems are the expression of vitamin D receptor (VDR), which is frequently low or absent, and the high doses of its ligands that are usually required to observe effects. A lack of VDR is linked to transcriptional (by silencing by DNA methylation or repression by SNAIL1/2), posttranscriptional (by several microRNAs) or posttranslational (phosphorylation, alteration of subcellular localization) inhibitory mechanisms, and low cell responsiveness to VDR ligands is often associated with upregulation of the 1,25-$(OH)_2D_3$ degrading enzyme CYP24A1 in tumor cells. These are two reasons for the absence of the 1,25-$(OH)_2D_3$ effects in some studies. An additional consideration is that, though fully convinced of the value of animal models, we will almost exclusively review studies performed in human systems in this paper.

2. Epidemiological Studies

2.1. Ecological Studies

Ecological studies treat defined populations as entities and compare health outcomes with respect to risk-modifying factors averaged for each population. The groups are usually defined by geographical location but also can be defined by other factors such as occupation. For vitamin D, various indices related to solar UVB dose can be used—for example, annual solar radiation, summertime solar UVB dose, and latitude. Other risk-modifying factors can be added to adjust for confounding factors. Ecological studies offer some advantages: the data required are generally readily available, often with large datasets, and the analyses are easy to do.

Thus, it is not surprising that the first epidemiological study linking vitamin D to a reduced risk of cancer, albeit indirectly, was an ecological study. In 1936, Peller reported that people who developed skin cancer from light exposure, such as from their occupation, had lower rates of internal cancers [1]. In 1937, he showed that sailors in the U.S. Navy, who had extremely high sun exposure, had eight times the expected rate of skin cancer but only 40% of the expected rate of internal cancers [2]. In 1941, Apperly showed that skin cancer mortality rates increased directly in a non-linear fashion with respect to a solar radiation index in the U.S., while total cancer mortality rates decreased in a linear

fashion [3]. Evidently, the fact that these three articles were related to vitamin D production went unnoticed until they were cited in a review published in 1993 by Ainsleigh [4].

In 1974, the brothers Cedric and Frank Garland were beginning graduate school at the Johns Hopkins School of Public Health. They attended a lecture by Robert N. Hoover, one author of the *Atlas of Cancer Mortality for U.S. Counties*, *1950–1969* [5]. They were struck by the map for mortality, by county, for cancer of the large intestine except the rectum in white males. It showed low rates in three southwest states and high rates in approximately 15 northeast states. The Garlands reasoned that because vitamin D production is the most important health effect of sun exposure, vitamin D must reduce the risk of cancer in the large intestine (colon). They submitted manuscripts to several journals before one was finally accepted and published in the UK in 1980 [6]. They next found support for their hypothesis in terms of the reduced risk of colorectal cancer with respect to dietary vitamin D and calcium [7], prediagnostic serum 25(OH)D concentration, and risk of colon cancer [8]. They later published early ecological studies on solar radiation and the risk of breast cancer [9] and ovarian cancer [10]. Cedric Garland described their discovery and later work in an online posting at Grassrootshealth.net [11].

In 1999, the National Cancer Institute published the *Atlas of Cancer Mortality in the United States*, *1950–1994* [12]. That revised edition used 10 colors (five shades each of blue and red) to show mortality rates for 38 cancers (see the breast cancer map in Garland's web post [11] as well as for other cancers at www.sunarc.org, both accessed on 24 February 2022) rather than only five in the earlier version [5]. Data were also displayed for 3053 counties and 506 state economic areas (totals of data for contiguous counties), and showed results for white people (including Hispanics) and black people separately. Through the previous work of one author (W.B.G.) at NASA in Virginia at the time, a map was available of surface-level solar UVB doses in the United States for July 1992 [www.sunarc.org (accessed 24 on February 2022)]. Solar UVB decreases with increasing latitude, albeit with higher doses at any latitude west of the Rocky Mountains than to the east. That effect is due to a combination of higher surface elevation in the west as well as a thinner stratospheric ozone layer owing to the prevailing westerly winds pushing the tropopause up as the air masses cross the Rocky Mountains. Inverse correlations were found for 11 cancers with respect to solar UVB doses for white Americans and several types of cancer for black Americans [13]. A new set of analyses, this time by state, included several risk-modifying factors: alcohol consumption, Hispanic heritage, lung cancer as an index of smoking, poverty status, and urban/rural residence [14]. However, the attribution to solar UVB did not change much between the two articles.

Later, a separate analysis regarding cancer mortality rates for black Americans was published [15]. Significant inverse correlations were found for lung cancer for males and breast cancer for females. The results for colon, esophageal, gastric, and rectal cancer suggested an inverse correlation with respect to solar UVB, but alcohol consumption rates and lung cancer mortality rates also had similar regression coefficients. As a result, UVB did not have a low enough *p*-value to satisfy the Bonferroni criteria. The results were weak because of the lower numbers of black participants in addition to having lower 25(OH)D concentrations [16].

Several ecological studies of UVB and cancer incidence or mortality rates have been published, particularly between 2002 and 2012 [17]. They helped encourage observational studies, mechanism studies, and clinical trials to explore the relationship between vitamin D and cancer. Single-country studies are preferred because people in individual countries tend to have many similarities, such as clothing preferences, diet, and religion, as well as differences, such as smoking, socioeconomic status, and urban/rural residences. Those comparisons can often be modeled. In addition, variations in solar UVB doses tend to be significant [18,19].

Table 1 outlines the more important solar single-country UVB–cancer ecological studies starting in 2002. Most are from mid-latitude countries, but one is from a subtropical country (Iran) and two encompass the Arctic Circle. Most studies used UVB data from NASA's

Total Ozone Mapping Spectrometer (TOMS) satellite instrument [20], but other indices were used as well, including latitude and global solar radiation.

Table 1. Characteristics of large single-country ecological studies of cancer incidence or mortality rates with respect to solar UVB doses.

Country(ies)	Solar UVB Index	Latitude (°N)	Incidence or Mortality; Years of Data	No. of Cases	Confounding Factors	Ref.
U.S.	Surface UVB, July 1992, TOMS	25–45	Mortality, 1950–1994	9.5 million, 1970–1994	None	[13]
Japan	Annual hours of solar radiation	30–45	Mortality, 2000	180,000	Fat intake for colon, rectum, and prostate; salt intake for stomach cancer	[21]
U.S. (white pop.)	Surface UVB, July 1992	25–45	Mortality, 1950–1994	9.5 million, 1970–1994	Alcohol consumption, Hispanic heritage, lung cancer (index for smoking), poverty, urban/rural residence	[14]
U.S.	300–320 nm, TOMS, north vs. south	25–45	Incidence, 1998–2002; mortality, 1993–2002	Incidence, 3.4 million; mortality, 3.5 million	Age, air quality, alcohol, exercise, income, outdoor occupation, poverty, smoking, urban/rural residence	[22]
Japan	Global solar radiation	30–45	Mortality, 1998–2002	~900,000	Dietary factors, smoking, socioeconomic conditions	[23]
China	TOMS, 305 nm	22–50	Incidence, 1998–2002; mortality, 1990–1992		Urban/rural residence	[18]
Russia	Latitude	43–69	Incidence, mortality, 2008	incidence, ~250,000; deaths, ~140,000	None	[24]
Nordic countries	Lip cancer less lung cancer incidence	55–70	Incidence, 1961–2005	2.8 million	Lung cancer	[25]

Pop., population; TOMS, NASA's Total Ozone Mapping Spectrometer satellite instrument.

One ecological study was based on data by occupation from a study involving 2.8 million cancer incidence cases from 15 million inhabitants of the five Nordic countries aged 30–64 years in the 10-year censuses from 1960 to 1990 [26]. The study included 53 occupational categories. A novel index, lip cancer less lung cancer, was used for long-term UVB exposure [25]. A suspected important risk factor for lip cancer was solar UVB exposure [27]. A study conducted in Denmark reported that outdoor workers employed for more than 10 years had twice the rate of lip cancer than nonmelanoma skin cancer [28]. Smoking also is a well-known risk factor for lip cancer. As expected, people in occupational categories associated with outdoor work, such as farmers, forestry workers, and gardeners, had the lowest cancer incidence rates.

Table 2 presents findings regarding the incidence of specific cancers for males and females with respect to the UVB indices used. Cancers are listed in descending order of incidence rates in the United States in 2009 to show that as the number of cases decreases, so does the likelihood of finding significant correlations with solar UVB. Note that the results from the United States [22], Russia [24], and the Nordic countries [25] are in good agreement.

Table 2. Ecological studies of cancer incidence rates with respect to indices of solar UVB doses.

Incidence [29] (×1000)	Cancer	USA [22]	China [18]	Russia [24]	Nordic [25]
219.4	Lung		–M, FNS, –R, –U		M, FNS
194.3	Breast	F	–F, –R, –U		M, F
192.3	Prostate	M		–M	MNS
147.0	Colorectal		M, F, R		
106.1	Colon	M, F			M, F
71.0	Bladder, urinary	M, F	–M, –F, –R, –U		M, F
68.7	Melanoma	–M, –F		M + F	M
66.0	Non-Hodgkin lymphoma	M, F			NS
57.8	Kidney	M, F		M + F	M, FNS
44.8	Leukemia	M, F	MNS, FNS, R, –U		
42.5	Pancreas	M, F		M + F	M, FNS
42.2	Uterus, corpus	F			FNS
40.9	Rectum	M, F			M, FNS
37.2	Thyroid	MNS, F			
35.7	Oral cavity and pharynx	–M, –F			
23.1	Oral				M
22.6	Myeloma	M, F		M + F	
22.6	Liver		–M, –F, –R, –U		M, FNS
22.1	Brain				M
21.6	Ovary	FNS			
21.1	Stomach (gastric)	M, F	M, F, R, –U	M + F	M?, FNS
16.5	Esophagus	M	M, F, R, –U	M + F	MNS
12.6	Pharynx		–M, –F, –R, –U	–(M + F)	
12.3	Larynx				M
11.3	Cervix	–F	F, R,–U		
9.8	Gallbladder	F			M
9.8	Biliary, other	M, F		M + F	
8.5	Hodgkin lymphoma	M, F			
8.4	Testis				NS
6.2	Small intestine	M, F			M
5.9	Skin, other	–M, –F		–(M + F)	–M
5.3	Anus, etc.	–M, –F			
3.6	Vulva	F			

F, female; FNS, female nonsignificant; M, male; MNS, male nonsignificant; R, rural residence; U, urban residence, –, direct correlation; ?, uncertain.

Table 3 is similar to Table 2 except for showing mortality rates, not incidence rates, and cancers are listed in descending order with respect to cancer mortality rates in the United States in 2009. Note the good general agreement between the findings for mortality rates in Table 3 with incidence rates in Table 2. The main exception is that solar UVB dose was inversely correlated with mortality rates for several cancers in China, for which it was directly correlated with incidence rates.

Table 3. Ecological studies of cancer mortality rates with respect to indices of solar UVB doses.

Mortality [29] (×1000)	Cancer	Japan [23]	USA [14]	USA [22]	China [18]	Russia [24]
159.4	Lung	M, F			M, F, R, U	
69.1	Colorectal	M			M, F, R	
49.9	Colon		M, F	M, F		M + F
40.6	Breast	FNS	M, F	F	F, R	–(M + F)
35.2	Pancreas	M, F	M, FNS	M, F		M + F
27.4	Prostate	MNS	MNS	M		M
21.9	Leukemia			M, F	MNS, FNS	
19.5	Non-Hodgkin lymphoma		M, F	M, F		

Table 3. *Cont.*

Mortality [29] (×1000)	Cancer	Japan [23]	USA [14]	USA [22]	China [18]	Russia [24]
19.2	Rectum		M, F	M, F		M + F
18.2	Liver	M		–M, –F	M, F, R	
14.6	Ovary		F	F		F
14.5	Esophagus	M	M, F	M	M, F, R	M + F
14.3	Bladder, urinary		M, F	M, F	M, F, R	M + F
13.9	Kidney		M, F	M, F		M + F
12.9	Brain			–M, –F		
10.6	Myeloma			M, F		M + F
10.6	Stomach (gastric)	M, FNS	M, F	M, F	M, F, U	M + F
8.7	Melanoma			–M, –F		M + F
7.8	Uterus, corpus		F	F		
7.6	Oral cavity and pharynx			–M, –F		
5.4	Oral		MNS, FNS			
4.1	Cervix		F	–F	–F, –R, –U	
3.7	Larynx		M, F?	MNS, FNS		M + F
3.4	Gallbladder	MNS, F	M, F	M, F		
3.4	Biliary, other			M. F		
2.9	Skin, other			–M, –F		–(M + F)
2.2	Pharynx				–M. –F, –R, –U	
1.6	Thyroid			MNS, F		
1.5	Bone and joint			–M, –F		
1.3	Hodgkin lymphoma		M, F	M, F		
1.1	Small intestine			MNS, F		
0.9	Vulva			F		F
0.7	Anus, etc.			–M, –F		M + F

F, female; FNS, female nonsignificant; M, male; MNS, male nonsignificant; R, rural residence; U, urban residence, –, direct correlation; ?, uncertain.

2.2. Observational Studies Based on Residential UVB Doses

Related to ecological studies of solar UVB and cancer risk are observational studies of ambient solar UVB doses and cancer risk. Cancer incidence data from the prospective National Institutes of Health—AARP Diet and Health Study were used with solar UVB dose data at residential locations to assess the relationship between UVB and cancer risk [30]. The study was limited to participants living in California, Florida, Georgia (Atlanta), Louisiana, Michigan (Detroit), Pennsylvania, and North Carolina. During the 9 years of follow-up, 75,917 participants developed cancer. Erythemal UV data for July from TOMS for 1978–1993 and 1996–2005 were used. Data were adjusted for age; sex; body mass index (BMI); caloric intake; intake of fruit, vegetables, and red and white meat; alcohol consumption; tobacco smoking; education; physical activity; and median household income. Over 9 years of follow-up, UV exposure was inversely associated with total cancer risk (highest vs. lowest quartile) and decreased risk of non-Hodgkin lymphoma and colon, squamous-cell lung, pleural, prostate, kidney, and bladder cancers (all $p_{trend} < 0.05$). UV exposure was associated with increased melanoma risk.

Another example is a nested case–control (NCC) study using 373 esophageal and 249 gastric cancer cases from the UK Biobank with respect to UVB doses at the residential location [31]. Annual solar UVB doses ranged from ~500 kJ/m^2 in the south to ~750 kJ/m^2 in the north. Five controls were matched to each case. Data were available for many cancer risk-modifying factors. Significant reductions were found for adjusted esophageal cancer, adjusted lower-third esophageal cancer, and adjusted gastric cancer, in agreement with ecological studies noted previously.

A further discussion of observational studies of cancer incidence and death with respect to solar UVB is in progress.

2.3. Observational Studies Based on Serum 25(OH)D Concentrations

Observational studies examine correlations between risk-modifying factors and health outcomes such as cancer incidence, survival, and mortality rates. Observational studies include cohort studies, both prospective and retrospective; case–control (CC) studies; and cross-sectional studies. Each type has advantages and disadvantages. For example, most observational studies regarding vitamin D use serum 25(OH)D concentrations as the index of vitamin D status, but assays used to measure 25(OH)D concentrations vary in quality [32]. Furthermore, serum 25(OH)D concentrations change with the seasons and over long periods [33]. Some studies use dietary vitamin D, i.e., oral vitamin D, including dietary sources and supplements. However, using dietary sources to assess vitamin D intake is problematic because diet generally accounts for less than 300 IU/d in the United States. Although meat is an important source of vitamin D as 25(OH)D [34], most food frequency tables do not include data on meat [35]. Some studies use personal or geographical solar UVB doses. This review emphasizes those that use serum 25(OH)D concentrations but will also include a few that used solar UVB doses.

Generally, CC studies of cancer risk report a stronger reduction with respect to serum 25(OH)D concentrations than do other observational studies. However, observational studies using serum 25(OH)D concentration from blood drawn before cancer diagnosis are generally considered more accurate than those in which blood is drawn near the time of cancer diagnosis.

Researchers have hypothesized that because RCTs have generally not been able to confirm findings from observational studies for many health outcomes, including cancer, having the disease may reduce 25(OH)D concentrations; that is, "reverse causation" [36,37]. However, that effect has been shown only for acute inflammatory diseases such as acute respiratory tract infections [38].

Although systemic inflammation may play a role in cancer risk, the inflammation does not rise as high as in, say, COVID-19. Reports on levels of C-reactive protein levels, an index of systemic inflammation, at the time of diagnosis show that for COVID-19, values can range from 1 to 120 mg/L as severity increases [39], whereas for cancer, they are between 1 and 4 mg/L [40]. Thus, systemic inflammation is not high at the time of cancer diagnosis. We are not aware of any other factor that could result in reverse causality regarding 25(OH)D concentrations for undiagnosed cancer. As will be discussed, the main reason for discrepancies between observational studies and RCTs of vitamin D and cancer is that the RCTs have not been properly designed and conducted.

Two articles reported that the longer the follow-up time in observational studies of 25(OH)D concentration and cancer risk, the lower the effect of 25(OH)D concentration [41,42]. The same effect has been found for all-cause mortality rates [43]. The reasons include that serum 25(OH)D concentrations change for several reasons and that 25(OH)D concentration near the time of diagnosis is more important than earlier concentrations, even though cancer may develop over a long period. Figure 1 in Grant's 2012 report [43] shows that the correlation coefficient between serum 25(OH)D concentrations repeated in the same group of participants drops to approximately 0.4 after 14 years.

Most observational studies of 25(OH)D concentration and cancer incidence are prospective cohort or NCC studies. An NCC study of 25(OH)D concentration and incidence of colorectal cancer (CRC) based on two Harvard cohorts [44] is reviewed here to show the complexity of such studies. The Health Professionals Follow-up Study (HPFS), with 18,225 male participants who supplied a blood sample, had 179 cases of CRC during follow-up periods up to 8 years. The analysis of results from the cohort was combined with results from the Nurses' Health Study (NHS) of women, of whom 32,826 gave blood samples, and 193 developed CRC during 11 years of follow-up [45]. In the HPFS, values for many factors were recorded at baseline in 1994, including season of blood donation, BMI, physical activity, aspirin use, smoking, alcohol intake, intake of vitamin D, calcium and retinol, and meat intake. Analyses were made for colon, rectal, and CRC with respect to quantiles of 25(OH)D, showing that though the trend in 25(OH)D concentrations was not significant

for HPFS alone, it was significant when combined with results from NHS. The pooled odds ratio (OR) for CRC for high versus low quintile of 25(OH)D was 0.66 (95% confidence interval [95% CI], 0.42–1.05; p_{trend} = 0.01). The risk of rectal cancer increased with respect to 25(OH)D in the HPFS but decreased in the NHS. Interesting findings also were shown for lifestyle characteristics, including BMI, physical activity, calcium intake, retinol intake, and effect of 25(OH)D measured in winter or summer. Thus, with 372 CRC cases, it was possible to find support for 25(OH)D concentrations reducing the risk of colon cancer and CRC.

A meta-analysis published in 2007 based on five NCC studies found a predicted 50 ± 20% reduction in CRC for 34 ng/mL vs. 6 ng/mL [46].

A pooled analysis of 12 NCC studies for CRC for men showed a relative risk (RR) of 0.93 (95% CI, 0.86–1.00), whereas the pooled analysis for 13 studies for women reported an RR of 0.81 (95% CI, 0.75–0.87) [47]. For men and women combined, the RR was 0.87 (95% CI, 0.75–0.87). A significant reduction in RR was shown for women between approximately 25 and 45 ng/mL, but no significant reduction was evident for men at any range. This analysis did not adjust for follow-up time between blood draw and cancer diagnosis. To examine the effect of follow-up time, plots were made of the ORs or RRs from the meta-analysis by McCullough and colleagues [47]. Table 4 shows the data used. Information regarding the relative weight for each study was not available, so plots were made of OR against follow-up time. Figure 1 shows the results. The RR for zero follow-up time should be approximately 0.75 for men and 0.77 for women. The regression fit to the data for men is OR = 0.74 + 0.031x years, r = 0.79, adjusted r^2 = 0.59, p = 0.002; the regression fit to the data for women is OR = 0.77 + 0.008x years, r = 0.25, adjusted r^2 = 0, p = 0.42. Thus, the lower effect of 25(OH)D on men versus that of women shown in Figure 1 in McCullough and colleagues [47] is due to not accounting for the degradation of the 25(OH)D effect with a longer follow-up time. Providing evidence that the results for men and women should be similar is supported by ecological studies in the United States [14].

Table 4. Data related to Figure 2 in McCullough and colleagues [47].

Study	Follow-Up (Years)	RR	Ref.
Men			
ATBC2	12.5	1.17	[48]
PHS	9.50	1.06	[49]
CLUE II	3.20	0.99	[50]
HPFS	6.30	0.99	[51]
JANUS	5.10	0.93	[52]
EPIC	3.60	0.86	[53]
MEC	1.50	0.86	[54]
CPS-II	3.20	0.83	[55]
JPHC	5.10	0.83	[56]
CARET	4.90	0.82	[57]
PLCO	5.40	0.81	[58]
ABCT1	3.50	0.77	[59]
Women			
ORDET	10.8	1.03	[60]
JPHC	5.10	0.94	[56]
JANUS	5.10	0.90	[52]
BGS	2.30	0.90	[61]
CLUE-II	9.00	0.87	[50]
WHI	3.20	0.87	[62]
NHS	9.60	0.84	[51]
CPS-II	3.20	0.77	[55]
WHS	8.00	0.77	[63]
EPIC	3.60	0.73	[53]

Table 4. *Cont.*

Study	Follow-Up (Years)	RR	Ref.
NYUWHS	12.3	0.72	[64]
PLCO	5.40	0.67	[58]
MEC	1.50	0.63	[54]

ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; BGS, Breakthrough Generations Study; CARET, Carotene and Retinol Efficacy Trial; CLUE II, Cancer Prevention Study II Nutrition Cohort; CPS-II, Cancer Prevention Study II; EPIC, European Prospective Investigation into Cancer and Nutrition; HPFS, Health Professionals Follow-up Study; JANUS, JANUS Serum Bank, Norway; JPHC, Japan Public Health Center-Based Prospective Study; MEC, multiethnic cohort study'; NYUWHS; New York University, Women's Health Study; ORDET, Hormones and Diet in the Etiology of Breast Cancer Risk; PHS, Physicians' Health Study; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; RR, relative risk; WHI, Women's Health Initiative.

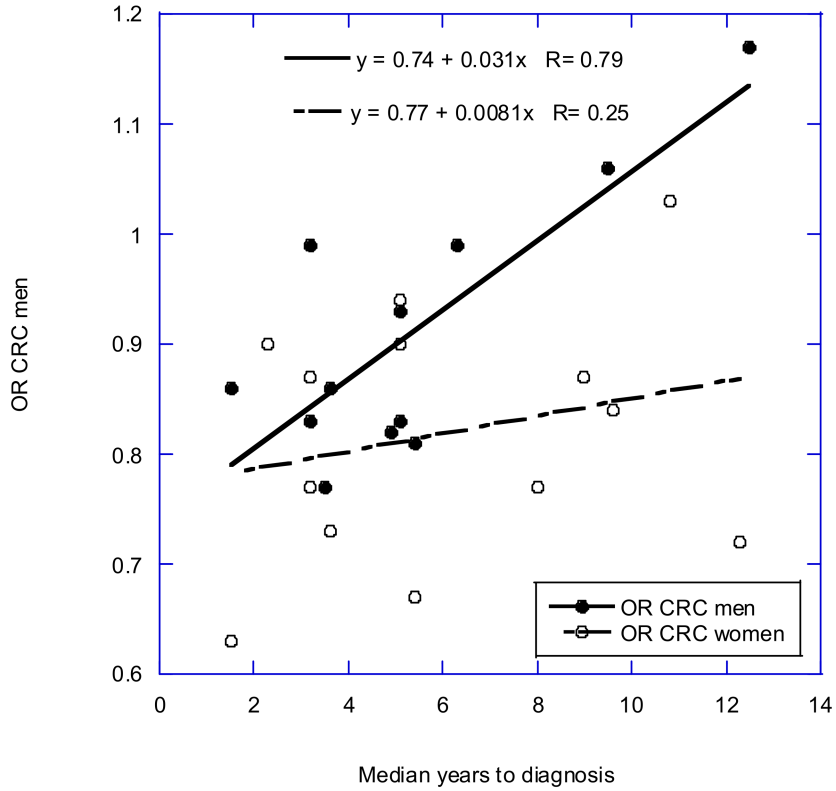

Figure 1. Plot of odds ratio (OR) for CRC against median years to diagnosis for data for men and women used in McCullough and colleagues [47].

In contrast to CRC, prospective and NCC studies with follow-up times greater than 4 years seldom show a significant inverse correlation between serum 25(OH)D concentration and incidence of breast cancer. Breast cancer can develop rapidly, with progression strongly affected by 25(OH)D concentration. Breast cancer is one of the few cancers that have a seasonality in diagnosis, with the highest diagnosis rates in spring and fall [65]. The authors of that study suggested that solar UVB, through producing vitamin D, lowers the risk of breast cancer in summer, whereas higher concentrations of melatonin reduce risk in winter. As a result, many more CC studies of breast cancer with 25(OH)D measured at the time of diagnosis exist than that for CRC.

CC studies of breast cancer incidence with respect to serum 25(OH)D concentrations in pre- and postmenopausal women are discussed first [66,67]. The premenopausal study included 289 cases and 595 matched controls; the postmenopausal study included 1394 cases and 1365 controls. In the premenopausal study, the adjusted OR (aOR) for 25(OH)D >24 ng/mL versus <12 ng/mL was 0.48 (95% CI, 0.29–0.70) and the p_{trend} value for the quantiles was 0.0006. In the postmenopausal study, the aOR for 25(OH)D >30 ng/mL versus <12 ng/mL was 0.31 (95% CI, 0.24–0.42) and the p_{trend} value of the

quintiles was <0.0001. In both studies, the risk increased more rapidly as 25(OH)D concentrations decreased below 12 ng/mL. Those two studies show that several individual factors affect cancer risk but, in general, have little impact on the role of 25(OH)D concentration.

The present study incorporated a search at Google Scholar and the National Library of Medicine's PubMed database for meta-analyses of cancer incidence or mortality rate with respect to serum 25(OH)D concentration. The most recent meta-analyses were favored. For several cancers, Table 5 includes more than one meta-analysis. Of the 44 studies listed as CC in the meta-analysis of breast cancer by Song and colleagues [68], 26 were true CC studies in which serum 25(OH)D concentration was measured near the time of cancer diagnosis for both cases and controls, with 14,851 cases and 30,979 controls. The remaining 18 studies were NCC studies or, in one case, a cross-sectional study. The number of breast cancer cases was 17,871, whereas the number of controls was 21,753. The analysis for cohort studies of breast cancer incidence in that study included the observational study of breast cancer incidence for participants in either two vitamin D plus calcium RCTs or the Grassrootshealth.net community-based cohort [69]. Because those participants generally had serum 25(OH)D measured every 6 months to 1–2 years, that study should have been combined with the CC studies. It reported an 82% lower risk of breast cancer for 25(OH)D concentration >60 ng/mL versus <20 ng/mL (rate ratio = 0.18 [95% CI, 0.04–0.62]).

Table 5. Meta-analyses of observational studies of incidence risk of individual cancer sites related to serum 25(OH)D concentration.

Cancer Site	*N* Studies, Cases, Controls	Type of Study	Follow-Up (Years)	RR (95% CI), High vs. Low	Ref.
All	8, —, —	Prospective, incidence	5–28	0.86 (0.73–1.02)	[70]
All	17, —, —	Prospective, mortality	5–28	0.81 (0.71–0.93)	[70]
Bladder	5, 1251, 1332	CC and NCC, incidence	0 (4), 12, 13	0.70 (0.56–0.88)	[71]
Bladder	2, 2264, 2258	Cohort, incidence	14, 28	0.80 (0.67–0.94)	[71]
Breast	44, 29,095, 53,060	CC and NCC, incidence		0.57 (0.48–0.66)	[68]
Breast	6, 2257, —	Cohort, incidence		1.17 (0.92–1.48)	[68]
Colorectal	11, —, —	1 CC, 9 NCC, 1 meta-analysis, incidence	0–20	0.60 (0.53–0.68)	[72]
Colorectal	6, 1252, —	Cohort, incidence	8–20	0.80 (0.66–0.97)	[72]
Colorectal	15, 6691, —	NCC, incidence		0.67 (0.59–0.76)	[73]
Head and neck	5, —, —	Cohort, incidence	7, 15	0.68 (0.59–0.78)	[74]
Liver	8, 992, —	Cohort, incidence	6–28	0.78 (0.63–0.95)	[75]
Liver	6, 776, —	Cohort, incidence	(0.75), 16–22	0.53 (0.41–0.68)	[76]
Lung	8, 1386, —	Cohort, incidence	7–26	0.72 (0.61–0.85)	[77]
Lung	9, —, —	7 Cohort, 2 CC, incidence		0.84 (0.74–0.95)	[78]
Lung	3, —, —	1 Cohort, 2 CC, mortality		0.76 (0.61–0.94)	[78]
Lung	12, —, —	7 Cohort, 5 CC		1.05 (0.95–1.16)	[79]
Ovarian	8, —, —	CC, cohort, NCC		0.86 (0.56–1.33)	[80]
Pancreatic	5, 1068, —	2 Cohort, 3 NCC, incidence	6.5–21	1.02 (0.66–1.57)	[81]
Pancreatic	5, 2003, —	Cohort, mortality	6.5–21	0.81 (0.68–0.96)	[81]
Prostate	19, 12,786	16 NCC, 3 cohort, incidence		1.15 (1.06–1.24)	[82]
Renal	5, —, —	4 Cohort (+1 CC, 3.5% weighting), incidence	(0), 7–22	0.76 (0.64–0.89)	[83]
Renal	1, —, —	CC, incidence	0	0.30 (0.13–0.72)	[83]
Thyroid	6, 387, 457	CC, incidence	0	Deficiency, 1.30 (1.00–1.69), $p = 0.05$	[84]

95% CI, 95% confidence interval; CC, case–control study; NCC, nested case–control study; parentheses for follow-up years indicate numbers for a very small percentage of the total; RR, relative risk; —, no data.

From the data in Table 5, it is apparent that CC and NCC studies report greater reductions in cancer risk for high versus low 25(OH)D concentration. The reason may be that cohort studies are conducted for longer than CC or NCC studies. That difference lowers the benefit due to 25(OH)D concentrations as a result of changes in 25(OH)D concentration, as discussed previously. Another finding is that studies of mortality rates show greater reductions than studies of incidence rates. That finding is similar to findings in RCTs of cancer as reported, for example, in the VITAL study [85] as well as in a meta-analysis

of results from vitamin D–cancer RCTs [86]. The reason for that finding is probably the presence of many risk-modifying factors that affect cancer incidence but few factors other than vitamin D that affect angiogenesis around tumors, cancer progression, and metastasis into stromal tissue.

Table 6 presents findings from a few meta-analyses of observational studies of vitamin D intake, both from diet and from supplements, and cancer risk. The reductions in cancer risk from oral intake are generally much lower than what is found with respect to serum 25(OH)D concentration studies, largely because differences in oral intakes did not have an observable effect on serum 25(OH)D concentrations. In addition, results with respect to serum 25(OH)D concentrations were not given.

Table 6. Meta-analyses of observational studies of the risk of incidence of individual cancer sites related to vitamin D intake.

Cancer Site	*N* Studies	Type of Study	RR (95% CI), High vs. Low Vitamin D Intake	Ref.
Breast	17	8 CC, 9 cohorts	0.97 (0.92–1.07), per 400 IU/d	[68]
Colorectal	12	CC	0.75 (0.67–0.81)	[72]
Colorectal	6	Cohort	0.89 (0.80–1.02)	[72]
Head and neck	3		0.75 (0.58–0.97)	[74]
Lung	6	Cohort	0.89 (0.83–0.97)	[77]
Lung	5	Cohort	0.85 (0.74–0.98)	[79]
Renal	4	CC	0.80 (0.67–0.95)	[83]
Renal	4	Cohort	0.97 (0.77–1.22)	[83]
Overall cancer death			0.84 (0.74–0.95)	[87]

CC, case–control study; NCC, nested case–control study.

Table 7 presents estimates of the OR for maximum 25(OH)D concentration compared with minimum concentration for several cancers. The reviews obtained from these values did not give numerical values, so they were estimated by inspecting the graphs.

Table 7. Estimates of odds ratio for maximum 25(OH)D concentration compared with minimum concentration for several cancers.

Cancer	Min 25(OH)D (ng/mL)	Max 25(OH)D (ng/mL)	OR (95% CI)	Ref.
All, inc	2	25	~0.6	[70]
Bladder, inc	3	30	~0.55 (0.35–0.70)	[71]
Breast, inc (Song et al.)	5	85	~0.2 (0.1–0.3)	[68]
Breast, inc	15	70	0.18 (0.04–0.62)	[69]
Colorectal, inc	4	55	~0.4 (0.3–0.5)	[73]
Colorectal, inc	10	50	~0.7 (0.4–1.0)	[88]
Liver, inc	4	30	0.35 (0.21–0.48)	[76]
Liver, inc	5	30	~0.6 (0.5–0.7)	[75]
Lung, inc	6	21	0.87 (0.76–0.97)	[89]
Lung, inc	10	24	0.80 (0.61–0.98)	[78]
Lung, mort	10	42	0.37 (0.25–0.53)	[78]
Prostate, inc	0	60	~1.3 (1.1–1.8)	[82]
Prostate, mort	4	43	~0.55 (0.2–1.1)	[90]

Inc, incidence; mort, mortality; OR, odds ratio.

Figure 2 shows the plot of OR for cancer incidence against the difference between minimum and maximum 25(OH)D concentration. The plot indicates a nearly linear relationship between serum 25(OH)D concentration and OR. The linearity between OR and 25(OH)D concentration is supported by results in the breast cancer study by McDonnell and colleagues [69]. Many studies have few participants with 25(OH)D concentrations above 40 ng/mL, thereby limiting the ability to investigate the effects of higher 25(OH)D concentrations.

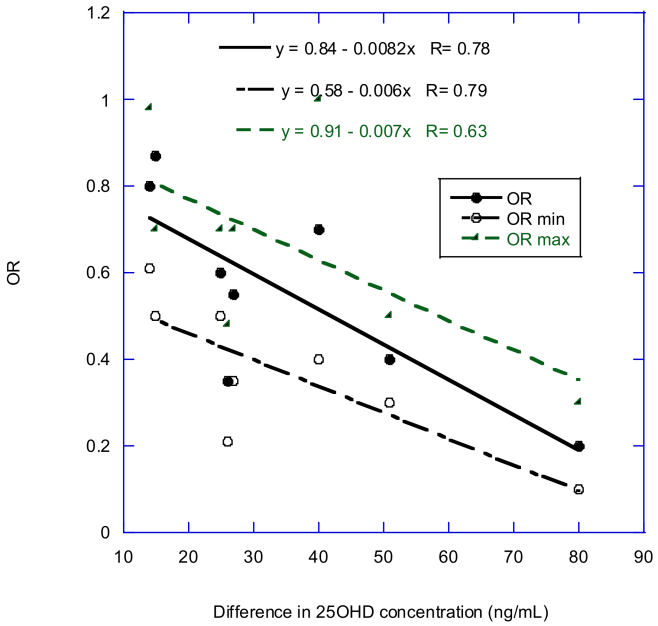

Figure 2. Plot of OR for cancer incidence versus the difference between minimum and maximum 25(OH)D concentration, using data from Table 7, omitting data for all cancer, breast cancer in McDonnell and colleagues [69], and data for prostate cancer.

2.4. RCTs of Vitamin D and Cancer Risk

According to a review published in 2019 [86], nine RCTs have studied how vitamin D supplementation affects cancer incidence, of which five also studied the effect on cancer mortality rate. The relative risk of vitamin D supplementation in the treatment versus placebo groups for cancer incidence was 0.98 (95% CI, 0.93–1.03), whereas for cancer, the mortality rate was 0.87 (95% CI 0.79–0.96). Results did not change significantly if they were analyzed by daily intake versus nondaily intake in a large bolus or attained 25(OH)D concentration >40 ng/mL. However, as pointed out in a recent review by Pilz and colleagues, RCTs rarely found a significant benefit from vitamin D supplementation [91].

The information on most of the trials discussed in [86] plus another published thereafter are presented in Tables 8 and 9. As can be seen in Table 8, none of the trials were well designed based on what is now known. Not all trials measured baseline 25(OH)D concentration and when they did, the concentrations were almost always above mean population values. Only five reported achieving 25(OH)D concentrations, and both baseline and achieved concentrations were generally based on a fraction of all participants. Four trials used infrequent bolus doses, which were done to improve compliance but resulted in large variations in 25(OH)D concentration between doses since the half-life of 25(OH)D is approximately two weeks. Some of the trials also gave calcium to the treatment arm but not the control arm. In all cases, participants were permitted to take modest vitamin D supplement doses and solar UVB exposure was not controlled. The mean BMI was generally high in the trials, which is a problem since those with higher BMI do not have the same response for a similar change in 25(OH)D concentration as those with lower BMI. For example, the VITAL study [86] reported that participants with BMI <25 kg/m^2 of body surface area had a significantly reduced risk of cancer from vitamin D supplementation (hazard ratio = 0.76 [95% CI, 0.63–0.90]) but not for higher BMI categories, even though the change in 25(OH)D was near 12 ng/mL for all three BMI categories. The apparent reason is that obesity is an important risk factor for cancer and vitamin D has a limited ability to overcome the mechanisms whereby obesity increases risk of cancer [92]. Finally, only a few of the trials were explicitly designed with cancer incidence a primary outcome.

Table 8. Characteristics of ten RCTs that investigated the effect of vitamin D supplementation on risk of cancer incidence and/or mortality rate.

Location	Mean Baseline and Achieved 25(OH)D (ng/mL), Treatment Arm	Vitamin D Dose (IU) Frequency in Treatment Arm	Duration (Years)	Mean BMI (kg/m^2)	Original Purpose	Reference
UK		100,000/ (4 months)	5.5	24 ± 3	fracture incidence, cause of death	[93]
USA		400/day + 1 g/day Ca	7	28?	colorectal cancer incidence, mortality	[94]
Nebraska, USA	29, 38	1100/day + 1.5 g/day Ca; 1.5 g/day Ca	4	29 ± 6	fracture incidence	[95]
Australia	21, 24–48	500,000/year			falls and fractures	[96]
England, Scotland		800/day; 1 g/d Ca; 800/day + 1 g/day Ca	3			[97]
Nebraska, USA	33, 44	2000/day + 1500 mg/day Ca	4	30 ± 7	cancer	[98]
New Zealand	26, –	100,000/mo	3.3 ± 0.8	28 ± 5	disease incidence with respect to bolus dose of vitamin D	[99]
USA	30, 41	2000/day	5.3	31	cancer and cardiovascular disease risk	[85]
Australia	31 ± 10, 46 ± 12	60,000/ month	5	27?	mortality by disease	[100]

Table 9. Outcomes of ten RCTs that investigated the effect of vitamin D supplementation on risk of cancer incidence and/or mortality rate with respect to intention to treat.

Location	Number of Participants, Cancer Cases, Deaths, Treatment Arm	Number of Participants, Cancer Cases, Deaths, Non-Vitamin D Arm	RR, Incidence (95% CI)	RR, Mortality (95% CI)	Reference
UK	1345, 163, 63	1341, 147, 72	1.11 (0.86–1.42)	0.86 (0.61–1.20)	[93]
USA	18,176, 1634, 344	18,106, 1655, 382	0.98 (0.91–1.05)	0.89 (0.77–1.03)	[94]
Nebraska, USA	446, 13, –	733, 37, –	0.76 (0.38–1.55)		[95]
Australia	1131, 7	1125, 10	0.70 (0.27–1.82)		[96]
England, Scotland	1306, 182, 78; 1311, 189, 95	1343, 187, 73; 1332, 165, 83	1.24 (0.80–2.28)	1.26 (0.73–3.26)	[97]
Nebraska, USA	1156, 45, –	1147, 64, –	0.70 (0.47–1.02)		[98]
New Zealand	2558, 302, –	2550, 293, –	1.01 (0.81–1.25)		[99]
USA	12,927, 793, 154	12,946, 824, 187	0.96 (0.88–1.06)	0.83 (0.67–1.02)	[85]
Meta-analysis for ten incidence trials and five mortality rate trials			0.98 (0.93–1.03)	0.87 (0.79–0.96)	[86]
Australia	21,315, –, 221	10,662, –, 189		1.15 (0.96–1.39)	[100]

Only one outcome based on intention to treat was significantly reduced, that of cancer mortality rate in the VITAL trial [85]. Nonetheless, a meta-analysis of five trials found a significant reduction in the cancer mortality rate [86].

The main problem with vitamin D RCTs seems to be that they are generally designed and conducted by following guidelines for pharmaceutical drugs rather than nutrients. For drugs, the only source of the agent is assumed to be what is given to participants in the treatment arm, and a linear dose–response relationship is presumed. Neither assumption is valid for vitamin D. As a result, participants generally have mean 25(OH)D concentrations

above the population's mean values, participants are given small doses of vitamin D, and participants in both the treatment and control arms are permitted to take additional vitamin D supplements as well as produce vitamin D through solar UVB exposure.

Robert Heaney outlined the guidelines for nutrient RCTs in 2014 [101], which were updated in 2018 [102]. The principal guidelines adapted for vitamin D are that:

- Baseline 25(OH)D concentrations should be measured and used as a criterion for inclusion in the study;
- The vitamin D dose should be large enough to increase 25(OH)D concentration to the point at which it would have an observable effect on health outcomes;
- Achieved 25(OH)D concentrations should be measured;
- Conutrient status must be optimized to ensure that vitamin D is the only nutrient-related limiting factor in the response.

No RCT investigating the role of vitamin D in reducing risk of cancer appears to have followed those guidelines.

Some secondary results of the vitamin D–cancer RCTs have yielded useful information. The VITAL study also reported that African American participants had a trend for reduced risk of cancer incidence (hazard ratio = 0.77 [95% CI, 0.59–1.01]). According to the report's supplementary material for African Americans who supplied 25(OH)D concentration values, the baseline 25(OH)D was 25.0 ng/mL, and the achieved 25(OH)D concentration was 39.7 ng/mL. Those values are in contrast to 31.4 and 42.4 ng/mL, respectively, for non-Hispanic white participants.

In addition, two RCTs showed some effect of vitamin D plus calcium supplementation on risk of cancer [95,98]. When those data were pooled with data from the Grassroots Health volunteer cohort and analyzed by achieved 25(OH)D concentration, the incidence rate of breast cancer for women with 25(OH)D concentrations $\geq$60 versus <20 ng/mL had a rate ratio of 0.18 (95% CI, 0.04–0.62; $p = 0.006$).

3. Perspectives on Epidemiological Studies

3.1. Ecological Studies

As would be generally expected, incidence and mortality rates are generally inversely correlated with solar UVB indices unless UVB exposure is linked to increased risk, such as that for melanoma and other skin cancer. The direct correlation with oral cavities and the pharynx in the United States is consistent with UVB exposure's being a risk factor for lip cancer. Solar UVB exposure increases human papillomavirus (HPV) concentrations, as evidenced by peak rates of positive Pap smears for cervical cancer in Denmark in August [103]. HPV is a risk factor for head and neck cancer [104]. HPV is also hypothesized to be an important risk factor for melanoma [105].

The finding that the incidence rates for several cancers are directly correlated with solar UV in China, whereas most of the cancer mortality rates are inversely correlated, is probably owing to the fact that air pollution levels are much higher in northern than in southern China [106]. In addition, vitamin D generally reduces the risk of cancer mortality rates rather than incidence rates. The reasons may include that although many factors affect cancer incidence, few factors affect cancer progression and metastasis.

Because the countries included are different in many respects, including diet, ethnicity, latitude, and pollution level, ecological studies offer strong evidence that UVB irradiance affects cancers similarly regardless of many other factors.

An important reason why ecological studies have shown robust relationships between indices of solar UVB doses is that they included many cases of cancer. Researchers conducting earlier ecological studies were more likely than researchers of more recent studies to find significant correlations with UVB doses because people back then spent more time in the sun without concern for skin cancer or photoaging, and obesity rates were lower.

3.2. Observational Studies

Several findings are important from the analyses presented regarding observational studies.

First, the inverse relationships between serum 25(OH)D concentration and cancer incidence or mortality rates are similar to those between solar UVB and cancer reported in ecological studies. The primary exception is for head and neck cancer; serum risk was inversely correlated with both serum 25(OH)D concentration and vitamin D intake. However, ecological studies showed direct correlations between solar UVB and both incidence and mortality rates for oral cavity/pharynx and pharynx cancers, although one study reported an inverse relationship for laryngeal cancer [25].

Secondly, a long follow-up time was again found to significantly decrease the observed beneficial effect of 25(OH)D concentration. For example, the meta-analysis of CRC risk with respect to 25(OH)D concentration by Hernandez-Alonso and colleagues [72] had 11 studies (one CC, nine NCC, and one meta-analysis) and six prospective cohort studies. The OR for the CC study was 0.45 (95% CI, 0.36–0.57). For the nine NCC studies, the mean follow-up time was near 8 years, and the OR was 0.63, whereas for the prospective cohort studies, the mean follow-up time was 13 years, and the OR was 0.80 (95% CI, 0.66–0.97).

Some parties have argued that CC studies with 25(OH)D concentration measured near the time of diagnosis would be the best type of observational study due to possible reverse causality [53]. There is no evidence to indicate that having undiagnosed cancer reduces 25(OH)D concentration other than perhaps decreasing with the progression cancer stage. Thus, CC studies, which are easier to conduct than prospective studies, are preferred.

The epidemiological and mechanical evidence regarding solar UVB exposure and vitamin D presented here generally satisfy Hill's criteria for causality in a biological system (based on Kosh's postulates) [107–109]. The only weakness is that RCTs have not yielded strong support, largely because they were poorly designed and conducted. However, as argued by Dr. Thomas R. Frieden, former head of the U.S. Centers for Disease Control and Prevention, in a review in *The New England Journal of Medicine*, RCTs have substantial limitations [110]. The review tabulates the strength and limitations of 11 study designs, including RCTs, prospective cohort, retrospective cohort, case-control, and ecological studies. It concludes by stating that there is no single, best approach to the study of health interventions, and clinical and public health decisions are almost always made with imperfect data.

3.3. Historical Overview

Many of the articles reviewed regarding epidemiological studies of solar UVB dose or exposure and vitamin D played important roles in developing the understanding of the role of vitamin D in reducing risk of cancer incidence and mortality rates. Table 10 lists a few of them in chronological order. Note that the importance of some of the articles, notably those reported prior to 1980, was not recognized until many years later.

Table 10. List of epidemiological studies that had important findings in the history of solar UVB exposure and/or vitamin D and cancer.

Year	Finding	Reference
1936	Sun exposure can cause skin cancer but reduce risk of internal cancer.	[1]
1937	US Navy personnel highly exposed to sun had high skin cancer rates but low internal cancer rates.	[2]
1941	Cancer mortality rates for whites in the U.S. found inversely related to a solar radiation index while skin cancer (melanoma) mortality rates were directly related.	[3]
1980	Annual solar radiation dose inversely correlated with colon cancer mortality rate, USA, vitamin D production suggested.	[6]
1985	Dietary vitamin D and calcium inversely correlated with colorectal cancer incidence.	[7]
1989	Serum 25(OH)D concentration inversely correlated with colon cancer incidence.	[8]

Table 10. *Cont.*

Year	Finding	Reference
1990	Annual solar radiation dose inversely correlated with breast cancer mortality rate in the U.S.	[9]
2002	Mortality rates for thirteen types of cancer are inversely correlated with solar UVB doses in the U.S., 1970–1994.	[13]
2006	A Harvard cohort study finding that incidence of several types of cancer were inversely correlated with predicted 25(OH)D concentration.	[111]
2006	An ecological study in the U.S. finding that incidence and mortality rates for many types of cancer were inversely correlated with solar UVB doses.	[22]
2007	A meta-analysis presenting a 25(OH)D concentration-colorectal cancer incidence relationship.	[46]
2007	An RCT conducted in the U.S. finding that vitamin D supplementation significantly reduced risk of all-cancer incidence rate.	[95]

4. Mechanisms Introduction

The first experimental studies supporting this effect of 1,25-$(OH)_2D_3$ were reported in 1981. They addressed the inhibition of human melanoma cell proliferation and the induction of the differentiation of mouse myeloid leukemia cells and were by D. Feldman's and T. Suda's groups, respectively [112,113]. Since then, many laboratories have described a high number of antitumoral effects of 1,25-$(OH)_2D_3$ on a variety of molecular mechanisms and cellular processes during carcinogenesis. Previous reviews have discussed some of these mechanisms in particular cancer types [114–119]. In this review, we update the current knowledge on 1,25-$(OH)_2D_3$ antitumor mechanisms.

4.1. Inhibition of Tumor Cell Proliferation

1,25-$(OH)_2D_3$ exerts an antiproliferative action on tumor cells by direct and indirect mechanisms that are partially redundant and sometimes function simultaneously in target cells. Of note, this action is mostly independent of *TP53* tumor suppressor gene status.

Direct mechanisms. In many cancer cell types, 1,25-$(OH)_2D_3$ directly arrests the cell cycle in the G_0/G_1 phase by downregulating cyclin-dependent kinases (CDKs: CDK4, CDK6) and repressing the genes that encode cyclins D1 and C (*CCND1, CCNC*) and CDK inhibitors $p21^{CIP1/WAF1}$ (*CDKN1A*), $p27^{KIP1}$ (*CDKN1B*) and p19 (*CDKN2D*) [116,119]. The induction of $p27^{KIP1}$ expression takes place at the promoter/transcriptional level and posttranslationally by the inhibition of its degradation [120–122]. These effects hamper retinoblastoma (Rb) protein phosphorylation and thus the activation of the E2F family of transcription factors, which trigger a series of target genes that are critical to entering the cell cycle from the quiescent state. In addition, an Rb-independent G_1 arrest has been described that is probably a consequence of the repression of the *MYC* oncogene [123]. Thus, 1,25-$(OH)_2D_3$ represses *MYC* expression via direct [124] or indirect transcriptional inhibition by antagonism of the Wnt/β-catenin pathway [125,126], the induction of cystatin D [127] or the MYC antagonist MAD/MXD1 [128], by repressing long non-coding *(lnc)RNA CCAT2* [129] or by promoting MYC protein degradation [130] in several carcinoma cell types.

In some systems (colon and gastric cancer cells), 1,25-$(OH)_2D_3$ downregulates other proliferative genes such as *FOS*, *JUN*, *JUNB*, and *JUND* proto-oncogenes, *G0S2* (G_0/G_1 switch 2), and *CD44*, while it upregulates *GADD45A* (growth arrest and DNA damage 45a), *MEG3* (Maternally expressed gene 3, a lncRNA) and *NAT2* (N-acetyltransferase 2) [131–134]. Additionally, 1,25-$(OH)_2D_3$ induces antiproliferative genes such as *CEBPA* (CCAAT-enhancer-binding protein-α) and *IGFBP3* (insulin-like growth factor binding protein-3) in breast, prostate, or colon carcinoma cells, respectively [131,135,136]. IGFBP3 mediates the induction of $p21^{CIP1/WAF1}$ by 1,25-$(OH)_2D_3$ in prostate carcinoma cells [136], and microRNA *miR-145* the repression of *CDK2*, *CDK6*, *CCNA2*, and *E2F3* genes and the antiproliferative effect

of 1,25-$(OH)_2D_3$ in gastric cancer cells [137]. In breast carcinoma and anaplastic thyroid cancer cells, 1,25-$(OH)_2D_3$ causes G_2/M phase arrest probably as a consequence of the downregulation of CDK2 activity due to the E2F blockade by non-phosphorylated Rb protein [138]. vitamin D analogues also inhibit proliferation through induction of G_1 phase arrest of some hematological cancer cells (lymphoma, myeloma, B-cell acute lymphoblastic leukemia and acute myeloid leukemia) [139].

Indirect mechanisms. 1,25-$(OH)_2D_3$ interferes with several mitogen signaling pathways in a context-dependent fashion. Thus, 1,25-$(OH)_2D_3$ decreases the expression of epidermal growth factor receptor (EGFR) and promotes its ligand-induced internalization in colon carcinoma cells [140,141]. Additionally, it diminishes EGFR signaling through the induction of E-cadherin and the repression of SPROUTY-2 and the renin-angiotensin system [125,142–144]. 1,25-$(OH)_2D_3$ and certain analogues interfere with the insulin-like growth factor (IGF)-I/II pathway by inhibiting IGF-II secretion and increasing IGFBP3 and IGFBP6 levels, and by inducing type II IGF receptor (IGFR-II), which accelerates IGF-II degradation and downregulates this pathway [145,146]. In oral squamous cell carcinoma cells, the 1,25-$(OH)_2D_3$ analogue Eldecalcitol antagonizes the mitogenic action of fibroblast growth factor (FGF)1/2 by repressing nuclear factor *kappa* B (NF-*k*B) and inducing *miR6887-5p*, which targets 3′UTR mRNA of heparin-binding protein 17/FGF-binding protein-1 (HBp17/FGFBP-1), a FGF2 chaperone [147,148]. In addition, 1,25-$(OH)_2D_3$ inhibits the mitogenic action of platelet-derived growth factor (PDGF)-BB in prostate cancer cells by downregulating PDGF receptor β [149]. The effect of 1,25-$(OH)_2D_3$ on hepatocyte growth factor (HGF) signaling is cell-type dependent. It is inhibitory in hepatocellular cells by reducing the expression of c-Met, the tyrosine kinase HGF receptor [150] and in promyelocytic leukemia cells by downregulating HGF RNA [151], but activating in some non-tumoral cell types [152].

1,25-$(OH)_2D_3$ also diminishes the proliferation of breast cancer cells by inhibiting estrogen synthesis and signaling through estrogen receptor (ER)α [153] and by downregulating RAS expression and the phosphorylation of its downstream effectors MEK and ERK1/2 [154]. The inhibition of pituitary transcription factor (Pit)-1 is another antiproliferative effect of 1,25-$(OH)_2D_3$ in breast cancer cells. Pit-1 expression is higher in tumors than in normal breast. It regulates growth hormone (GH) and prolactin (PRL) secretion and leads to increased cell proliferation, invasiveness, and metastasis [155]. 1,25-$(OH)_2D_3$ reduces Pit-1 expression and the increase in cell proliferation either directly or indirectly through GH and/or PRL [156].

Another indirect mechanism of the antiproliferative effect of 1,25-$(OH)_2D_3$ is the regulation of miRs. Thus, *miR-22* is induced by 1,25-$(OH)_2D_3$ and contributes to its antiproliferative effect on colon carcinoma cells 1,25-$(OH)_2D_3$ [157] and has antitumor effects in other carcinomas. Additionally, a recent study indicates that *miR-1278* sensitizes cells to 1,25-$(OH)_2D_3$ by suppressing the expression of CYP24A1 [158].

Transforming growth factor (TGF)-β is a strong inhibitor of epithelial cell proliferation in normal cells and at early steps in the tumorigenic process. 1,25-$(OH)_2D_3$ activates latent TGF-β and induces the expression of type I TGF-β receptor, which sensitizes breast and colon carcinoma cells to the growth inhibitory action of TGF-β [159,160]. Of note, TGF-β signaling is blocked in around 30% of colon cancers due to mutation of the genes encoding TGF-β receptor type II, SMAD2, or SMAD4. In contrast, TGF-β promotes at late stages epithelial-to-mesenchymal transition (EMT), migration, invasion, immunosuppression, and metastasis. As discussed in the following sections, these protumorigenic effects of TGF-β on tumor and stromal cells later in carcinogenesis are counteracted by 1,25$(OH)_2D_3$.

Concordantly with the association between low vitamin D status and poorer overall survival and progression-free survival in myeloid and lymphoid malignancies [161], in several types of leukemic cells, 1,25-$(OH)_2D_3$ regulates essential pathways for survival and proliferation such as TLR, STAT1/3 or PI3K/AKT that are induced by immune cell–cell or cytokine activation [162,163].

4.2. Sensitization to Apoptosis, Combined Action with Chemotherapy and Radiotherapy

Obviously, 1,25-$(OH)_2D_3$ per se does not induce apoptosis or any other type of cell death. However, it controls the expression of genes involved in apoptosis in cell systems in a way that is compatible with sensitization to the induction of apoptosis by other agents. Thus, in colon, prostate, and breast carcinoma cells, 1,25-$(OH)_2D_3$ upregulates several pro-apoptotic proteins (BAX, BAK, BAG, BAD, G0S2) and suppresses survival and anti-apoptotic proteins (thymidylate synthase, survivin, BCL-2, BCL-XL). In this way, it favors the release of cytochrome C from mitochondria and the activation of caspases 3 and 9 that lead to apoptosis promoted by a variety of signals [116,117]. Moreover, 1,25-$(OH)_2D_3$ induces apoptosis in ovarian carcinoma cells by caspase 9 activation [164] and by downregulation of telomerase reverse transcriptase (hTERT) via the induction of *miR-498* [165,166]. Intriguingly, while the aforementioned effects seem to be independent of the *TP53* gene, a study has proposed that mutant p53 protein interacts physically with VDR in breast cancer cells, converting the ligand into an anti-apoptotic agent by mechanisms that remain unclear [167].

In addition, 1,25-$(OH)_2D_3$ and metformin have additive/synergistic antiproliferative and proapoptotic effects in colon carcinoma and other types of cells, which are modulated but not hampered by *TP53* status [168]. Moreover, in an in vitro model developed to evaluate the crosstalk between tumor-associated macrophages and colon carcinoma cells, 1,25-$(OH)_2D_3$ restored the sensitivity of these cells to TRAIL-induced apoptosis by interfering with the release of interleukin (IL)-1β by macrophages [169]. Interestingly, the *TP53* mutation and suppression of *miR-17~92* polycistron are highly toxic in non-small lung cancer cell lines due to the upregulation of VDR signaling [170].

Based on these data, many completed and ongoing studies investigate the antitumor action of the combination of 1,25-$(OH)_2D_3$ and a variety of chemotherapeutic agents (5-fluorouracil, gemcitabine, paclitaxel, imatinib, and cisplatin, among others), inhibitors (of EGFR, HER2, HER4, JAK1/2 tyrosine kinases, estrogen or aromatase) and apoptosis inducers (dexamethasone, trichostatin A and 5-aza-2′-deoxycytidine, among others) in cells and animal models of several types of cancers see [116,119] and references therein. The definitive results of these studies are expected to constitute the foundation for clinical trials.

4.3. Regulation of Autophagy

Autophagy is a process of elimination of cytoplasmic waste materials and dysfunctional organelles that serves as a cytoprotective mechanism but that, when excessive, leads to cell death. vitamin D activates autophagy in many organs in healthy conditions to preserve homeostasis. It can also induce autophagy as protection against cell damage caused by intracellular microbial infection, oxidative stress, inflammation, aging, and cancer [171].

In cancer, VDR ligands trigger autophagic death by inducing crucial genes in several cancer cell types. Thus, 1,25-$(OH)_2D_3$ and its analogues de-repress the key autophagic MAP1LC3B (LC3B) gene and activate 5′-AMP-activated protein kinase (AMPK) via increased cytosolic Ca^{2+} and activation of Ca^{2+}/calmodulin-dependent protein kinase β in breast carcinoma cells [172]. In Kaposi's sarcoma cells [173] and myeloid leukemia cells [174], vitamin D compounds inhibit PI3K/AKT/mTOR signaling and activate Beclin-1-dependent autophagy. 1,25-$(OH)_2D_3$ also induces autophagy through the mTOR pathway in Pfeiffer diffuse large B lymphoma cells [175] and is mediated by activation of DNA damage-inducible transcript 4 (DDIT4), in cutaneous squamous cell carcinoma cells [176]. In addition, a recent study has shown that 1,25-$(OH)_2D_3$ promotes autophagy in acute myeloid leukemia cells by inhibiting miR-17-5p-induced Beclin-1 overexpression [177].

Moreover, 1,25-$(OH)_2D_3$ or EB1089 increase radiation efficiency via promotion of autophagic cell death in a VDR- and p53-dependent fashion in non-small cell lung cancer and breast cancer cells [178–181]. Additionally, synergy between 1,25-$(OH)_2D_3$ and temozolomide in tumor reduction and prolonged survival time has been reported in rat-cultured glioblastoma cells and in an orthotopic xenograft model [182].

4.4. Induction of Cell Differentiation, Inhibition of Epithelial-to-Mesenchymal Transition

Cell differentiation is usually, but not necessarily, linked to an arrest in proliferation, and both processes put a brake on tumorigenesis. Carcinoma is the most frequent type of solid cancer. Carcinomas originate from the transformation of epithelial cells in a process that involves the early loss of two key features of their differentiated phenotype: apical-basal polarity and adhesiveness (cell–cell and cell–extracellular matrix, ECM). Loss of epithelial differentiation results from the acquisition of a cellular program called epithelial-mesenchymal transition (EMT), which implies changes in gene expression, triggered by a group of transcription factors (EMT-TFs: mainly SNAIL1, SNAIL2, ZEB1, ZEB2 and TWIST1). EMT provides tumor cells with features of malignancy such as migratory capacity, stemness and diminished apoptosis that facilitate invasion and metastasis and possibly cause resistance to cytotoxic chemotherapy and radiotherapy, and to immunotherapy [183]. The EMT process is activated by a variety of agents and signals that induce or activate the EMT-TFs, such as TGF-β, Wnt, Notch, and ligands of several receptors with tyrosine kinase activity and cytokine receptors.

1,25-$(OH)_2D_3$ has a prodifferentiation effect on several types of carcinoma cells either by direct upregulation of epithelial genes and/or the repression of key EMT-TFs, as shown in [184,185]. In breast cancer cells, 1,25-$(OH)_2D_3$ promotes the formation of focal adhesion contacts, structures of binding to the ECM, by increasing the expression of several integrins, paxillin and focal adhesion kinase. Additionally, 1,25-$(OH)_2D_3$ reduces the expression of the mesenchymal marker N-cadherin and the myoepithelial proteins P-cadherin, integrins α_6 and β_4, and α-smooth muscle actin, which are associated with more aggressive and lethal forms of human breast cancer [186]. In colon carcinoma cells, 1,25-$(OH)_2D_3$ upregulates an array of intercellular adhesion molecules that are constituents of adherens junctions and tight junctions, including E-cadherin, occludin, claudin-2 and -12, and ZO-1 and -2 [125,131]. As mentioned by JoEllen Welsh in an excellent recent review [187], breast cancer heterogeneity is reflected in available model systems of this disease, including human breast cancer cell lines. These differ in the expression of VDR and other hormone receptors and in their global gene expression profile and phenotype. Consequently, results vary widely in laboratory studies of 1,25-$(OH)_2D_3$ and other VDR ligands, which show a heterogeneous, usually multilevel protective action that affects a variety of pathways (ERBB2/NEU-ERK-AKT, WNT/β-catenin, JAK-STAT, NF-κB, ERα). These studies have rendered only a few genes that are commonly regulated: *CYP24A1*, *CLMN*, *EFTD1* and *SERPINB1*.

Remarkably, the induction of E-cadherin by 1,25-$(OH)_2D_3$ in colon carcinoma cells has been reproduced in tumor cell lines derived from breast, prostate, non-small cell lung, and squamous cell carcinomas, usually associated with an increase in epithelial differentiation [184]. The mechanism of E-cadherin induction by 1,25$(OH)_2D_3$ in human colon cancer cells is transcriptional indirect. It requires transient activation of the RhoA-ROCK-p38MAPK-MSK1 signaling pathway [126]. Phosphatidylinositol 5-phosphate 4-kinase type II β is also needed for E-cadherin induction by 1,25-$(OH)_2D_3$ in these cells [188]. In agreement with the transcriptional regulation, 1,25-$(OH)_2D_3$ treatment causes partial demethylation of CpG sites of *CDH1* promoter in MDA-MB-231 triple-negative breast cancer cells [189]. In addition, 1,25-$(OH)_2D_3$ induces and/or redistributes several cytokeratins, F-actin, vinculin, plectin, filamin A and paxillin that modulate the actin cytoskeleton and the intermediate filament network, changing stress fibers and the ECM binding structures (focal adhesion contacts and hemidesmosomes) [125,126]. In summary, 1,25$(OH)_2D_3$ increases cell–cell and cell-ECM adhesion.

1,25-$(OH)_2D_3$ inhibits SNAIL1 and ZEB1 expression in non-small cell lung carcinoma cells, accompanied by an increase in E-cadherin expression, vimentin downregulation, and maintenance of epithelial morphology [190]. The 1,25-$(OH)_2D_3$ analogue MART-10 inhibits EMT in breast and pancreatic cancer cells through the downregulation of SNAIL1, SNAIL2 and TWIST1 in breast cancer cells [191,192]. 1,25-$(OH)_2D_3$ causes the downregulation of SNAIL1 and SNAIL2 in colon and ovarian carcinoma cells [193,194].

In addition, 1,25-$(OH)_2D_3$ induces several modulators of the epithelial phenotype that can influence the expression of these EMT-TF. Thus, it increases by a transcriptional indirect mechanism the expression of *KDM6B*, a histone H3 lysine 27 demethylase that mediates the induction of a highly adhesive epithelial phenotype in human colon cancer cells [195]. *KDM6B* depletion upregulates SNAIL1, ZEB1, and ZEB2 and increases the expression of mesenchymal markers fibronectin and LEF-1, and claudin-7. Accordingly, *KDM6B* and *SNAI1* RNA expression correlate inversely in samples from human colon cancer patients [195]. Furthermore, 1,25-$(OH)_2D_3$ directly upregulates the expression of cystatin D, which represses SNAIL1, SNAIL2, ZEB1, and ZEB2, and induces the expression of E-cadherin and other adhesion proteins such as occludin and p120-catenin. Accordingly, cystatin D and E-cadherin protein expression directly correlate in colon cancer, and loss of cystatin D is associated with poor tumor differentiation [127]. The *SPRY2* gene encodes SPROUTY-2, a modulator of tyrosine kinase receptor signaling that is strongly repressed by 1,25$(OH)_2D_3$ in colon carcinoma cells [143]. SPROUTY-2 promotes EMT through upregulation of ZEB1 and downregulation of the epithelial splicing regulator ESRP1. Consequently, SPROUTY-2 represses genes that encode E-cadherin, claudin-7, and occludin and the important regulators of the polarized epithelial phenotype LLGL2, PATJ, and ST14 [143,196].

The induction of differentiation seems to be a less important protective mechanism of 1,25-$(OH)_2D_3$ in hematological malignancies than in solid cancers. 1,25-$(OH)_2D_3$ induces differentiation almost exclusively of acute myeloid leukemia cells [197–199]. Thus, 1,25$(OH)_2D_3$ increases the expression of markers of the monocyte-macrophage phenotype such as CD14 and some proteins involved in phagocytosis and adherence to substratum, including CD11b [139,200]. A number of genes and proteins have been proposed as mediators of this prodifferentiation action of 1,25-$(OH)_2D_3$, such as PI3K, *CEBPB*, and *CDKN1A* [201–203]. Differentiation of acute myeloid leukemia cells was also described by the combination of 1,25-$(OH)_2D_3$ with l-asparaginase [204]. Interestingly, a recent study reports that liganded VDR has a strong prodifferentiation effect in acute myeloid leukemia cells harboring mutations in *IDH* gene encoding isocitrate dehydrogenase. This is the case because the oncometabolite 2-hydroxyglutarate that is produced by mutant IDH potentiates VDR signaling in a CEBPα-dependent manner [205]. In addition, prodifferentiation effects of VDR agonists have been reported in follicular non-Hodgkin's lymphoma cells, with increased expression of mature B-cell markers [206].

4.5. Antagonism of Wnt/β-Catenin Signaling Pathway

The Wnt/β-catenin signaling pathway is activated by several members of the Wnt family of secreted proteins (19 in humans) during ontogenesis and adult life, which play important roles in the development and homeostasis of many tissues and organs. The binding of these Wnt factors to plasma membrane co-receptor (Frizzled-LRP) complexes inhibits the degradation of β-catenin protein in the cytoplasm that is promoted by the products of tumor suppressor genes APC and AXIN, which leads to β-catenin accumulation and partial translocation into the cell nucleus. Nuclear β-catenin acts as a transcriptional co-activator of genes bound by the T-cell factor (TCF) family of transcriptional repressors [207]. The long list of β-catenin/TCF target genes includes some that are crucial for cell survival and proliferation (MYC, CCND1), EMT, migration/invasion, and other tumoral processes (Stanford University Wnt homepage: https://web.stanford.edu/group/nusselab/cgi-bin/wnt/) (accessed on 19 March 2022). These genes are active during ontogenesis but remain mostly silent in adult life except in some situations such as wound healing. Recent data suggest that Wnt factors only prime β-catenin signaling. This causes basal activation of the pathway that only becomes fully activated in the presence of R-spondin (RSPO)1–4. Upon binding to their membrane LGR4–6 receptors, the secreted RSPO family members inactivate two E3 ubiquitin ligases (RNF43, ZNRF3) that mediate Frizzled degradation. In this way, RSPOs extend Frizzled half-life at the cell surface and so potentiate Wnt signaling.

The Wnt/β-catenin pathway is an important player in cancer as it is aberrantly activated by mutation (APC, AXIN, CTNNB1/β-catenin, RSPO2/3, and RNF43 genes), overexpression of Wnt factors/receptors or silencing of Wnt signaling inhibitors (DICKKOPF/DKKs, SFRPs) leading to the activation or potentiation of carcinogenesis [208]. This is particularly important in colorectal cancer, as massive sequencing efforts have revealed that the mutation of at least one Wnt/β-catenin pathway gene is present in over 94% of primary tumors and metastases [209,210], while a variable proportion of other cancers (liver, breast, lung and leukemia, among others) also show abnormal pathway activation. Despite its clinical relevance, no inhibitors of the Wnt/β-catenin pathway have been approved up to now.

The first description of the antagonism of the Wnt/β-catenin pathway by 1,25-$(OH)_2D_3$ was reported in colon carcinoma cells by a double mechanism: (a) liganded VDR binds nuclear β-catenin, which hampers the formation of transcriptionally active β-catenin/TCF complexes, and (b) induction E-cadherin expression that attracts newly synthesized β-catenin protein to the plasma membrane adherens junctions. In that way, it decreases β-catenin nuclear accumulation [125]. Other mechanisms of interference of the Wnt/β-catenin signaling pathway by 1,25-$(OH)_2D_3$ have been subsequently described in colon, breast, ovarian, hepatocellular, renal, head, and neck carcinomas, and in Kaposi's sarcoma, see [211]. These mechanisms include the increase in AXIN, TCF4 or DKK1 level, modulation of TLR7, reduction of total or nuclear β-catenin, and enhancement of LRP6 degradation [212–217]. In addition, a paracrine mechanism of Wnt/β-catenin signaling has been proposed based on interruption by 1,25-$(OH)_2D_3$ of the secretion of the Wnt stimulator IL-β by environmental macrophages [218].

4.6. Inhibition of Angiogenesis

1,25-$(OH)_2D_3$ inhibits cancer angiogenesis by acting at two levels: tumor cells and endothelial cells. In diverse types of carcinoma cells (colon, prostate, and breast), the antiangiogenic action of 1,25-$(OH)_2D_3$ relies to a great extent on its ability to inhibit two major angiogenesis promoters: it suppresses the expression and activity of hypoxia-inducible factor (HIF)-1α, a key transcription factor in hypoxia-induced angiogenesis, and of vascular endothelial growth factor (VEGF)-A. Additionally, 1,25-$(OH)_2D_3$ induces the angiogenesis inhibitor thrombospondin-1 [219,220]. In colon tumor cells, modulation of the angiogenic phenotype is also mediated by the control of genes encoding inhibitors of differentiation (ID)-1/2 and by the repression of DKK4, a weak Wnt antagonist that promotes angiogenesis and invasion and is upregulated in colon tumors [219,221]. 1,25-$(OH)_2D_3$ alone and more strongly in combination with cisplatin suppresses VEGF activity in ovarian cancer cells [222]. By modulating VEGF receptor (VEGFR) 2, 1,25-$(OH)_2D_3$ or calcipotriol, it enhances the efficacy of the VEGFR inhibitor Cediranib in malignant melanoma cells [223]. Another antiangiogenic mechanism of 1,25-$(OH)_2D_3$ is the reduction of IL-8 secretion by prostate cancer cells through the inhibition of NF-κB [224]. Intriguingly, variable and sometimes opposite effects of 1,25-$(OH)_2D_3$ on angiogenesis have been reported, as in a xenograft breast cancer model, where it inhibits TSP-1 and increases VEGF expression [225]. Likewise, 1,25-$(OH)_2D_3$ induces VEGF synthesis and action in some non-tumoral cell systems, see [152].

1,25-$(OH)_2D_3$ also has inhibitory effects on tumor-derived endothelial cells. It reduces their proliferation and sprouting in vitro and diminishes the blood vessel density in xenograft tumors in breast, squamous cell carcinoma, bladder and prostate cancer models [226–230].

4.7. Inhibition of Cancer Cell Migration, Invasion and Metastasis

1,25-$(OH)_2D_3$ inhibits the migratory and invasive phenotype of cancer cells as a result of its effects on the cytoskeleton and adhesive properties and on the expression of proteases, protease inhibitors and ECM proteins. To a variable extent, these effects are linked to inhibition of EMT and the TGF-β and Wnt/β-catenin signaling pathways.

As mentioned above, in carcinoma cells, 1,25-$(OH)_2D_3$ induces E-cadherin and other proteins of adhesion structures and modulates actin and intermediate filament networks, which results in increased cell–cell and cell–ECM adhesion [125,186,194,217,231–233]. By promoting intercellular adhesion via upregulation of E-cadherin, 1,25-$(OH)_2D_3$ suppresses prostate cancer cell rolling and adhesion to microvascular endothelial cells, which is a step in extravasation that precedes metastasis [234]. In addition, vitamin D deficiency increases breast cancer metastasis to the lung by enhancing EMT and the CXCL12/CXCR4 chemokine axis [235].

1,25-$(OH)_2D_3$ reduces breast, renal, and prostate carcinoma cell migration and invasion by downregulating the expression and/or activity of N-cadherin, the ECM components tenascin C and periostin, several integrins and metalloproteases (MMP-1, -2, and -9) and serine proteases (plasminogen activator), while it upregulates protease inhibitors and the pro-adhesive actin cytoskeleton adaptor protein PDLIM2 [236–240]. In triple-negative breast cancer cells, 1,25-$(OH)_2D_3$ decreases hyaluronic acid synthesis [241], and inhibits bladder cancer cell migration partially via the induction of miR-101-3p [242]. In pancreatic adenocarcinoma cells, 1,25-$(OH)_2D_3$ ameliorates the pro-invasive action of tumor necrosis factor (TNF)-α by decreasing the expression of miR-221 and increasing that of the tissue inhibitor of metalloproteinase (TIMP)-3 [243].

4.8. Stromal Effects: Cancer-Associated Fibroblasts

Today, the critical role of stroma in the carcinogenic process is clear. Fibroblasts are the main cellular component of tumor stroma (Cancer-Associated Fibroblasts, CAF). This is a heterogeneous cell population of multiple origins (tissue-resident fibroblasts, myeloid precursors, pericytes and adipocytes, among others) and features that is acquired via the change to an "activation phenotype". It is thought to promote cancer invasion, angiogenesis and metastasis; inhibit the immune response; and reduce intratumoral delivery and the activity of chemotherapeutic agents [244,245]. However, the protective effects of CAF have also been described in some systems, and reprogramming their phenotype is accepted as a more advisable strategy than their elimination [246,247]. Early studies showed that VDR agonists have antifibrotic and antitumoral effects by antagonizing TGF-β in the intestine, liver, and pancreas [248–252].

1,25-$(OH)_2D_3$ regulated over one hundred genes in human CAF isolated from tumor biopsies of five breast cancer patients [253]. The induced gene signature reflects an antiproliferative and anti-inflammatory effect of 1,25$(OH)_2D_3$. Importantly, 1,25-$(OH)_2D_3$ inhibits the protumoral action of human colon CAF by reprograming them to a less activated phenotype. Thus, 1,25$(OH)_2D_3$ reduces the capacity of CAF to alter the ECM and their ability to promote the migration of colon carcinoma cells [254]. 1,25-$(OH)_2D_3$ regulates over one thousand genes in colon CAF that are involved in cell adhesion, differentiation and migration, tissue remodeling, blood vessel development, and the inflammatory response. Remarkably, 1,25$(OH)_2D_3$ imposes a gene signature that correlates with a better prognosis for colon cancer patients [254]. Curiously, in contrast to the antagonism reported in colon carcinoma cells, 1,25-$(OH)_2D_3$ and Wnt3A have an additive, partially overlapping effect in colon fibroblasts [255,256]. In line with the results in colon CAF, 1,25$(OH)_2D_3$ decreases the amount of miR-10a-5p found in the exosomes secreted by human pancreatic CAF, which attenuates the promigratory and pro-invasive effects that these CAF exert on pancreatic carcinoma cells [257]. Of note, a recent study reported that calcipotriol promotes an anti-tumorigenic phenotype of pancreatic CAF by reducing the release of prostaglandin (PG) E_2, IL-6, periostin, and other factors. However, it reduces T-cell-mediated immunity [258]. Clearly, the action of VDR agonists on fibroblasts associated with distinct human cancers is a highly interesting, open line of research.

4.9. Effects on Cancer Stem Cells

Cancer stem cells (CSC) are supposedly a small population of cells present in tumors that are responsible for tumor initiation, growth, malignization, metastasis, and resistance

to therapies. They originate from the mutational and epigenetic alteration of normal stem cells that maintain the homeostasis of tissues in adult life and behave as a source of new functional differentiated cells following injuries or in aging. The characterization and study of CSC present two unresolved problems: (a) the lack of confirmed universal or even tissue-specific markers, and (b) the existence of cell plasticity in tumors that implies differentiation/dedifferentiation processes during tumorigenesis and thus the lack of a stable stem phenotype but, instead, interconversion of stem and non-stem cells.

At present, there are two systems to study CSC: organoid cultures generated by CSC present in patient-derived tumor biopsies and subcultures of established, immortal tumor cell lines enriched in populations of cells expressing putative CSC markers and/or selected by their capacity to grow in suspension. Clearly, fresh, primary organoids are a more valuable system. They are three-dimensional (3D), self-organized multicellular structures generated by normal stem cells or CSC (that allow matched normal and tumor organoids to be obtained from a patient) that grow embedded in an ECM covered by a complex, tissue-specific, usually serum-free medium [259,260]. Organoids recapitulate some of the features of a particular organ or tumor of origin and are quite stable genetically, and thus are considered a better system to study cancer processes than 2D cell lines grown for decades on plastic dishes [261]. 1,25$(OH)_2D_3$ profoundly and differentially regulates the gene expression profile of colon cancer patient-derived normal and tumor organoid cultures. 1,25$(OH)_2D_3$ induced stemness-related genes (*LGR5*, *SMOC2*, *LRIG1*, and others) in normal but not tumor organoids [262]. In both normal and tumor organoids, 1,25$(OH)_2D_3$ reduced cell proliferation and the expression of proliferation and tumorigenesis genes that affected only a few Wnt/β-catenin target genes (*MYC, DKK4*). Importantly, 1,25$(OH)_2D_3$ induced some features of epithelial differentiation in tumor organoids cultured in proliferation medium, such as microvilli, adhesion structures, partial chromatin condensation, and increased cytoplasmic organelles. These effects were also observed in rectal tumor organoids [263].

Concordantly, 1,25$(OH)_2D_3$-regulated genes were involved in cell proliferation, differentiation, adhesion, and migration in another study using patient-derived colon organoids [264]. Moreover, MDL-811, an allosteric activator of the sirtuin (SIRT)6 deacetylase, reduced cell proliferation in colon carcinoma cell lines and patient-derived organoids and has a synergistic antitumoral effect in combination with vitamin D in *Apc*$^{min/+}$ mice [265]. However, conflicting data have been found in normal, nontumoral organoids: whereas 1,25-$(OH)_2D_3$ increased the stemness genes and the undifferentiated associated cell phenotype in organoids from healthy colon and rectum tissues of a dozen individuals [262,263], it enhanced the differentiation of organoids established from a benign region of a radical prostatectomy from a single patient [266].

A series of studies have examined the action of VDR agonists on putative breast cancer stem or progenitor cells identified by some markers (CD44^{hi}/CD24^{low} and/or ADH1^{+}) that can grow as floating, nonadherent spheres (mammospheres). In these systems, 1,25$(OH)_2D_3$ or the BXL1024 analogue reduced the population of putative CSC and the formation of mammospheres and the expression of pluripotency markers (OCT4, KL-4), Notch ligands and target genes, and genes involved in proliferation, EMT, invasion, metastasis, and chemoresistance 32,467,291 [267–269].

Organoids formed by cells isolated from patient-derived xenografts (not obtained directly from human biopsies but on injection and growth in mice) that acquired resistance in vitro to Trastuzumab-emtansine (T-DM1; composed of the humanized monoclonal anti-HER2 antibody Trastuzumab covalently linked to the microtubule-inhibitory agent DMI) constitute an intermediate system to the two discussed above. In this system, two vitamin D analogues (UVB1 and EM1) reduce the formation and growth of organoids [270].

4.10. Effects on the Immune System

1,25-$(OH)_2D_3$ is an important modulator of the immune system, as reflected by the expression of VDR by almost all types of immune cells [271–273]. 1,25-$(OH)_2D_3$ is an

enhancer of innate immune reactions against infections and tumor cells by activating the responsive cells (macrophages, natural killer (NK) cells, and neutrophils). Conversely, and in line with its accepted anti-inflammatory action (that may contribute to the inhibition of cancers associated with chronic inflammation), 1,25-$(OH)_2D_3$ is commonly presented as a repressor of the adaptive immune reactions by deactivating antigen-presenting cells (induction of tolerogenic dendritic cells) and $CD4^+$ type-1 helper T (Th1) response (production of interferon-γ, IL-1, IL-6, IL-12...), and by promoting the suppressive Th2 and Treg responses (production of IL-10, IL-4, IL-5, IL-13...) [273,274]. Moreover, in macrophages, 1,25-$(OH)_2D_3$ has been proposed to promote a switch from the pro-inflammatory M1 phenotype (producing IL-1β, IL-6, TNF-α, RANKL, COX) towards the anti-inflammatory protumoral M2 phenotype and to reduce the T-cell stimulatory capacity of macrophages [275,276]. This is somehow counterintuitive as it would represent a potential protumoral effect that cannot be easily attributed to a conserved evolutionary agent such as vitamin D. Some other studies discussed below have introduced putative explanations.

Since naïve T-cells express VDR at a very low level that increases only after activation of the T-cell receptor [277], the role of 1,25-$(OH)_2D_3$ may conceivably be related to the late downregulation of the activated adaptive response. This view agrees with the usual description of repressive 1,25-$(OH)_2D_3$ action in experimental settings following overstimulation of the cells, and it may constitute a safety mechanism to prevent undesirable long-lasting immune activation, potentially leading to inflammation or autoimmunity [278,279]. Concordant with this idea and the anticancer action of 1,25-$(OH)_2D_3$, a series of studies have revealed antitumor effects at the level of several types of immune cells.

Interestingly, a study in mice orthotopically implanted with breast tumors has revealed that vitamin D decreases tumor growth and increases the amount of tumor-infiltrating cytolytic CD8+ T-cells, a usual marker of antitumor response. This effect is lost in high-fat diet conditions [280]. Moreover, in pancreatic cancer, 1,25-$(OH)_2D_3$ inhibits the T-cell suppressive function of myeloid-derived suppressor cells [281].

An important mechanism of 1,25-$(OH)_2D_3$ is the inhibition of the NF-κB pathway. In turn, this causes the downregulation of multiple cytokines and their effects [282]. 1,25-$(OH)_2D_3$ inhibits NF–κB at different levels: by inactivating the p65 subunit of the NF-κB complex and upregulating the inhibitor subunit IκB. In addition, 1,25-$(OH)_2D_3$ inhibits the PG-endoperoxide synthase (PTGS-2, also known as COX-2) [283–285]. 1,25$(OH)_2D_3$ reduces the protumorigenic effect of PG E_2 in prostate cancer cells by inhibiting COX-2 and so decreasing the levels of PG E_2 and two PG receptors (EP2 and FP) [286]. Importantly, vitamin D and calcium favorably modulate the balance of expression of COX-2 and 15-hydroxyPG dehydrogenase, its physiological antagonist, in the normal-appearing colorectal mucosa of patients with colorectal adenoma [287]. vitamin D enhances the tumoricidal activity of NK cells and macrophages [288,289]. 1,25-$(OH)_2D_3$ probably has a dual effect of stimulating the differentiation from monocytes to macrophages and their cell killing activity, including antibody-dependent cell cytotoxicity (ADCC). It may later balance these effects by promoting the M1 to M2 phenotypic switch ([279] and references therein). In addition, 1,25-$(OH)_2D_3$ enhances the susceptibility of hematological and solid cancer cells to NK cell cytotoxicity through downregulation of *miR-302c* and *miR-520c* [289].

The potentiation of ADCC of macrophages and NK cells may be a relevant antitumor action of 1,25-$(OH)_2D_3$ in clinical cases, particularly in patients treated with antibodies, of which the major mechanism of action is ADCC. Thus, several studies have shown that vitamin D deficiency impairs the macrophage and/or NK cell-mediated cytotoxicity of Rituximab (anti-CD20) in diffuse large B-cell, follicular, and Burkitt lymphoma patients [288,290,291], and of Cetuximab (anti-EGFR) in colon cancer cell lines [292]. In addition, some evidence of benefit has been observed in breast cancer patients treated with Trastuzumab (anti-HER2) and in melanoma patients treated with Bevacizumab (anti-VEGF) [290,293].

Agents that target programmed death (PD)-1 or its ligand PD-L1 immune checkpoint inhibitors (ICI) have attracted great attention in cancer therapy. Interestingly, 1,25-$(OH)_2D_3$

upregulates PD-L1 in human (but not mouse)-cultured epithelial and immune cells [294], while vitamin D treatment increases PD-1 expression in $CD24^{+}CD25^{+int}$ T-cells in Crohn's disease patients [295] and PD-L1 in epithelial and immune cells in melanoma patients [296]. These data suggest the possibility of combined treatments with VDR agonists and these ICIs, and perhaps others in development.

In conclusion, it is conceivable that 1,25-$(OH)_2D_3$ works as a general homeostatic regulator of the immune system, ensuring an appropriate global defense against challenges like tumors and infections.

4.11. Animal Models

Many studies on animal diet, chemical, genetic, and xenograft models (mainly for colon and breast cancer) have shown the antitumor actions of vitamin D compounds. This in vivo action is difficult to dissect and probably results from a variable combination of mechanisms in the distinct systems that were assayed, including the inhibition of tumor cell growth, EMT, invasiveness, angiogenesis, and metastasis. Importantly, as occurs in cultured cancer cells, vitamin D antitumor action is mostly independent of *TP53* gene status [119,187].

4.12. Systemic Effects: Detoxification and Microbiome

4.12.1. Detoxification

The elimination of xenobiotics or the detoxification process involves chemical modification (phase I reactions: oxidation, hydrolysis, etc.) and subsequent conjugations to water-soluble molecules (phase II reactions) carried out by a large number of enzymes. 1,25-$(OH)_2D_3$ regulates some of these enzymes in the intestine and liver [297]. This may have a positive effect on the prevention of tumorigenesis and perhaps another more controversial impact on the inactivation of chemotherapeutic drugs [298].

1,25-$(OH)_2D_3$ induces CYP3A4, a major human drug-metabolizing enzyme, SULT2A, a phase II sulfotransferase, and members of the multidrug resistance-associated protein (MRP) family in colon carcinoma cells [299,300]. CYP3A4, SULT2A1, and MRP3 are involved in the elimination of lithocholic acid (LCA), a secondary bile acid LCA that induces DNA damage and inhibits DNA repair enzymes in colonic cells. Accordingly, LCA promotes colon cancer in experimental animals, and high levels of LCA have been found in colon cancer patients [301,302]. Interestingly, LCA binds weakly and activates VDR, and so it activates its own degradation [303]. Another example is enhancement by 1,25$(OH)_2D_3$ of the benzo[a]pyrene metabolism via CYP1A1 in macrophages [304].

4.12.2. Microbiome

Alteration of the intestinal microbiome (dysbiosis) is connected to colon cancer and possibly other neoplasias [305]. Many experimental studies in mice have shown that vitamin D deficiency promotes gut permeability, colon mucosa bacterial infiltration, and translocation of intestinal pathogens. These effects lead to changes in immune cell populations and gut inflammation, and cancer—an overall condition that is improved after vitamin D supplementation [306,307]. As bacteria lack VDR, the effect of vitamin D is mediated by the host. Importantly, genome-wide association analysis of the gut microbiome in two large cohorts of individuals identified VDR as a factor that influences the gut microbiota [308]. A conditioned medium from probiotic lactic acid bacteria showed increased expression of VDR and of its target *CAMP* gene encoding cathelicidin in cultured colon carcinoma cells and organoids. It protected against the inflammatory response induced by TNF-α [309]. The protective action against dysbiosis and the intestinal tumorigenesis of liganded VDR have been proposed to be at least partially mediated by the inhibition of the JAK/STAT pathway [310].

4.13. Discussion of Mechanistic Studies

The vast array of effects that 1,25-$(OH)_2D_3$ has in a wide variety of experimental systems of a high number of cancer types agrees with a selected evolutionary role in protection against tumoral processes. The underlying mechanisms include the control of tumor cell survival (autophagy, apoptosis) and phenotype (differentiation), and the inhibition of their proliferation, invasiveness, and metastasis; attenuation of the proliferation and phenotypic features of some CSC; modulation of the physiology of diverse non-tumoral stromal cells (fibroblasts, endothelial cells); and the regulation of several types of immune cells and responses. Table 11 summarizes the references corresponding to key studies focused on the most relevant topics of the anticancer action of vitamin D.

Table 11. vitamin D anticancer mechanisms in experimental model systems. List of key representative references.

Mechanism	Cancer Type Model	References
Inhibition of cell proliferation	Breast, prostate, colon, ovarian, gastric thyroid, hepatocellular, leukemias, lymphomas	[111,119–150,152–156,158,159,161,162]
Induction of differentiation	Leukemia, colon, breast	[112,124–126,138,176,185,187,196–205]
EMT inhibition	Colon, ovarian, breast, pancreas	[126,142,189–195]
Sensitization of autophagy	Colon, prostate, breast, ovarian, lung	[115,116,118,163–165,168,169]
Induction of autophagy	Breast, Kaposi's sarcoma, lymphoma, cutaneous squamous cell carcinoma, leukemia	[171–181]
Wnt/β-catenin antagonism	Colon, breast, ovarian, hepatocellular, renal, head and neck, Kaposi's sarcoma	[124,210–217]
Invasion, angiogenesis, metastasis	Colon, prostate, breast, ovarian, renal, pancreas	[193–216,218–223,230–242]
Cancer-associated fibroblasts	Breast, colon, pancreas, liver	[248,250,252–257]
Normal/cancer stem cells	Breast, colon, pancreas, liver	[261–269]
Detoxification and microbiome	Colon, perhaps other cancer types	[296–303,305–309]
Immune system regulation	Many	[272–288]
Combination with immunotherapy	Lymphoma, melanoma, colon, breast	[289–295]

Together, these effects reflect a multilevel anticancer action of vitamin D. Therefore, an appropriate vitamin D status of the organism should be maintained to minimize the risk and severe consequences of many neoplasias. Further supporting this, the toxicity of vitamin D supplementation is limited, acceptable, and clearly lower than that of current anticancer drugs and therapies. We are not aware of any other natural or synthetic compound that has such an array of antitumor activities combined with low toxicity. Doubtless, the available experimental results meet Koch's postulate for biological causality regarding the existence of a global mechanism of action behind the association between vitamin D deficiency and high incidence and, especially, the mortality of several major cancer types found in observational and epidemiological studies. Hopefully, the further development of current and possibly, novel studies on the wide range of mechanisms of VDR agonists in a variety of biological systems will allow us to elucidate the anticancer action of vitamin D (Figure 3).

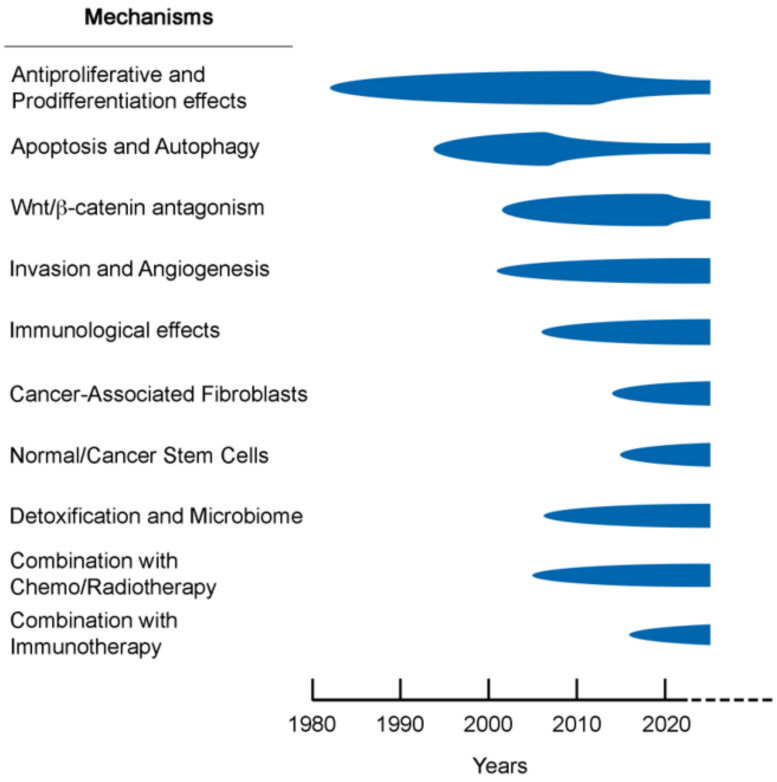

Figure 3. Time flow-chart of studies on the anticancer mechanisms of vitamin D compounds with some key references that are discussed in the text.

5. Outlook

On the basis of this review of ecological and observational studies, it seems that an efficient way to strengthen the links between vitamin D and cancer is to conduct more CC studies of cancer incidence. Such studies would measure 25(OH)D concentration, C-reactive protein, and other relevant factors, as well as obtain the history of UVB exposure, vitamin D supplementation, and dietary sources of vitamin D. The next step is to then find appropriate controls using, perhaps, the propensity score analysis, as done in a study of breast cancer survival with respect to de novo vitamin D supplementation [311]. In addition, care should be taken to investigate the effect of vitamin D supplementation and 25(OH)D concentration on cancer risk for various subgroups based on such factors as age, BMI, diet, ethnicity, geographical location, etc.

Future laboratory research on the anticancer action of vitamin D is desirable to develop a deeper understanding of the individual response to treatment with VDR agonists. To this end, *omics* studies using genomic, epigenomic, transcriptomic, proteomic, and metabolomic approaches must be integrated to understand and foresee personal susceptibility/sensitivity to each compound, which has been defined as "the personal vitamin D response index" [312]. Clearly, the characterization of biomarkers of compound activity and patient response in different cancer types will be important. Since 1,25-$(OH)_2D_3$ regulates the same pathways but distinct genes of them in mice and humans [313], studies should preferentially be carried out in human systems. Among them, it seems that primary cell cultures and organoids should be used instead of classical, long-term established cell lines.

Given the increasingly important role attributed to the stroma in tumorigenesis, the effects of vitamin D compounds on CAF, endothelial cells, and specific types of immune cells require attention. Likewise, the association of chronic inflammation with several types of cancer and the pro-inflammatory action of adipocytes suggest the interest in studying the effects of vitamin D in this context.

Another open field for research is combination therapies. Up until now, experimental studies have focused on the combination of VDR agonists and chemotherapeutic agents,

sometimes with radiotherapy. Obviously, this should be continued and extended to the exponentially growing field of cancer immunotherapies.

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References

1. Peller, S. Carcinogenesis as a means of reducing cancer mortlity. *Lancet* **1936**, *228*, 552–556. [CrossRef]
2. Peller, S.; Stephenson, C.S. Skin ittittion and cancer in the United States Navy. *Am. J. Med. Sci.* **1937**, *194*, 326–333. [CrossRef]
3. Apperly, F.L. The Relation of Solar Radiation to Cancer Mortality in North America. *Cancer Res.* **1941**, *1*, 191–195.
4. Ainsleigh, H.G. Beneficial effects of sun exposure on cancer mortality. *Prev. Med.* **1993**, *22*, 132–140. [CrossRef] [PubMed]
5. Mason, T.J.; McKay, F.W.; Hoover, R.; Blot, W.J.; Fraumeni, J.F., Jr. *Atlas of Cancer Mortality for U.S. Counties: 1950–1969*; U.S. Department of Health, Education, and Welfare: Washington, DC, USA, 1975.
6. Garland, C.F.; Garland, F.C. Do sunlight and vitamin D reduce the likelihood of colon cancer? *Int. J. Epidemiol.* **1980**, *9*, 227–231. [CrossRef] [PubMed]
7. Garland, C.; Shekelle, R.B.; Barrett-Connor, E.; Criqui, M.H.; Rossof, A.H.; Paul, O. Dietary vitamin D and calcium and risk of colorectal cancer: A 19-year prospective study in men. *Lancet* **1985**, *1*, 307–309. [CrossRef]
8. Garland, C.F.; Comstock, G.W.; Garland, F.C.; Helsing, K.J.; Shaw, E.K.; Gorham, E.D. Serum 25-hydroxyvitamin D and colon cancer: Eight-year prospective study. *Lancet* **1989**, *2*, 1176–1178. [CrossRef]
9. Garland, F.C.; Garland, C.F.; Gorham, E.D.; Young, J.F. Geographic variation in breast cancer mortality in the United States: A hypothesis involving exposure to solar radiation. *Prev. Med.* **1990**, *19*, 614–622. [CrossRef]
10. Lefkowitz, E.S.; Garland, C.F. Sunlight, vitamin D, and ovarian cancer mortality rates in US women. *Int. J. Epidemiol.* **1994**, *23*, 1133–1136. [CrossRef]
11. Garland, C. The Summer of 1974, Or...How I Found My Life's Mission. Available online: https://www.grassrootshealth.net/?s=The+Summer+of+1974%2C+Or...How+I+Found+My+Life%27s+Mission (accessed on 23 February 2022).
12. Devesa, S.S.; Grauman, D.J.; Blot, W.J.; Pennello, G.A.; Hoover, R.N.; Fraumeni, J.F., Jr. *Atlas of Cancer Mortality in the United States, 1950–1994*; National Institutes of Health; National Cancer Institue: Bethesda, MD, USA, 1999.
13. Grant, W.B. An estimate of premature cancer mortality in the U.S. due to inadequate doses of solar ultraviolet-B radiation. *Cancer* **2002**, *94*, 1867–1875. [CrossRef] [PubMed]
14. Grant, W.B.; Garland, C.F. The association of solar ultraviolet B (UVB) with reducing risk of cancer: Multifactorial ecologic analysis of geographic variation in age-adjusted cancer mortality rates. *Anticancer Res.* **2006**, *26*, 2687–2699. [PubMed]
15. Grant, W.B. Lower vitamin-D production from solar ultraviolet-B irradiance may explain some differences in cancer survival rates. *J. Natl. Med. Assoc.* **2006**, *98*, 357–364. [PubMed]
16. Ames, B.N.; Grant, W.B.; Willett, W.C. Does the High Prevalence of vitamin D Deficiency in African Americans Contribute to Health Disparities? *Nutrients* **2021**, *13*, 499. [CrossRef] [PubMed]
17. Moukayed, M.; Grant, W.B. Molecular link between vitamin D and cancer prevention. *Nutrients* **2013**, *5*, 3993–4021. [CrossRef]
18. Chen, W.; Clements, M.; Rahman, B.; Zhang, S.; Qiao, Y.; Armstrong, B.K. Relationship between cancer mortality/incidence and ambient ultraviolet B irradiance in China. *Cancer Causes Control* **2010**, *21*, 1701–1709. [CrossRef]
19. Fioletov, V.E.; McArthur, L.J.; Mathews, T.W.; Marrett, L. Estimated ultraviolet exposure levels for a sufficient vitamin D status in North America. *J. Photochem. Photobiol. B* **2010**, *100*, 57–66. [CrossRef]
20. Herman, J.R.; Krotkov, N.; Celarier, E.; Larko, D.; Lebow, G. Distribution of UV radiation at the Earth's surface from TOMSmeasured UV-backscattered radiances. *J. Geophys. Res.* **1999**, *104*, 12059–12076. [CrossRef]
21. Mizoue, T. Ecological study of solar radiation and cancer mortality in Japan. *Health Phys.* **2004**, *87*, 532–538. [CrossRef]
22. Boscoe, F.P.; Schymura, M.J. Solar ultraviolet-B exposure and cancer incidence and mortality in the United States, 1993–2002. *BMC Cancer* **2006**, *6*, 264. [CrossRef]
23. Fukuda, Y.; Nakaya, T.; Nakao, H.; Yahata, Y.; Imai, H. Multilevel analysis of solar radiation and cancer mortality using ecological data in Japan. *Biosci. Trends* **2008**, *2*, 235–240.
24. Borisenkov, M.F. Latitude of residence and position in time zone are predictors of cancer incidence, cancer mortality, and life expectancy at birth. *Chronobiol. Int.* **2011**, *28*, 155–162. [CrossRef] [PubMed]
25. Grant, W.B. Role of solar UVB irradiance and smoking in cancer as inferred from cancer incidence rates by occupation in Nordic countries. *Dermatoendocrinology* **2012**, *4*, 203–211. [CrossRef] [PubMed]

26. Pukkala, E.; Martinsen, J.I.; Lynge, E.; Gunnarsdottir, H.K.; Sparen, P.; Tryggvadottir, L.; Weiderpass, E.; Kjaerheim, K. Occupation and cancer—Follow-up of 15 million people in five Nordic countries. *Acta Oncol.* **2009**, *48*, 646–790. [CrossRef]
27. Grant, W.B. A meta-analysis of second cancers after a diagnosis of nonmelanoma skin cancer: Additional evidence that solar ultraviolet-B irradiance reduces the risk of internal cancers. *J. Steroid Biochem. Mol. Biol.* **2007**, *103*, 668–674. [CrossRef] [PubMed]
28. Kenborg, L.; Jorgensen, A.D.; Budtz-Jorgensen, E.; Knudsen, L.E.; Hansen, J. Occupational exposure to the sun and risk of skin and lip cancer among male wage earners in Denmark: A population-based case-control study. *Cancer Causes Control* **2010**, *21*, 1347–1355. [CrossRef] [PubMed]
29. Jemal, A.; Siegel, R.; Ward, E.; Hao, Y.; Xu, J.; Thun, M.J. Cancer statistics, 2009. *CA Cancer J. Clin.* **2009**, *59*, 225–249. [CrossRef] [PubMed]
30. Lin, S.W.; Wheeler, D.C.; Park, Y.; Cahoon, E.K.; Hollenbeck, A.R.; Freedman, D.M.; Abnet, C.C. Prospective study of ultraviolet radiation exposure and risk of cancer in the United States. *Int. J. Cancer* **2012**, *131*, E1015–E1023. [CrossRef] [PubMed]
31. O'Sullivan, F.; van Geffen, J.; van Weele, M.; Zgaga, L. Annual Ambient UVB at Wavelengths that Induce vitamin D Synthesis is Associated with Reduced Esophageal and Gastric Cancer Risk: A Nested Case-Control Study. *Photochem. Photobiol.* **2018**, *94*, 797–806. [CrossRef]
32. Sempos, C.T.; Durazo-Arvizu, R.A.; Binkley, N.; Jones, J.; Merkel, J.M.; Carter, G.D. Developing vitamin D dietary guidelines and the lack of 25-hydroxyvitamin D assay standardization: The ever-present past. *J. Steroid Biochem. Mol. Biol.* **2016**, *164*, 115–119. [CrossRef]
33. Ginde, A.A.; Liu, M.C.; Camargo, C.A., Jr. Demographic differences and trends of vitamin D insufficiency in the US population, 1988–2004. *Arch. Intern. Med.* **2009**, *169*, 626–632. [CrossRef]
34. Crowe, F.L.; Steur, M.; Allen, N.E.; Appleby, P.N.; Travis, R.C.; Key, T.J. Plasma concentrations of 25-hydroxyvitamin D in meat eaters, fish eaters, vegetarians and vegans: Results from the EPIC-Oxford study. *Public Health Nutr.* **2011**, *14*, 340–346. [CrossRef] [PubMed]
35. Cashman, K.D.; O'Sullivan, S.M.; Galvin, K.; Ryan, M. Contribution of vitamin D2 and D3 and Their Respective 25-Hydroxy Metabolites to the Total vitamin D Content of Beef and Lamb. *Curr. Dev. Nutr.* **2020**, *4*, nzaa112. [CrossRef] [PubMed]
36. Autier, P.; Boniol, M.; Pizot, C.; Mullie, P. vitamin D status and ill health: A systematic review. *Lancet Diabetes Endocrinol.* **2014**, *2*, 76–89. [CrossRef]
37. Autier, P.; Mullie, P.; Macacu, A.; Dragomir, M.; Boniol, M.; Coppens, K.; Pizot, C.; Boniol, M. Effect of vitamin D supplementation on non-skeletal disorders: A systematic review of meta-analyses and randomised trials. *Lancet Diabetes Endocrinol.* **2017**, *5*, 986–1004. [CrossRef]
38. Smolders, J.; van den Ouweland, J.; Geven, C.; Pickkers, P.; Kox, M. Letter to the Editor: vitamin D deficiency in COVID-19: Mixing up cause and consequence. *Metabolism* **2021**, *115*, 154434. [CrossRef] [PubMed]
39. Wang, L. C-reactive protein levels in the early stage of COVID-19. *Med. Mal. Infect.* **2020**, *50*, 332–334. [CrossRef] [PubMed]
40. Allin, K.H.; Bojesen, S.E.; Nordestgaard, B.G. Baseline C-reactive protein is associated with incident cancer and survival in patients with cancer. *J. Clin. Oncol.* **2009**, *27*, 2217–2224. [CrossRef]
41. Grant, W.B. Effect of interval between serum draw and follow-up period on relative risk of cancer incidence with respect to 25-hydroxyvitamin D level: Implications for meta-analyses and setting vitamin D guidelines. *Dermatoendocrinology* **2011**, *3*, 199–204. [CrossRef]
42. Grant, W.B. 25-hydroxyvitamin D and breast cancer, colorectal cancer, and colorectal adenomas: Case-control versus nested case-control studies. *Anticancer Res.* **2015**, *35*, 1153–1160.
43. Grant, W.B. Effect of follow-up time on the relation between prediagnostic serum 25-hydroxyvitamin D and all-cause mortality rate. *Dermatoendocrinology* **2012**, *4*, 198–202. [CrossRef]
44. Wu, K.; Feskanich, D.; Fuchs, C.S.; Willett, W.C.; Hollis, B.W.; Giovannucci, E.L. A nested case control study of plasma 25-hydroxyvitamin D concentrations and risk of colorectal cancer. *J. Natl. Cancer Inst.* **2007**, *99*, 1120–1129. [CrossRef] [PubMed]
45. Feskanich, D.; Ma, J.; Fuchs, C.S.; Kirkner, G.J.; Hankinson, S.E.; Hollis, B.W.; Giovannucci, E.L. Plasma vitamin D metabolites and risk of colorectal cancer in women. *Cancer Epidemiol. Biomark. Prev.* **2004**, *13*, 1502–1508.
46. Gorham, E.D.; Garland, C.F.; Garland, F.C.; Grant, W.B.; Mohr, S.B.; Lipkin, M.; Newmark, H.L.; Giovannucci, E.; Wei, M.; Holick, M.F. Optimal vitamin D status for colorectal cancer prevention: A quantitative meta analysis. *Am. J. Prev. Med.* **2007**, *32*, 210–216. [CrossRef] [PubMed]
47. McCullough, M.L.; Zoltick, E.S.; Weinstein, S.J.; Fedirko, V.; Wang, M.; Cook, N.R.; Eliassen, A.H.; Zeleniuch-Jacquotte, A.; Agnoli, C.; Albanes, D.; et al. Circulating vitamin D and Colorectal Cancer Risk: An International Pooling Project of 17 Cohorts. *J. Natl. Cancer Inst.* **2019**, *111*, 158–169. [CrossRef] [PubMed]
48. Weinstein, S.J.; Yu, K.; Horst, R.L.; Ashby, J.; Virtamo, J.; Albanes, D. Serum 25-hydroxyvitamin D and risks of colon and rectal cancer in Finnish men. *Am. J. Epidemiol.* **2011**, *173*, 499–508. [CrossRef]
49. Lee, J.E.; Li, H.; Chan, A.T.; Hollis, B.W.; Lee, I.M.; Stampfer, M.J.; Wu, K.; Giovannucci, E.; Ma, J. Circulating levels of vitamin D and colon and rectal cancer: The Physicians' Health Study and a meta-analysis of prospective studies. *Cancer Prev. Res.* **2011**, *4*, 735–743. [CrossRef] [PubMed]
50. Kakourou, A.; Koutsioumpa, C.; Lopez, D.S.; Hoffman-Bolton, J.; Bradwin, G.; Rifai, N.; Helzlsouer, K.J.; Platz, E.A.; Tsilidis, K.K. Interleukin-6 and risk of colorectal cancer: Results from the CLUE II cohort and a meta-analysis of prospective studies. *Cancer Causes Control* **2015**, *26*, 1449–1460. [CrossRef] [PubMed]

51. Song, M.; Wu, K.; Chan, A.T.; Fuchs, C.S.; Giovannucci, E.L. Plasma 25-hydroxyvitamin D and risk of colorectal cancer after adjusting for inflammatory markers. *Cancer Epidemiol. Biomark. Prev.* **2014**, *23*, 2175–2180. [CrossRef] [PubMed]
52. Langseth, H.; Gislefoss, R.E.; Martinsen, J.I.; Dillner, J.; Ursin, G. Cohort Profile: The Janus Serum Bank Cohort in Norway. *Int. J. Epidemiol.* **2017**, *46*, 403–404. [CrossRef] [PubMed]
53. Jenab, M.; Bueno-de-Mesquita, H.B.; Ferrari, P.; van Duijnhoven, F.J.; Norat, T.; Pischon, T.; Jansen, E.H.; Slimani, N.; Byrnes, G.; Rinaldi, S.; et al. Association between pre-diagnostic circulating vitamin D concentration and risk of colorectal cancer in European populations:a nested case-control study. *BMJ* **2010**, *340*, b5500. [CrossRef]
54. Woolcott, C.G.; Wilkens, L.R.; Nomura, A.M.; Horst, R.L.; Goodman, M.T.; Murphy, S.P.; Henderson, B.E.; Kolonel, L.N.; Le Marchand, L. Plasma 25-hydroxyvitamin D levels and the risk of colorectal cancer: The multiethnic cohort study. *Cancer Epidemiol. Biomark. Prev.* **2010**, *19*, 130–134. [CrossRef]
55. McCullough, M.L.; Robertson, A.S.; Rodriguez, C.; Jacobs, E.J.; Chao, A.; Carolyn, J.; Calle, E.E.; Willett, W.C.; Thun, M.J. Calcium, vitamin D, dairy products, and risk of colorectal cancer in the Cancer Prevention Study II Nutrition Cohort (United States). *Cancer Causes Control* **2003**, *14*, 1–12. [CrossRef] [PubMed]
56. Otani, T.; Iwasaki, M.; Sasazuki, S.; Inoue, M.; Tsugane, S.; Japan Public Health Center-Based Prospective Study, G. Plasma vitamin D and risk of colorectal cancer: The Japan Public Health Center-Based Prospective Study. *Br. J. Cancer* **2007**, *97*, 446–451. [CrossRef] [PubMed]
57. Cheng, T.Y.; Goodman, G.E.; Thornquist, M.D.; Barnett, M.J.; Beresford, S.A.; LaCroix, A.Z.; Zheng, Y.; Neuhouser, M.L. Estimated intake of vitamin D and its interaction with vitamin A on lung cancer risk among smokers. *Int. J. Cancer* **2014**, *135*, 2135–2145. [CrossRef] [PubMed]
58. Weinstein, S.J.; Purdue, M.P.; Smith-Warner, S.A.; Mondul, A.M.; Black, A.; Ahn, J.; Huang, W.Y.; Horst, R.L.; Kopp, W.; Rager, H.; et al. Serum 25-hydroxyvitamin D, vitamin D binding protein and risk of colorectal cancer in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. *Int. J. Cancer* **2015**, *136*, E654–E664. [CrossRef]
59. Tangrea, J.; Helzlsouer, K.; Pietinen, P.; Taylor, P.; Hollis, B.; Virtamo, J.; Albanes, D. Serum levels of vitamin D metabolites and the subsequent risk of colon and rectal cancer in Finnish men. *Cancer Causes Control* **1997**, *8*, 615–625. [CrossRef] [PubMed]
60. Schernhammer, E.S.; Sperati, F.; Razavi, P.; Agnoli, C.; Sieri, S.; Berrino, F.; Krogh, V.; Abbagnato, C.; Grioni, S.; Blandino, G.; et al. Endogenous sex steroids in premenopausal women and risk of breast cancer: The ORDET cohort. *Breast Cancer Res.* **2013**, *15*, R46. [CrossRef] [PubMed]
61. Swerdlow, A.J.; Jones, M.E.; Schoemaker, M.J.; Hemming, J.; Thomas, D.; Williamson, J.; Ashworth, A. The Breakthrough Generations Study: Design of a long-term UK cohort study to investigate breast cancer aetiology. *Br. J. Cancer* **2011**, *105*, 911–917. [CrossRef]
62. Neuhouser, M.L.; Manson, J.E.; Millen, A.; Pettinger, M.; Margolis, K.; Jacobs, E.T.; Shikany, J.M.; Vitolins, M.; Adams-Campbell, L.; Liu, S.; et al. The influence of health and lifestyle characteristics on the relation of serum 25-hydroxyvitamin D with risk of colorectal and breast cancer in postmenopausal women. *Am. J. Epidemiol.* **2012**, *175*, 673–684. [CrossRef] [PubMed]
63. Chandler, P.D.; Buring, J.E.; Manson, J.E.; Giovannucci, E.L.; Moorthy, M.V.; Zhang, S.; Lee, I.M.; Lin, J.H. Circulating vitamin D Levels and Risk of Colorectal Cancer in Women. *Cancer Prev. Res.* **2015**, *8*, 675–682. [CrossRef] [PubMed]
64. Scarmo, S.; Afanasyeva, Y.; Lenner, P.; Koenig, K.L.; Horst, R.L.; Clendenen, T.V.; Arslan, A.A.; Chen, Y.; Hallmans, G.; Lundin, E.; et al. Circulating levels of 25-hydroxyvitamin D and risk of breast cancer: A nested case-control study. *Breast Cancer Res.* **2013**, *15*, R15. [CrossRef]
65. Oh, E.Y.; Ansell, C.; Nawaz, H.; Yang, C.H.; Wood, P.A.; Hrushesky, W.J. Global breast cancer seasonality. *Breast Cancer Res. Treat.* **2010**, *123*, 233–243. [CrossRef] [PubMed]
66. Abbas, S.; Linseisen, J.; Slanger, T.; Kropp, S.; Mutschelknauss, E.J.; Flesch-Janys, D.; Chang-Claude, J. Serum 25-hydroxyvitamin D and risk of post-menopausal breast cancer–results of a large case-control study. *Carcinogenesis* **2008**, *29*, 93–99. [CrossRef] [PubMed]
67. Abbas, S.; Chang-Claude, J.; Linseisen, J. Plasma 25-hydroxyvitamin D and premenopausal breast cancer risk in a German case-control study. *Int. J. Cancer* **2009**, *124*, 250–255. [CrossRef] [PubMed]
68. Song, D.; Deng, Y.; Liu, K.; Zhou, L.; Li, N.; Zheng, Y.; Hao, Q.; Yang, S.; Wu, Y.; Zhai, Z.; et al. vitamin D intake, blood vitamin D levels, and the risk of breast cancer: A dose-response meta-analysis of observational studies. *Aging* **2019**, *11*, 12708–12732. [CrossRef]
69. McDonnell, S.L.; Baggerly, C.A.; French, C.B.; Baggerly, L.L.; Garland, C.F.; Gorham, E.D.; Hollis, B.W.; Trump, D.L.; Lappe, J.M. Breast cancer risk markedly lower with serum 25-hydroxyvitamin D concentrations >/=60 vs >20 ng/mL (150 vs 50 nmol/L): Pooled analysis of two randomized trials and a prospective cohort. *PLoS ONE* **2018**, *13*, e0199265. [CrossRef]
70. Han, J.; Guo, X.; Yu, X.; Liu, S.; Cui, X.; Zhang, B.; Liang, H. 25-Hydroxyvitamin D and Total Cancer Incidence and Mortality: A Meta-Analysis of Prospective Cohort Studies. *Nutrients* **2019**, *11*, 2295. [CrossRef] [PubMed]
71. Zhao, Y.; Chen, C.; Pan, W.; Gao, M.; He, W.; Mao, R.; Lin, T.; Huang, J. Comparative efficacy of vitamin D status in reducing the risk of bladder cancer: A systematic review and network meta-analysis. *Nutrition* **2016**, *32*, 515–523. [CrossRef] [PubMed]
72. Hernandez-Alonso, P.; Boughanem, H.; Canudas, S.; Becerra-Tomas, N.; Fernandez de la Puente, M.; Babio, N.; Macias-Gonzalez, M.; Salas-Salvado, J. Circulating vitamin D levels and colorectal cancer risk: A meta-analysis and systematic review of case-control and prospective cohort studies. *Crit. Rev. Food Sci. Nutr.* **2021**, *61*, 1–17. [CrossRef] [PubMed]
73. Garland, C.F.; Gorham, E.D. Dose-response of serum 25-hydroxyvitamin D in association with risk of colorectal cancer: A meta-analysis. *J. Steroid Biochem. Mol. Biol.* **2017**, *168*, 1–8. [CrossRef] [PubMed]

74. Pu, Y.; Zhu, G.; Xu, Y.; Zheng, S.; Tang, B.; Huang, H.; Wu, I.X.Y.; Huang, D.; Liu, Y.; Zhang, X. Association between vitamin D Exposure and Head and Neck Cancer: A Systematic Review with Meta-Analysis. *Front. Immunol.* **2021**, *12*, 627226. [CrossRef] [PubMed]
75. Guo, X.F.; Zhao, T.; Han, J.M.; Li, S.; Li, D. vitamin D and liver cancer risk: A meta-analysis of prospective studies. *Asia Pac. J. Clin. Nutr.* **2020**, *29*, 175–182. [CrossRef] [PubMed]
76. Zhang, Y.; Jiang, X.; Li, X.; Gaman, M.A.; Kord-Varkaneh, H.; Rahmani, J.; Salehi-Sahlabadi, A.; Day, A.S.; Xu, Y. Serum vitamin D Levels and Risk of Liver Cancer: A Systematic Review and Dose-Response Meta-Analysis of Cohort Studies. *Nutr. Cancer* **2021**, *73*, 1–9. [CrossRef] [PubMed]
77. Liu, J.; Dong, Y.; Lu, C.; Wang, Y.; Peng, L.; Jiang, M.; Tang, Y.; Zhao, Q. Meta-analysis of the correlation between vitamin D and lung cancer risk and outcomes. *Oncotarget* **2017**, *8*, 81040–81051. [CrossRef]
78. Feng, J.; Shan, L.; Du, L.; Wang, B.; Li, H.; Wang, W.; Wang, T.; Dong, H.; Yue, X.; Xu, Z.; et al. Clinical improvement following vitamin D3 supplementation in Autism Spectrum Disorder. *Nutr. Neurosci.* **2017**, *20*, 284–290. [CrossRef]
79. Wei, H.; Jing, H.; Wei, Q.; Wei, G.; Heng, Z. Associations of the risk of lung cancer with serum 25-hydroxyvitamin D level and dietary vitamin D intake: A dose-response PRISMA meta-analysis. *Medicine* **2018**, *97*, e12282. [CrossRef]
80. Xu, J.; Chen, K.; Zhao, F.; Huang, D.; Zhang, H.; Fu, Z.; Xu, J.; Wu, Y.; Lin, H.; Zhou, Y.; et al. Association between vitamin D/calcium intake and 25-hydroxyvitamin D and risk of ovarian cancer: A dose-response relationship meta-analysis. *Eur. J. Clin. Nutr.* **2021**, *75*, 417–429. [CrossRef]
81. Zhang, X.; Huang, X.Z.; Chen, W.J.; Wu, J.; Chen, Y.; Wu, C.C.; Wang, Z.N. Plasma 25-hydroxyvitamin D levels, vitamin D intake, and pancreatic cancer risk or mortality: A meta-analysis. *Oncotarget* **2017**, *8*, 64395–64406. [CrossRef]
82. Gao, J.; Wei, W.; Wang, G.; Zhou, H.; Fu, Y.; Liu, N. Circulating vitamin D concentration and risk of prostate cancer: A dose-response meta-analysis of prospective studies. *Ther. Clin. Risk Manag.* **2018**, *14*, 95–104. [CrossRef]
83. Wu, J.; Yang, N.; Youan, M. Dietary and circulating vitamin D and risk of renal cell carcinoma: A meta-analysis of observational studies. *Int. Braz. J. Urol.* **2021**, *47*, 733–744. [CrossRef]
84. Zhao, J.; Wang, H.; Zhang, Z.; Zhou, X.; Yao, J.; Zhang, R.; Liao, L.; Dong, J. vitamin D deficiency as a risk factor for thyroid cancer: A meta-analysis of case-control studies. *Nutrition* **2019**, *57*, 5–11. [CrossRef] [PubMed]
85. Manson, J.E.; Cook, N.R.; Lee, I.M.; Christen, W.; Bassuk, S.S.; Mora, S.; Gibson, H.; Gordon, D.; Copeland, T.; D'Agostino, D.; et al. vitamin D Supplements and Prevention of Canc.cer and Cardiovascular Disease. *N. Engl. J. Med.* **2019**, *380*, 33–44. [CrossRef] [PubMed]
86. Keum, N.; Lee, D.H.; Greenwood, D.C.; Manson, J.E.; Giovannucci, E. vitamin D supplementation and total cancer incidence and mortality: A meta-analysis of randomized controlled trials. *Ann. Oncol.* **2019**, *30*, 733–743. [CrossRef]
87. Zhang, X.; Niu, W. Meta-analysis of randomized controlled trials on vitamin D supplement and cancer incidence and mortality. *Biosci. Rep.* **2019**, *39*, BSR20190396. [CrossRef] [PubMed]
88. Ekmekcioglu, C.; Haluza, D.; Kundi, M. 25-Hydroxyvitamin D Status and Risk for Colorectal Cancer and Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of Epidemiological Studies. *Int. J. Environ. Res. Public Health* **2017**, *14*, 20127. [CrossRef] [PubMed]
89. Chen, G.C.; Zhang, Z.L.; Wan, Z.; Wang, L.; Weber, P.; Eggersdorfer, M.; Qin, L.Q.; Zhang, W. Circulating 25-hydroxyvitamin D and risk of lung cancer: A dose-response meta-analysis. *Cancer Causes Control* **2015**, *26*, 1719–1728. [CrossRef]
90. Song, Z.Y.; Yao, Q.; Zhuo, Z.; Ma, Z.; Chen, G. Circulating vitamin D level and mortality in prostate cancer patients: A dose-response meta-analysis. *Endocr. Connect.* **2018**, *7*, R294–R303. [CrossRef]
91. Pilz, S.; Trummer, C.; Theiler-Schwetz, V.; Grubler, M.R.; Verheyen, N.D.; Odler, B.; Karras, S.N.; Zittermann, A.; Marz, W. Critical Appraisal of Large vitamin D Randomized Controlled Trials. *Nutrients* **2022**, *14*, 303. [CrossRef]
92. De Pergola, G.; Silvestris, F. Obesity as a major risk factor for cancer. *J. Obes.* **2013**, *2013*, 291546. [CrossRef]
93. Trivedi, D.P.; Doll, R.; Khaw, K.T. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: Randomised double blind controlled trial. *BMJ* **2003**, *326*, 469. [CrossRef]
94. Wactawski-Wende, J.; Kotchen, J.M.; Anderson, G.L.; Assaf, A.R.; Brunner, R.L.; O'Sullivan, M.J.; Margolis, K.L.; Ockene, J.K.; Phillips, L.; Pottern, L.; et al. Calcium plus vitamin D supplementation and the risk of colorectal cancer. *N. Engl. J. Med.* **2006**, *354*, 684–696. [CrossRef] [PubMed]
95. Lappe, J.M.; Travers-Gustafson, D.; Davies, K.M.; Recker, R.R.; Heaney, R.P. vitamin D and calcium supplementation reduces cancer risk: Results of a randomized trial. *Am. J. Clin. Nutr.* **2007**, *85*, 1586–1591. [CrossRef] [PubMed]
96. Sanders, K.M.; Stuart, A.L.; Williamson, E.J.; Simpson, J.A.; Kotowicz, M.A.; Young, D.; Nicholson, G.C. Annual high-dose oral vitamin D and falls and fractures in older women: A randomized controlled trial. *JAMA* **2010**, *303*, 1815–1822. [CrossRef] [PubMed]
97. Avenell, A.; MacLennan, G.S.; Jenkinson, D.J.; McPherson, G.C.; McDonald, A.M.; Pant, P.R.; Grant, A.M.; Campbell, M.K.; Anderson, F.H.; Cooper, C.; et al. Long-term follow-up for mortality and cancer in a randomized placebo-controlled trial of vitamin D(3) and/or calcium (RECORD trial). *J. Clin. Endocrinol. Metab.* **2012**, *97*, 614–622. [CrossRef] [PubMed]
98. Lappe, J.; Garland, C.; Gorham, E. vitamin D Supplementation and Cancer Risk. *JAMA* **2017**, *318*, 299–300. [CrossRef]
99. Scragg, R.; Khaw, K.T.; Toop, L.; Sluyter, J.; Lawes, C.M.M.; Waayer, D.; Giovannucci, E.; Camargo, C.A., Jr. Monthly High-Dose vitamin D Supplementation and Cancer Risk: A Post Hoc Analysis of the vitamin D Assessment Randomized Clinical Trial. *JAMA Oncol.* **2018**, *4*, e182178. [CrossRef]

100. Neale, R.E.; Baxter, C.; Romero, B.D.; McLeod, D.S.A.; English, D.R.; Armstrong, B.K.; Ebeling, P.R.; Hartel, G.; Kimlin, M.G.; O'Connell, R.; et al. The D-Health Trial: A randomised controlled trial of the effect of vitamin D on mortality. *Lancet Diabetes Endocrinol.* **2022**, *10*, 120–128. [CrossRef]
101. Heaney, R.P. Guidelines for optimizing design and analysis of clinical studies of nutrient effects. *Nutr. Rev.* **2014**, *72*, 48–54. [CrossRef]
102. Grant, W.B.; Boucher, B.J.; Bhattoa, H.P.; Lahore, H. Why vitamin D clinical trials should be based on 25-hydroxyvitamin D concentrations. *J. Steroid Biochem. Mol. Biol.* **2018**, *177*, 266–269. [CrossRef]
103. Hrushesky, W.J.; Sothern, R.B.; Rietveld, W.J.; Du Quiton, J.; Boon, M.E. Season, sun, sex, and cervical cancer. *Cancer Epidemiol. Biomark. Prev.* **2005**, *14*, 1940–1947. [CrossRef]
104. Marur, S.; D'Souza, G.; Westra, W.H.; Forastiere, A.A. HPV-associated head and neck cancer: A virus-related cancer epidemic. *Lancet Oncol.* **2010**, *11*, 781–789. [CrossRef]
105. Merrill, S.J.; Subramanian, M.; Godar, D.E. Worldwide cutaneous malignant melanoma incidences analyzed by sex, age, and skin type over time (1955–2007): Is HPV infection of androgenic hair follicular melanocytes a risk factor for developing melanoma exclusively in people of European-ancestry? *Dermatoendocrinology* **2016**, *8*, e1215391. [CrossRef] [PubMed]
106. Loomis, D.; Huang, W.; Chen, G. The International Agency for Research on Cancer (IARC) evaluation of the carcinogenicity of outdoor air pollution: Focus on China. *Chin. J. Cancer* **2014**, *33*, 189–196. [CrossRef] [PubMed]
107. Hill, A.B. The Environment and Disease: Association or Causation? *Proc. R Soc. Med.* **1965**, *58*, 295–300. [CrossRef]
108. Grant, W.B. How strong is the evidence that solar ultraviolet B and vitamin D reduce the risk of cancer?: An examination using Hill's criteria for causality. *Dermatoendocrinology* **2009**, *1*, 17–24. [CrossRef] [PubMed]
109. Mohr, S.B.; Gorham, E.D.; Alcaraz, J.E.; Kane, C.I.; Macera, C.A.; Parsons, J.K.; Wingard, D.L.; Garland, C.F. Does the evidence for an inverse relationship between serum vitamin D status and breast cancer risk satisfy the Hill criteria? *Dermatoendocrinology* **2012**, *4*, 152–157. [CrossRef]
110. Frieden, T.R. Evidence for Health Decision Making—Beyond Randomized, Controlled Trials. *N. Engl. J. Med.* **2017**, *377*, 465–475. [CrossRef]
111. Giovannucci, E.; Liu, Y.; Rimm, E.B.; Hollis, B.W.; Fuchs, C.S.; Stampfer, M.J.; Willett, W.C. Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. *J. Natl. Cancer Inst.* **2006**, *98*, 451–459. [CrossRef]
112. Colston, K.; Colston, M.J.; Feldman, D. 1,25-dihydroxyvitamin D3 and malignant melanoma: The presence of receptors and inhibition of cell growth in culture. *Endocrinology* **1981**, *108*, 1083–1086. [CrossRef]
113. Abe, E.; Miyaura, C.; Sakagami, H.; Takeda, M.; Konno, K.; Yamazaki, T.; Yoshiki, S.; Suda, T. Differentiation of mouse myeloid leukemia cells induced by 1alpha,25-dihydroxyvitamin D3. *Proc. Natl. Acad. Sci. USA* **1981**, *78*, 4990–4994. [CrossRef]
114. Feldman, D.; Krishnan, A.V.; Swami, S.; Giovannucci, E.; Feldman, B.J. The role of vitamin D in reducing cancer risk and progression. *Nat. Rev. Cancer* **2014**, *14*, 342–357. [CrossRef] [PubMed]
115. Ferrer-Mayorga, G.; Larriba, M.J.; Crespo, P.; Muñoz, A. Mechanisms of action of vitamin D in colon cancer. *J. Steroid Biochem. Mol. Biol.* **2019**, *185*, 1–6. [CrossRef]
116. Wu, X.; Hu, W.; Lu, L.; Zhao, Y.; Zhou, Y.; Xiao, Z.; Zhang, L.; Zhang, H.; Li, X.; Li, W.; et al. Repurposing vitamin D for treatment of human malignancies via targeting tumor microenvironment. *Acta Pharm. Sinica B* **2019**, *9*, 203–219. [CrossRef] [PubMed]
117. Markowska, A.; Antoszczak, M.; Kojs, Z.; Bednarek, W.; Markowska, J.; Huczynski, A. Role of vitamin D3 in selected malignant neoplasms. *Nutrition* **2020**, *79*, 110964. [CrossRef]
118. Carlberg, C.; Velleuer, E. vitamin D and the risk for cancer: A molecular analysis. *Biochem. Pharmacol.* **2022**, *196*, 114735. [CrossRef] [PubMed]
119. Vanhevel, J.; Verlinden, L.; Doms, S.; Wildiers, H.; Verstuyf, A. The role of vitamin D in breast cancer risk and progression. *Endocr. Relat. Cancer* **2022**, *29*, R33–R55. [CrossRef] [PubMed]
120. Huang, Y.-C.; Chen, J.-Y.; Hung, W.-C. vitamin D_3 receptor/Sp1 complex is required for the induction of $p27^{KIP1}$ expression by vitamin D_3. *Oncogene* **2004**, *23*, 4856–4861. [CrossRef] [PubMed]
121. Yang, E.S.; Burnstein, K.L. vitamin D inhibits G1 to S progression in LNCaP prostate cancer cells through p27Kip1 stabilization and Cdk2 mislocalization to the cytoplasm. *J. Biol. Chem.* **2003**, *278*, 46862–46868. [CrossRef]
122. Li, P.; Li, C.; Zhao, X.; Zhang, X.; Nicosia, S.V.; Bai, W. $p27^{Kip1}$ stabilization and G_1 arrest by 1,25-dihydroxyvitamin D_3 in ovarian cancer cells mediated through down-regulation of cyclin E/cyclin-dependent kinase 2 and Skp1-Cullin-F-box protein/Skp2 ubiquitin ligase. *J. Biol. Chem.* **2004**, *279*, 25260–25267. [CrossRef]
123. Washington, M.N.; Kim, J.S.; Weigel, N.L. 1alpha,25-dihydroxyvitamin D3 inhibits C4-2 prostate cancer cell growth via a retinoblastoma protein (Rb)-independent G1 arrest. *Prostate* **2011**, *71*, 98–110. [CrossRef]
124. Toropainen, S.; Väisänen, S.; Heikkinen, S.; Carlberg, C. The down-regulation of the human MYC gene by the nuclear hormone 1alpha,25-dihydroxyvitamin D3 is associated with cycling of corepressors and histone deacetylases. *J. Mol. Biol.* **2010**, *400*, 284–294. [CrossRef]
125. Pálmer, H.G.; González-Sancho, J.M.; Espada, J.; Berciano, M.T.; Puig, I.; Baulida, J.; Quintanilla, M.; Cano, A.; García de Herreros, A.; Lafarga, M.; et al. vitamin D_3 promotes the differentiation of colon carcinoma cells by the induction of E-cadherin and the inhibition of b-catenin signaling. *J. Cell Biol.* **2001**, *154*, 369–387. [CrossRef] [PubMed]

126. Ordóñez-Morán, P.; Larriba, M.J.; Pálmer, H.G.; Valero, R.A.; Barbáchano, A.; Duñach, M.; García de Herreros, A.; Villalobos, C.; Berciano, M.T.; Lafarga, M.; et al. RhoA-ROCK and p38MAPK-MSK1 mediate vitamin D effects on gene expression, phenotype, and Wnt pathway in colon cancer cells. *J. Cell Biol.* **2008**, *183*, 697–710. [CrossRef]
127. Álvarez-Díaz, S.; Valle, N.; García, J.M.; Peña, C.; Freije, J.M.; Quesada, V.; Astudillo, A.; Bonilla, F.; López-Otín, C.; Muñoz, A. Cystatin D is a candidate tumor suppressor gene induced by vitamin D in human colon cancer cells. *J. Clin. Investig.* **2009**, *119*, 2343–2358. [CrossRef] [PubMed]
128. Salehi-Tabar, R.; Nguyen-Yamamoto, L.; Tavera-Mendoza, L.E.; Quail, T.; Dimitrov, V.; An, B.S.; Glass, L.; Goltzman, D.; White, J.H. vitamin D receptor as a master regulator of the c-MYC/MXD1 network. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 18827–18832. [CrossRef] [PubMed]
129. Wang, L.; Zhou, S.; Guo, B. vitamin D Suppresses Ovarian Cancer Growth and Invasion by Targeting Long Non-Coding RNA CCAT2. *Int. J. Mol. Sci.* **2020**, *21*, 72334. [CrossRef] [PubMed]
130. Salehi-Tabar, R.; Memari, B.; Wong, H.; Dimitrov, V.; Rochel, N.; White, J.H. The Tumor Suppressor FBW7 and the vitamin D Receptor Are Mutual Cofactors in Protein Turnover and Transcriptional Regulation. *Mol. Cancer Res. MCR* **2019**, *17*, 709–719. [CrossRef] [PubMed]
131. Pálmer, H.G.; Sánchez-Carbayo, M.; Ordóñez-Morán, P.; Larriba, M.J.; Cordón-Cardó, C.; Muñoz, A. Genetic signatures of differentiation induced by 1a,25-dihydroxyvitamin D_3 in human colon cancer cells. *Cancer Res.* **2003**, *63*, 7799–7806. [PubMed]
132. Zhu, Y.; Chen, P.; Gao, Y.; Ta, N.; Zhang, Y.; Cai, J.; Zhao, Y.; Liu, S.; Zheng, J. MEG3 Activated by vitamin D Inhibits Colorectal Cancer Cells Proliferation and Migration via Regulating Clusterin. *EBioMedicine* **2018**, *30*, 148–157. [CrossRef] [PubMed]
133. Zhu, C.; Wang, Z.; Cai, J.; Pan, C.; Lin, S.; Zhang, Y.; Chen, Y.; Leng, M.; He, C.; Zhou, P.; et al. VDR Signaling via the Enzyme NAT2 Inhibits Colorectal Cancer Progression. *Front. Pharmacol.* **2021**, *12*, 727704. [CrossRef] [PubMed]
134. Li, Q.; Li, Y.; Jiang, H.; Xiao, Z.; Wu, X.; Zhang, H.; Zhao, Y.; Du, F.; Chen, Y.; Wu, Z.; et al. vitamin D suppressed gastric cancer cell growth through downregulating CD44 expression in vitro and in vivo. *Nutrition* **2021**, *91*, 111413. [CrossRef] [PubMed]
135. Dhawan, P.; Weider, R.; Christakos, S. CCAAT enhancer-binding protein alpha is a molecular target of 1,25-dihydroxyvitamin D3 in MCF-7 breast cancer cells. *J. Biol. Chem.* **2009**, *284*, 3086–3095. [CrossRef]
136. Boyle, B.J.; Zhao, X.Y.; Cohen, P.; Feldman, D. Insulin-like growth factor binding protein-3 mediates 1 alpha,25-dihydroxyvitamin D(3) growth inhibition in the LNCaP prostate cancer cell line through p21/WAF1. *J. Urol.* **2001**, *165*, 1319–1324. [CrossRef]
137. Chang, S.; Gao, L.; Yang, Y.; Tong, D.; Guo, B.; Liu, L.; Li, Z.; Song, T.; Huang, C. miR-145 mediates the antiproliferative and gene regulatory effects of vitamin D3 by directly targeting E2F3 in gastric cancer cells. *Oncotarget* **2015**, *6*, 7675–7685. [CrossRef] [PubMed]
138. Peng, W.; Wang, K.; Zheng, R.; Derwahl, M. 1,25 dihydroxyvitamin D3 inhibits the proliferation of thyroid cancer stem-like cells via cell cycle arrest. *Endocr. Res.* **2016**, *41*, 71–80. [CrossRef]
139. Kulling, P.M.; Olson, K.C.; Olson, T.L.; Feith, D.J.; Loughran, T.P., Jr. vitamin D in hematological disorders and malignancies. *Eur. J. Haematol.* **2017**, *98*, 187–197. [CrossRef]
140. Tong, W.-M.; Kállay, E.; Hofer, H.; Hulla, W.; Manhardt, T.; Peterlik, M.; Cross, H.S. Growth regulation of human colon cancer cells by epidermal growth factor and 1,25-dihydroxyvitamin D_3 is mediated by mutual modulation of receptor expression. *Eur. J. Cancer* **1998**, *34*, 2119–2125. [CrossRef]
141. Tong, W.-M.; Hofer, H.; Ellinger, A.; Peterlik, M.; Cross, H.S. Mechanism of antimitogenic action of vitamin D in human colon carcinoma cells: Relevance for suppression of epidermal growth factor-stimulated cell growth. *Oncol. Res.* **1999**, *11*, 77–84. [PubMed]
142. Andl, C.D.; Rustgi, A.K. No one-way street: Cross-talk between e-cadherin and receptor tyrosine kinase (RTK) signaling: A mechanism to regulate RTK activity. *Cancer Biol. Ther.* **2005**, *4*, 28–31. [CrossRef] [PubMed]
143. Barbáchano, A.; Ordóñez-Morán, P.; García, J.M.; Sánchez, A.; Pereira, F.; Larriba, M.J.; Martínez, N.; Hernández, J.; Landolfi, S.; Bonilla, F.; et al. SPROUTY-2 and E-cadherin regulate reciprocally and dictate colon cancer cell tumourigenicity. *Oncogene* **2010**, *29*, 4800–4813. [CrossRef] [PubMed]
144. Dougherty, U.; Mustafi, R.; Sadiq, F.; Almoghrabi, A.; Mustafi, D.; Kreisheh, M.; Sundaramurthy, S.; Liu, W.; Konda, V.J.; Pekow, J.; et al. The renin-angiotensin system mediates EGF receptor-vitamin D receptor cross-talk in colitis-associated colon cancer. *Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res.* **2014**, *20*, 5848–5859. [CrossRef]
145. Oh, Y.S.; Kim, E.J.; Schaffer, B.S.; Kang, Y.H.; Binderup, L.; MacDonald, R.G.; Park, J.H.Y. Synthetic low-calcaemic vitamin D_3 analogues inhibit secretion of insulin-like growth factor II and stimulate production of insulin-like growth factor-binding protein-6 in conjunction with growth suppression of HT-29 colon cancer cells. *Mol. Cell. Endocrinol.* **2001**, *183*, 141–149. [CrossRef]
146. Leng, S.L.; Leeding, K.S.; Whitehead, R.H.; Bach, L.A. Insulin-like growth factor (IGF)-binding protein-6 inhibits IGF-II-induced but not basal proliferation and adhesion of LIM 1215 colon cancer cells. *Mol. Cell. Endocrinol.* **2001**, *174*, 121–127. [CrossRef]
147. Rosli, S.N.; Shintani, T.; Toratani, S.; Usui, E.; Okamoto, T. 1alpha,25(OH)(2)D(3) inhibits FGF-2 release from oral squamous cell carcinoma cells through down-regulation of HBp17/FGFBP-1. *In Vitro Cell. Dev. Biol. Anim.* **2014**, *50*, 802–806. [CrossRef]
148. Higaki, M.; Shintani, T.; Hamada, A.; Rosli, S.N.Z.; Okamoto, T. Eldecalcitol (ED-71)-induced exosomal miR-6887-5p suppresses squamous cell carcinoma cell growth by targeting heparin-binding protein 17/fibroblast growth factor-binding protein-1 (HBp17/FGFBP-1). *In Vitro Cell. Dev. Biol. Anim.* **2020**, *56*, 222–233. [CrossRef]
149. Nazarova, N.; Golovko, O.; Blauer, M.; Tuohimaa, P. Calcitriol inhibits growth response to Platelet-Derived Growth Factor-BB in human prostate cells. *J. Steroid Biochem. Mol. Biol.* **2005**, *94*, 189–196. [CrossRef]

150. Wu, F.S.; Zheng, S.S.; Wu, L.J.; Teng, L.S.; Ma, Z.M.; Zhao, W.H.; Wu, W. Calcitriol inhibits the growth of MHCC97 heptocellular cell lines by down-modulating c-met and ERK expressions. *Liver Int.* **2007**, *27*, 700–707. [CrossRef]
151. Inaba, M.; Koyama, H.; Hino, M.; Okuno, S.; Terada, M.; Nishizawa, Y.; Nishino, T.; Morii, H. Regulation of release of hepatocyte growth factor from human promyelocytic leukemia cells, HL-60, by 1,25-dihydroxyvitamin D3, 12-O-tetradecanoylphorbol 13-acetate, and dibutyryl cyclic adenosine monophosphate. *Blood* **1993**, *82*, 53–59. [CrossRef]
152. Larriba, M.J.; González-Sancho, J.M.; Bonilla, F.; Muñoz, A. Interaction of vitamin D with membrane-based signaling pathways. *Front. Physiol.* **2014**, *5*, 60. [CrossRef]
153. Krishnan, A.V.; Swami, S.; Feldman, D. vitamin D and breast cancer: Inhibition of estrogen synthesis and signaling. *J. Steroid Biochem. Mol. Biol.* **2010**, *121*, 343–348. [CrossRef]
154. Zheng, W.; Cao, L.; Ouyang, L.; Zhang, Q.; Duan, B.; Zhou, W.; Chen, S.; Peng, W.; Xie, Y.; Fan, Q.; et al. Anticancer activity of 1,25-(OH)2D3 against human breast cancer cell lines by targeting Ras/MEK/ERK pathway. *OncoTargets Ther.* **2019**, *12*, 721–732. [CrossRef] [PubMed]
155. Ben-Batalla, I.; Seoane, S.; García-Caballero, T.; Gallego, R.; Macia, M.; González, L.O.; Vizoso, F.; Pérez-Fernández, R. Deregulation of the Pit-1 transcription factor in human breast cancer cells promotes tumor growth and metastasis. *J. Clin. Investig.* **2010**, *120*, 4289–4302. [CrossRef]
156. Perez-Fernandez, R.; Seoane, S.; Garcia-Caballero, T.; Segura, C.; Macia, M. vitamin D, Pit-1, GH, and PRL: Possible roles in breast cancer development. *Curr. Med. Chem.* **2007**, *14*, 3051–3058. [CrossRef] [PubMed]
157. Álvarez-Díaz, S.; Valle, N.; Ferrer-Mayorga, G.; Lombardía, L.; Herrera, M.; Domínguez, O.; Segura, M.F.; Bonilla, F.; Hernando, E.; Muñoz, A. MicroRNA-22 is induced by vitamin D and contributes to its antiproliferative, antimigratory and gene regulatory effects in colon cancer cells. *Hum. Mol. Genet.* **2012**, *21*, 2157–2165. [CrossRef] [PubMed]
158. Lin, W.; Zou, H.; Mo, J.; Jin, C.; Jiang, H.; Yu, C.; Jiang, Z.; Yang, Y.; He, B.; Wang, K. Micro1278 Leads to Tumor Growth Arrest, Enhanced Sensitivity to Oxaliplatin and vitamin D and Inhibits Metastasis via KIF5B, CYP24A1, and BTG2, Respectively. *Front. Oncol.* **2021**, *11*, 637878. [CrossRef] [PubMed]
159. Yang, L.; Yang, J.; Venkateswarlu, S.; Ko, T.; Brattain, M.G. Autocrine TGFbeta signaling mediates vitamin D3 analog-induced growth inhibition in breast cells. *J. Cell. Physiol.* **2001**, *188*, 383–393. [CrossRef] [PubMed]
160. Chen, A.; Davis, B.H.; Sitrin, M.D.; Brasitus, T.A.; Bissonnette, M. Transforming growth factor-b 1 signaling contributes to Caco-2 cell growth inhibition induced by $1,25(OH)_2D_3$. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2002**, *283*, G864–G874. [CrossRef] [PubMed]
161. Ito, Y.; Honda, A.; Kurokawa, M. Impact of vitamin D level at diagnosis and transplantation on the prognosis of hematological malignancy: A meta-analysis. *Blood Adv.* **2021**, *6*, 1499–1511. [CrossRef]
162. Gerousi, M.; Psomopoulos, F.; Kotta, K.; Tsagiopoulou, M.; Stavroyianni, N.; Anagnostopoulos, A.; Anastasiadis, A.; Gkanidou, M.; Kotsianidis, I.; Ntoufa, S.; et al. The Calcitriol/vitamin D Receptor System Regulates Key Immune Signaling Pathways in Chronic Lymphocytic Leukemia. *Cancers* **2021**, *13*, 285. [CrossRef]
163. Olson, K.C.; Kulling, P.M.; Olson, T.L.; Tan, S.F.; Rainbow, R.J.; Feith, D.J.; Loughran, T.P., Jr. vitamin D decreases STAT phosphorylation and inflammatory cytokine output in T-LGL leukemia. *Cancer Biol. Ther.* **2017**, *18*, 290–303. [CrossRef]
164. McGlorthan, L.; Paucarmayta, A.; Casablanca, Y.; Maxwell, G.L.; Syed, V. Progesterone induces apoptosis by activation of caspase-8 and calcitriol via activation of caspase-9 pathways in ovarian and endometrial cancer cells in vitro. *Apoptosis Int. J. Program. Cell Death* **2021**, *26*, 184–194. [CrossRef] [PubMed]
165. Jiang, F.; Bao, J.; Li, P.; Nicosia, S.V.; Bai, W. Induction of ovarian cancer cell apoptosis by 1,25-dihydroxyvitamin D3 through the down-regulation of telomerase. *J. Biol. Chem.* **2004**, *279*, 53213–53221. [CrossRef] [PubMed]
166. Kasiappan, R.; Shen, Z.; Tse, A.K.; Jinwal, U.; Tang, J.; Lungchukiet, P.; Sun, Y.; Kruk, P.; Nicosia, S.V.; Zhang, X.; et al. 1,25-Dihydroxyvitamin D3 suppresses telomerase expression and human cancer growth through microRNA-498. *J. Biol. Chem.* **2012**, *287*, 41297–41309. [CrossRef]
167. Stambolsky, P.; Tabach, Y.; Fontemaggi, G.; Weisz, L.; Maor-Aloni, R.; Siegfried, Z.; Shiff, I.; Kogan, I.; Shay, M.; Kalo, E.; et al. Modulation of the vitamin D3 response by cancer-associated mutant p53. *Cancer Cell* **2010**, *17*, 273–285. [CrossRef] [PubMed]
168. Abu El Maaty, M.A.; Wölfl, S. Effects of 1,25(OH)(2)D(3) on Cancer Cells and Potential Applications in Combination with Established and Putative Anti-Cancer Agents. *Nutrients* **2017**, *9*, 87. [CrossRef]
169. Kaler, P.; Galea, V.; Augenlicht, L.; Klampfer, L. Tumor associated macrophages protect colon cancer cells from TRAIL-induced apoptosis through IL-1beta-dependent stabilization of Snail in tumor cells. *PLoS ONE* **2010**, *5*, e11700. [CrossRef] [PubMed]
170. Borkowski, R.; Du, L.; Zhao, Z.; McMillan, E.; Kosti, A.; Yang, C.R.; Suraokar, M.; Wistuba, I.I.; Gazdar, A.F.; Minna, J.D.; et al. Genetic mutation of p53 and suppression of the miR-17 approximately 92 cluster are synthetic lethal in non-small cell lung cancer due to upregulation of vitamin D Signaling. *Cancer Res.* **2015**, *75*, 666–675. [CrossRef] [PubMed]
171. Bhutia, S.K. vitamin D in autophagy signaling for health and diseases: Insights on potential mechanisms and future perspectives. *J. Nutr. Biochem.* **2022**, *99*, 108841. [CrossRef] [PubMed]
172. Hoyer-Hansen, M.; Bastholm, L.; Szyniarowski, P.; Campanella, M.; Szabadkai, G.; Farkas, T.; Bianchi, K.; Fehrenbacher, N.; Elling, F.; Rizzuto, R.; et al. Control of macroautophagy by calcium, calmodulin-dependent kinase kinase-beta, and Bcl-2. *Mol. Cell* **2007**, *25*, 193–205. [CrossRef]
173. Suares, A.; Tapia, C.; Gonzalez-Pardo, V. VDR agonists down regulate PI3K/Akt/mTOR axis and trigger autophagy in Kaposi's sarcoma cells. *Heliyon* **2019**, *5*, e02367. [CrossRef] [PubMed]

174. Wang, J.; Lian, H.; Zhao, Y.; Kauss, M.A.; Spindel, S. vitamin D3 induces autophagy of human myeloid leukemia cells. *J. Biol. Chem.* **2008**, *283*, 25596–25605. [CrossRef] [PubMed]
175. Han, J.; Tang, Y.; Zhong, M.; Wu, W. Antitumor effects and mechanisms of 1,25(OH)2D3 in the Pfeiffer diffuse large B lymphoma cell line. *Mol. Med. Rep.* **2019**, *20*, 5064–5074. [CrossRef] [PubMed]
176. Zhang, X.; Luo, F.; Li, J.; Wan, J.; Zhang, L.; Li, H.; Chen, A.; Chen, J.; Cai, T.; He, X.; et al. DNA damage-inducible transcript 4 is an innate guardian for human squamous cell carcinoma and an molecular vector for anti-carcinoma effect of 1,25(OH)2 D3. *Exp. Dermatol.* **2019**, *28*, 45–52. [CrossRef] [PubMed]
177. Wang, W.; Liu, J.; Chen, K.; Wang, J.; Dong, Q.; Xie, J.; Yuan, Y. vitamin D promotes autophagy in AML cells by inhibiting miR-17-5p-induced Beclin-1 overexpression. *Mol. Cell. Biochem.* **2021**, *476*, 3951–3962. [CrossRef] [PubMed]
178. Demasters, G.; Di, X.; Newsham, I.; Shiu, R.; Gewirtz, D.A. Potentiation of radiation sensitivity in breast tumor cells by the vitamin D3 analogue, EB 1089, through promotion of autophagy and interference with proliferative recovery. *Mol. Cancer Ther.* **2006**, *5*, 2786–2797. [CrossRef] [PubMed]
179. Wilson, E.N.; Bristol, M.L.; Di, X.; Maltese, W.A.; Koterba, K.; Beckman, M.J.; Gewirtz, D.A. A switch between cytoprotective and cytotoxic autophagy in the radiosensitization of breast tumor cells by chloroquine and vitamin D. *Horm. Cancer* **2011**, *2*, 272–285. [CrossRef] [PubMed]
180. Bristol, M.L.; Di, X.; Beckman, M.J.; Wilson, E.N.; Henderson, S.C.; Maiti, A.; Fan, Z.; Gewirtz, D.A. Dual functions of autophagy in the response of breast tumor cells to radiation: Cytoprotective autophagy with radiation alone and cytotoxic autophagy in radiosensitization by vitamin D 3. *Autophagy* **2012**, *8*, 739–753. [CrossRef] [PubMed]
181. Sharma, K.; Goehe, R.W.; Di, X.; Hicks, M.A., 2nd; Torti, S.V.; Torti, F.M.; Harada, H.; Gewirtz, D.A. A novel cytostatic form of autophagy in sensitization of non-small cell lung cancer cells to radiation by vitamin D and the vitamin D analog, EB 1089. *Autophagy* **2014**, *10*, 2346–2361. [CrossRef] [PubMed]
182. Bak, D.H.; Kang, S.H.; Choi, D.R.; Gil, M.N.; Yu, K.S.; Jeong, J.H.; Lee, N.S.; Lee, J.H.; Jeong, Y.G.; Kim, D.K.; et al. Autophagy enhancement contributes to the synergistic effect of vitamin D in temozolomide-based glioblastoma chemotherapy. *Exp. Ther. Med.* **2016**, *11*, 2153–2162. [CrossRef] [PubMed]
183. Dongre, A.; Weinberg, R.A. New insights into the mechanisms of epithelial-mesenchymal transition and implications for cancer. *Nat. Rev. Mol. Cell Biol.* **2019**, *20*, 69–84. [CrossRef] [PubMed]
184. Larriba, M.J.; Garcia de Herreros, A.; Muñoz, A. vitamin D and the Epithelial to Mesenchymal Transition. *Stem Cells Int.* **2016**, *2016*, 6213872. [CrossRef] [PubMed]
185. Fernández-Barral, A.; Bustamante-Madrid, P.; Ferrer-Mayorga, G.; Barbáchano, A.; Larriba, M.J.; Muñoz, A. vitamin D Effects on Cell Differentiation and Stemness in Cancer. *Cancers* **2020**, *12*, 2413. [CrossRef] [PubMed]
186. Pendás-Franco, N.; González-Sancho, J.M.; Suarez, Y.; Aguilera, O.; Steinmeyer, A.; Gamallo, C.; Berciano, M.T.; Lafarga, M.; Muñoz, A. vitamin D regulates the phenotype of human breast cancer cells. *Differ. Res. Biol. Divers.* **2007**, *75*, 193–207. [CrossRef] [PubMed]
187. Welsh, J. vitamin D and Breast Cancer: Mechanistic Update. *J. Bone Miner. Res. Plus* **2021**, *5*, e10582. [CrossRef] [PubMed]
188. Kouchi, Z.; Fujiwara, Y.; Yamaguchi, H.; Nakamura, Y.; Fukami, K. Phosphatidylinositol 5-phosphate 4-kinase type II beta is required for vitamin D receptor-dependent E-cadherin expression in SW480 cells. *Biochem. Biophys. Res. Commun.* **2011**, *408*, 523–529. [CrossRef] [PubMed]
189. Lopes, N.; Carvalho, J.; Duraes, C.; Sousa, B.; Gomes, M.; Costa, J.L.; Oliveira, C.; Paredes, J.; Schmitt, F. 1Alpha,25-dihydroxyvitamin D3 induces de novo E-cadherin expression in triple-negative breast cancer cells by CDH1-promoter demethylation. *Anticancer Res.* **2012**, *32*, 249–257. [PubMed]
190. Upadhyay, S.K.; Verone, A.; Shoemaker, S.; Qin, M.; Liu, S.; Campbell, M.; Hershberger, P.A. 1,25-Dihydroxyvitamin D3 (1,25(OH)2D3) Signaling Capacity and the Epithelial-Mesenchymal Transition in Non-Small Cell Lung Cancer (NSCLC): Implications for Use of 1,25(OH)2D3 in NSCLC Treatment. *Cancers* **2013**, *5*, 1504–1521. [CrossRef] [PubMed]
191. Chiang, K.C.; Chen, S.C.; Yeh, C.N.; Pang, J.H.; Shen, S.C.; Hsu, J.T.; Liu, Y.Y.; Chen, L.W.; Kuo, S.F.; Takano, M.; et al. MART-10, a less calcemic vitamin D analog, is more potent than 1alpha,25-dihydroxyvitamin D3 in inhibiting the metastatic potential of MCF-7 breast cancer cells in vitro. *J. Steroid Biochem. Mol. Biol.* **2014**, *139*, 54–60. [CrossRef] [PubMed]
192. Chiang, K.C.; Yeh, C.N.; Hsu, J.T.; Jan, Y.Y.; Chen, L.W.; Kuo, S.F.; Takano, M.; Kittaka, A.; Chen, T.C.; Chen, W.T.; et al. The vitamin D analog, MART-10, represses metastasis potential via downregulation of epithelial-mesenchymal transition in pancreatic cancer cells. *Cancer Lett.* **2014**, *354*, 235–244. [CrossRef] [PubMed]
193. Findlay, V.J.; Moretz, R.E.; Wang, C.; Vaena, S.G.; Bandurraga, S.G.; Ashenafi, M.; Marshall, D.T.; Watson, D.K.; Camp, E.R. Slug expression inhibits calcitriol-mediated sensitivity to radiation in colorectal cancer. *Mol. Carcinog.* **2014**, *53*, E130–E139. [CrossRef] [PubMed]
194. Hou, Y.F.; Gao, S.H.; Wang, P.; Zhang, H.M.; Liu, L.Z.; Ye, M.X.; Zhou, G.M.; Zhang, Z.L.; Li, B.Y. 1alpha,25(OH)(2)D(3) Suppresses the Migration of Ovarian Cancer SKOV-3 Cells through the Inhibition of Epithelial-Mesenchymal Transition. *Int. J. Mol. Sci.* **2016**, *17*, 1285. [CrossRef] [PubMed]
195. Pereira, F.; Barbáchano, A.; Silva, J.; Bonilla, F.; Campbell, M.J.; Muñoz, A.; Larriba, M.J. KDM6B/JMJD3 histone demethylase is induced by vitamin D and modulates its effects in colon cancer cells. *Hum. Mol. Genet.* **2011**, *20*, 4655–4665. [CrossRef] [PubMed]

196. Barbáchano, A.; Fernández-Barral, A.; Pereira, F.; Segura, M.F.; Ordóñez-Morán, P.; Carrillo-de Santa Pau, E.; González-Sancho, J.M.; Hanniford, D.; Martinez, N.; Costales-Carrera, A.; et al. SPROUTY-2 represses the epithelial phenotype of colon carcinoma cells via upregulation of ZEB1 mediated by ETS1 and miR-200/miR-150. *Oncogene* **2016**, *35*, 2991–3003. [CrossRef] [PubMed]
197. Koeffler, H.P.; Amatruda, T.; Ikekawa, N.; Kobayashi, Y.; DeLuca, H.F. Induction of macrophage differentiation of human normal and leukemic myeloid stem cells by 1,25-dihydroxyvitamin D3 and its fluorinated analogues. *Cancer Res.* **1984**, *44*, 5624–5628. [PubMed]
198. Tanaka, H.; Abe, E.; Miyaura, C.; Shiina, Y.; Suda, T. 1 alpha,25-dihydroxyvitamin D3 induces differentiation of human promyelocytic leukemia cells (HL-60) into monocyte-macrophages, but not into granulocytes. *Biochem. Biophys. Res. Commun.* **1983**, *117*, 86–92. [CrossRef]
199. Abe, J.; Moriya, Y.; Saito, M.; Sugawara, Y.; Suda, T.; Nishii, Y. Modulation of cell growth, differentiation, and production of interleukin-3 by 1 alpha,25-dihydroxyvitamin D3 in the murine myelomonocytic leukemia cell line WEHI-3. *Cancer Res.* **1986**, *46*, 6316–6321.
200. Gocek, E.; Studzinski, G.P. vitamin D and differentiation in cancer. *Crit. Rev. Clin. Lab. Sci.* **2009**, *46*, 190–209. [CrossRef]
201. Hmama, Z.; Nandan, D.; Sly, L.; Knutson, K.L.; Herrera-Velit, P.; Reiner, N.E. 1alpha,25-dihydroxyvitamin D(3)-induced myeloid cell differentiation is regulated by a vitamin D receptor-phosphatidylinositol 3-kinase signaling complex. *J. Exp. Med.* **1999**, *190*, 1583–1594. [CrossRef]
202. Ji, Y.; Studzinski, G.P. Retinoblastoma protein and CCAAT/enhancer-binding protein beta are required for 1,25-dihydroxyvitamin D3-induced monocytic differentiation of HL60 cells. *Cancer Res.* **2004**, *64*, 370–377. [CrossRef]
203. Marchwicka, A.; Marcinkowska, E. Regulation of Expression of CEBP Genes by Variably Expressed vitamin D Receptor and Retinoic Acid Receptor alpha in Human Acute Myeloid Leukemia Cell Lines. *Int. J. Mol. Sci.* **2018**, *19*, 1918. [CrossRef]
204. Song, J.H.; Park, E.; Kim, M.S.; Cho, K.M.; Park, S.H.; Lee, A.; Song, J.; Kim, H.J.; Koh, J.T.; Kim, T.S. l-Asparaginase-mediated downregulation of c-Myc promotes 1,25(OH)2 D3-induced myeloid differentiation in acute myeloid leukemia cells. *Int. J. Cancer* **2017**, *140*, 2364–2374. [CrossRef]
205. Sabatier, M.; Boet, E.; Zaghdoudi, S.; Guiraud, N.; Hucteau, A.; Polley, N.; Cognet, G.; Saland, E.; Lauture, L.; Farge, T.; et al. Activation of vitamin D Receptor Pathway Enhances Differentiating Capacity in Acute Myeloid Leukemia with Isocitrate Dehydrogenase Mutations. *Cancers* **2021**, *13*, 5243. [CrossRef]
206. Hickish, T.; Cunningham, D.; Colston, K.; Millar, B.C.; Sandle, J.; Mackay, A.G.; Soukop, M.; Sloane, J. The effect of 1,25-dihydroxyvitamin D3 on lymphoma cell lines and expression of vitamin D receptor in lymphoma. *Br. J. Cancer* **1993**, *68*, 668–672. [CrossRef]
207. Nusse, R.; Clevers, H. Wnt/beta-Catenin Signaling, Disease, and Emerging Therapeutic Modalities. *Cell* **2017**, *169*, 985–999. [CrossRef] [PubMed]
208. Polakis, P. Wnt signaling in cancer. *Cold Spring Harb. Perspect. Biol.* **2012**, *4*, a008052. [CrossRef] [PubMed]
209. The_Cancer_Genome_Atlas_Network. Comprehensive molecular characterization of human colon and rectal cancer. *Nature* **2012**, *487*, 330–337. [CrossRef]
210. Yaeger, R.; Chatila, W.K.; Lipsyc, M.D.; Hechtman, J.F.; Cercek, A.; Sanchez-Vega, F.; Jayakumaran, G.; Middha, S.; Zehir, A.; Donoghue, M.T.A.; et al. Clinical Sequencing Defines the Genomic Landscape of Metastatic Colorectal Cancer. *Cancer Cell* **2018**, *33*, 125–136. [CrossRef]
211. González-Sancho, J.M.; Larriba, M.J.; Muñoz, A. Wnt and vitamin D at the Crossroads in Solid Cancer. *Cancers* **2020**, *12*, 3434. [CrossRef]
212. Aguilera, O.; Peña, C.; García, J.M.; Larriba, M.J.; Ordóñez-Morán, P.; Navarro, D.; Barbáchano, A.; López de Silanes, I.; Ballestar, E.; Fraga, M.F.; et al. The Wnt antagonist DICKKOPF-1 gene is induced by 1alpha,25-dihydroxyvitamin D_3 associated to the differentiation of human colon cancer cells. *Carcinogenesis* **2007**, *28*, 1877–1884. [CrossRef] [PubMed]
213. Beildeck, M.E.; Islam, M.; Shah, S.; Welsh, J.; Byers, S.W. Control of TCF-4 expression by VDR and vitamin D in the mouse mammary gland and colorectal cancer cell lines. *PLoS ONE* **2009**, *4*, e7872. [CrossRef] [PubMed]
214. Jin, D.; Zhang, Y.G.; Wu, S.; Lu, R.; Lin, Z.; Zheng, Y.; Chen, H.; Cs-Szabo, G.; Sun, J. vitamin D receptor is a novel transcriptional regulator for Axin1. *J. Steroid Biochem. Mol. Biol.* **2017**, *165*, 430–437. [CrossRef] [PubMed]
215. Arensman, M.D.; Nguyen, P.; Kershaw, K.M.; Lay, A.R.; Ostertag-Hill, C.A.; Sherman, M.H.; Downes, M.; Liddle, C.; Evans, R.M.; Dawson, D.W. Calcipotriol Targets LRP6 to Inhibit Wnt Signaling in Pancreatic Cancer. *Mol. Cancer Res. MCR* **2015**, *13*, 1509–1519. [CrossRef] [PubMed]
216. Chen, J.; Katz, L.H.; Munoz, N.M.; Gu, S.; Shin, J.H.; Jogunoori, W.S.; Lee, M.H.; Belkin, M.D.; Kim, S.B.; White, J.C.; et al. vitamin D Deficiency Promotes Liver Tumor Growth in Transforming Growth Factor-beta/Smad3-Deficient Mice Through Wnt and Toll-like Receptor 7 Pathway Modulation. *Sci. Rep.* **2016**, *6*, 30217. [CrossRef]
217. Xu, S.; Zhang, Z.H.; Fu, L.; Song, J.; Xie, D.D.; Yu, D.X.; Xu, D.X.; Sun, G.P. Calcitriol inhibits migration and invasion of renal cell carcinoma cells by suppressing Smad2/3-, STAT3- and beta-catenin-mediated epithelial-mesenchymal transition. *Cancer Sci.* **2020**, *111*, 59–71. [CrossRef] [PubMed]
218. Kaler, P.; Augenlicht, L.; Klampfer, L. Macrophage-derived IL-1beta stimulates Wnt signaling and growth of colon cancer cells: A crosstalk interrupted by vitamin D3. *Oncogene* **2009**, *28*, 3892–3902. [CrossRef] [PubMed]

219. Fernández-García, N.I.; Pálmer, H.G.; García, M.; González-Martín, A.; del Rio, M.; Barettino, D.; Volpert, O.; Muñoz, A.; Jiménez, B. 1a,25-Dihydroxyvitamin D_3 regulates the expression of *Id1* and *Id2* genes and the angiogenic phenotype of human colon carcinoma cells. *Oncogene* **2005**, *24*, 6533–6544. [CrossRef] [PubMed]
220. Ben-Shoshan, M.; Amir, S.; Dang, D.T.; Dang, L.H.; Weisman, Y.; Mabjeesh, N.J. 1alpha,25-dihydroxyvitamin D3 (Calcitriol) inhibits hypoxia-inducible factor-1/vascular endothelial growth factor pathway in human cancer cells. *Mol. Cancer Ther.* **2007**, *6*, 1433–1439. [CrossRef] [PubMed]
221. Pendás-Franco, N.; García, J.M.; Peña, C.; Valle, N.; Pálmer, H.G.; Heinaniemi, M.; Carlberg, C.; Jiménez, B.; Bonilla, F.; Muñoz, A.; et al. DICKKOPF-4 is induced by TCF/beta-catenin and upregulated in human colon cancer, promotes tumour cell invasion and angiogenesis and is repressed by 1alpha,25-dihydroxyvitamin D_3. *Oncogene* **2008**, *27*, 4467–4477. [CrossRef] [PubMed]
222. Kim, J.H.; Park, W.H.; Suh, D.H.; Kim, K.; No, J.H.; Kim, Y.B. Calcitriol Combined with Platinum-based Chemotherapy Suppresses Growth and Expression of Vascular Endothelial Growth Factor of SKOV-3 Ovarian Cancer Cells. *Anticancer Res.* **2021**, *41*, 2945–2952. [CrossRef]
223. Piotrowska, A.; Beserra, F.P.; Wierzbicka, J.M.; Nowak, J.I.; Zmijewski, M.A. vitamin D Enhances Anticancer Properties of Cediranib, a VEGFR Inhibitor, by Modulation of VEGFR2 Expression in Melanoma Cells. *Front. Oncol.* **2021**, *11*, 763895. [CrossRef] [PubMed]
224. Bao, B.Y.; Yao, J.; Lee, Y.F. 1alpha, 25-dihydroxyvitamin D3 suppresses interleukin-8-mediated prostate cancer cell angiogenesis. *Carcinogenesis* **2006**, *27*, 1883–1893. [CrossRef] [PubMed]
225. García-Quiroz, J.; Rivas-Suárez, M.; Garcia-Becerra, R.; Barrera, D.; Martínez-Reza, I.; Ordaz-Rosado, D.; Santos-Martinez, N.; Villanueva, O.; Santos-Cuevas, C.L.; Avila, E.; et al. Calcitriol reduces thrombospondin-1 and increases vascular endothelial growth factor in breast cancer cells: Implications for tumor angiogenesis. *J. Steroid Biochem. Mol. Biol.* **2014**, *144*, 215–222. [CrossRef] [PubMed]
226. Mantell, D.J.; Owens, P.E.; Bundred, N.J.; Mawer, E.B.; Canfield, A.E. 1 alpha,25-dihydroxyvitamin D(3) inhibits angiogenesis in vitro and in vivo. *Circ. Res.* **2000**, *87*, 214–220. [CrossRef] [PubMed]
227. Bernardi, R.J.; Johnson, C.S.; Modzelewski, R.A.; Trump, D.L. Antiproliferative effects of 1alpha,25-dihydroxyvitamin D(3) and vitamin D analogs on tumor-derived endothelial cells. *Endocrinology* **2002**, *143*, 2508–2514. [CrossRef] [PubMed]
228. Chung, I.; Wong, M.K.; Flynn, G.; Yu, W.D.; Johnson, C.S.; Trump, D.L. Differential antiproliferative effects of calcitriol on tumor-derived and matrigel-derived endothelial cells. *Cancer Res.* **2006**, *66*, 8565–8573. [CrossRef] [PubMed]
229. Chung, I.; Han, G.; Seshadri, M.; Gillard, B.M.; Yu, W.D.; Foster, B.A.; Trump, D.L.; Johnson, C.S. Role of vitamin D receptor in the antiproliferative effects of calcitriol in tumor-derived endothelial cells and tumor angiogenesis in vivo. *Cancer Res.* **2009**, *69*, 967–975. [CrossRef] [PubMed]
230. Flynn, G.; Chung, I.; Yu, W.D.; Romano, M.; Modzelewski, R.A.; Johnson, C.S.; Trump, D.L. Calcitriol (1,25-dihydroxycholecalciferol) selectively inhibits proliferation of freshly isolated tumor-derived endothelial cells and induces apoptosis. *Oncology* **2006**, *70*, 447–457. [CrossRef] [PubMed]
231. Sung, V.; Feldman, D. 1,25-Dihydroxyvitamin D3 decreases human prostate cancer cell adhesion and migration. *Mol. Cell. Endocrinol.* **2000**, *164*, 133–143. [CrossRef]
232. Tokar, E.J.; Webber, M.M. Cholecalciferol (vitamin D3) inhibits growth and invasion by up-regulating nuclear receptors and 25-hydroxylase (CYP27A1) in human prostate cancer cells. *Clin. Exp. Metastasis* **2005**, *22*, 275–284. [CrossRef] [PubMed]
233. Chen, S.; Zhu, J.; Zuo, S.; Ma, J.; Zhang, J.; Chen, G.; Wang, X.; Pan, Y.; Liu, Y.; Wang, P. 1,25(OH)2D3 attenuates TGF-beta1/beta2-induced increased migration and invasion via inhibiting epithelial-mesenchymal transition in colon cancer cells. *Biochem. Biophys. Res. Commun.* **2015**, *468*, 130–135. [CrossRef]
234. Hsu, J.W.; Yasmin-Karim, S.; King, M.R.; Wojciechowski, J.C.; Mickelsen, D.; Blair, M.L.; Ting, H.J.; Ma, W.L.; Lee, Y.F. Suppression of prostate cancer cell rolling and adhesion to endothelium by 1alpha,25-dihydroxyvitamin D3. *Am. J. Pathol.* **2011**, *178*, 872–880. [CrossRef] [PubMed]
235. Li, J.; Luco, A.L.; Camirand, A.; St-Arnaud, R.; Kremer, R. vitamin D Regulates CXCL12/CXCR4 and Epithelial-to-Mesenchymal Transition in a Model of Breast Cancer Metastasis to Lung. *Endocrinology* **2021**, *162*, bqab049. [CrossRef]
236. González-Sancho, J.M.; Alvarez-Dolado, M.; Muñoz, A. 1,25-Dihydroxyvitamin D3 inhibits tenascin-C expression in mammary epithelial cells. *FEBS Lett.* **1998**, *426*, 225–228. [CrossRef]
237. Koli, K.; Keski-Oja, J. 1alpha,25-dihydroxyvitamin D3 and its analogues down-regulate cell invasion-associated proteases in cultured malignant cells. *Cell Growth Differ. Mol. Biol. J. Am. Assoc. Cancer Res.* **2000**, *11*, 221–229.
238. Bao, B.Y.; Yeh, S.D.; Lee, Y.F. 1alpha,25-dihydroxyvitamin D3 inhibits prostate cancer cell invasion via modulation of selective proteases. *Carcinogenesis* **2006**, *27*, 32–42. [CrossRef] [PubMed]
239. Wilmanski, T.; Barnard, A.; Parikh, M.R.; Kirshner, J.; Buhman, K.; Burgess, J.; Teegarden, D. 1alpha,25-Dihydroxyvitamin D Inhibits the Metastatic Capability of MCF10CA1a and MDA-MB-231 Cells in an In Vitro Model of Breast to Bone Metastasis. *Nutr. Cancer* **2016**, *68*, 1202–1209. [CrossRef] [PubMed]
240. Vanoirbeek, E.; Eelen, G.; Verlinden, L.; Carmeliet, G.; Mathieu, C.; Bouillon, R.; O'Connor, R.; Xiao, G.; Verstuyf, A. PDLIM2 expression is driven by vitamin D and is involved in the pro-adhesion, and anti-migration and -invasion activity of vitamin D. *Oncogene* **2014**, *33*, 1904–1911. [CrossRef] [PubMed]
241. Narvaez, C.J.; Grebenc, D.; Balinth, S.; Welsh, J.E. vitamin D regulation of HAS2, hyaluronan synthesis and metabolism in triple negative breast cancer cells. *J. Steroid Biochem. Mol. Biol.* **2020**, *201*, 105688. [CrossRef]

242. Ma, Y.; Luo, W.; Bunch, B.L.; Pratt, R.N.; Trump, D.L.; Johnson, C.S. 1,25D3 differentially suppresses bladder cancer cell migration and invasion through the induction of miR-101-3p. *Oncotarget* **2017**, *8*, 60080–60093. [CrossRef] [PubMed]
243. Cheng, Y.H.; Chiang, E.I.; Syu, J.N.; Chao, C.Y.; Lin, H.Y.; Lin, C.C.; Yang, M.D.; Tsai, S.Y.; Tang, F.Y. Treatment of 13-cis retinoic acid and 1,25-dihydroxyvitamin D3 inhibits TNF-alpha-mediated expression of MMP-9 protein and cell invasion through the suppression of JNK pathway and microRNA 221 in human pancreatic adenocarcinoma cancer cells. *PLoS ONE* **2021**, *16*, e0247550. [CrossRef] [PubMed]
244. Ohlund, D.; Elyada, E.; Tuveson, D. Fibroblast heterogeneity in the cancer wound. *J. Exp. Med.* **2014**, *211*, 1503–1523. [CrossRef] [PubMed]
245. Barrett, R.L.; Pure, E. Cancer-associated fibroblasts and their influence on tumor immunity and immunotherapy. *eLife* **2020**, *9*, e57243. [CrossRef] [PubMed]
246. Rhim, A.D.; Oberstein, P.E.; Thomas, D.H.; Mirek, E.T.; Palermo, C.F.; Sastra, S.A.; Dekleva, E.N.; Saunders, T.; Becerra, C.P.; Tattersall, I.W.; et al. Stromal elements act to restrain, rather than support, pancreatic ductal adenocarcinoma. *Cancer Cell* **2014**, *25*, 735–747. [CrossRef] [PubMed]
247. Ozdemir, B.C.; Pentcheva-Hoang, T.; Carstens, J.L.; Zheng, X.; Wu, C.C.; Simpson, T.R.; Laklai, H.; Sugimoto, H.; Kahlert, C.; Novitskiy, S.V.; et al. Depletion of carcinoma-associated fibroblasts and fibrosis induces immunosuppression and accelerates pancreas cancer with reduced survival. *Cancer Cell* **2014**, *25*, 719–734. [CrossRef]
248. Abramovitch, S.; Dahan-Bachar, L.; Sharvit, E.; Weisman, Y.; Ben Tov, A.; Brazowski, E.; Reif, S. vitamin D inhibits proliferation and profibrotic marker expression in hepatic stellate cells and decreases thioacetamide-induced liver fibrosis in rats. *Gut* **2011**, *60*, 1728–1737. [CrossRef] [PubMed]
249. Sherman, M.H.; Yu, R.T.; Engle, D.D.; Ding, N.; Atkins, A.R.; Tiriac, H.; Collisson, E.A.; Connor, F.; Van Dyke, T.; Kozlov, S.; et al. vitamin D receptor-mediated stromal reprogramming suppresses pancreatitis and enhances pancreatic cancer therapy. *Cell* **2014**, *159*, 80–93. [CrossRef] [PubMed]
250. Ding, N.; Yu, R.T.; Subramaniam, N.; Sherman, M.H.; Wilson, C.; Rao, R.; Leblanc, M.; Coulter, S.; He, M.; Scott, C.; et al. A vitamin D receptor/SMAD genomic circuit gates hepatic fibrotic response. *Cell* **2013**, *153*, 601–613. [CrossRef] [PubMed]
251. Durán, A.; Hernández, E.D.; Reina-Campos, M.; Castilla, E.A.; Subramaniam, S.; Raghunandan, S.; Roberts, L.R.; Kisseleva, T.; Karin, M.; Diaz-Meco, M.T.; et al. p62/SQSTM1 by Binding to vitamin D Receptor Inhibits Hepatic Stellate Cell Activity, Fibrosis, and Liver Cancer. *Cancer Cell* **2016**, *30*, 595–609. [CrossRef] [PubMed]
252. Tao, Q.; Wang, B.; Zheng, Y.; Jiang, X.; Pan, Z.; Ren, J. vitamin D prevents the intestinal fibrosis via induction of vitamin D receptor and inhibition of transforming growth factor-beta1/Smad3 pathway. *Dig. Dis. Sci.* **2015**, *60*, 868–875. [CrossRef] [PubMed]
253. Campos, L.T.; Brentani, H.; Roela, R.A.; Katayama, M.L.; Lima, L.; Rolim, C.F.; Milani, C.; Folgueira, M.A.; Brentani, M.M. Differences in transcriptional effects of 1alpha,25 dihydroxyvitamin D3 on fibroblasts associated to breast carcinomas and from paired normal breast tissues. *J. Steroid Biochem. Mol. Biol.* **2013**, *133*, 12–24. [CrossRef]
254. Ferrer-Mayorga, G.; Gómez-López, G.; Barbáchano, A.; Fernández-Barral, A.; Peña, C.; Pisano, D.G.; Cantero, R.; Rojo, F.; Muñoz, A.; Larriba, M.J. vitamin D receptor expression and associated gene signature in tumour stromal fibroblasts predict clinical outcome in colorectal cancer. *Gut* **2017**, *66*, 1449–1462. [CrossRef] [PubMed]
255. Niell, N.; Larriba, M.J.; Ferrer-Mayorga, G.; Sánchez-Pérez, I.; Cantero, R.; Real, F.X.; Del Peso, L.; Muñoz, A.; González-Sancho, J.M. The human PKP2/plakophilin-2 gene is induced by Wnt/beta-catenin in normal and colon cancer-associated fibroblasts. *Int. J. Cancer* **2018**, *142*, 792–804. [CrossRef] [PubMed]
256. Ferrer-Mayorga, G.; Niell, N.; Cantero, R.; González-Sancho, J.M.; Del Peso, L.; Muñoz, A.; Larriba, M.J. vitamin D and Wnt3A have additive and partially overlapping modulatory effects on gene expression and phenotype in human colon fibroblasts. *Sci. Rep.* **2019**, *9*, 8085. [CrossRef] [PubMed]
257. Kong, F.; Li, L.; Wang, G.; Deng, X.; Li, Z.; Kong, X. VDR signaling inhibits cancer-associated-fibroblasts' release of exosomal miR-10a-5p and limits their supportive effects on pancreatic cancer cells. *Gut* **2019**, *68*, 950–951. [CrossRef] [PubMed]
258. Gorchs, L.; Ahmed, S.; Mayer, C.; Knauf, A.; Fernandez Moro, C.; Svensson, M.; Heuchel, R.; Rangelova, E.; Bergman, P.; Kaipe, H. The vitamin D analogue calcipotriol promotes an anti-tumorigenic phenotype of human pancreatic CAFs but reduces T cell mediated immunity. *Sci. Rep.* **2020**, *10*, 17444. [CrossRef]
259. Fujii, M.; Sato, T. Somatic cell-derived organoids as prototypes of human epithelial tissues and diseases. *Nat. Mater.* **2021**, *20*, 156–169. [CrossRef]
260. Schutgens, F.; Clevers, H. Human Organoids: Tools for Understanding Biology and Treating Diseases. *Annu. Rev. Pathol.* **2020**, *15*, 211–234. [CrossRef]
261. Barbachano, A.; Fernández-Barral, A.; Bustamante-Madrid, P.; Prieto, I.; Rodriguez-Salas, N.; Larriba, M.J.; Muñoz, A. Organoids and Colorectal Cancer. *Cancers* **2021**, *13*, 2657. [CrossRef]
262. Fernández-Barral, A.; Costales-Carrera, A.; Buira, S.P.; Jung, P.; Ferrer-Mayorga, G.; Larriba, M.J.; Bustamante-Madrid, P.; Dominguez, O.; Real, F.X.; Guerra-Pastrián, L.; et al. vitamin D differentially regulates colon stem cells in patient-derived normal and tumor organoids. *FEBS J.* **2020**, *287*, 53–72. [CrossRef]
263. Costales-Carrera, A.; Fernández-Barral, A.; Bustamante-Madrid, P.; Dominguez, O.; Guerra-Pastrián, L.; Cantero, R.; Del Peso, L.; Burgos, A.; Barbáchano, A.; Muñoz, A. Comparative Study of Organoids from Patient-Derived Normal and Tumor Colon and Rectal Tissue. *Cancers* **2020**, *12*, 2302. [CrossRef]

264. Vaughan-Shaw, P.G.; Blackmur, J.P.; Grimes, G.; Ooi, L.Y.; Ochocka-Fox, A.M.; Dunbar, K.; von Kriegsheim, A.; Rajasekaran, V.; Timofeeva, M.; Walker, M.; et al. vitamin D treatment induces in vitro and ex vivo transcriptomic changes indicating anti-tumor effects. *FASEB J.* **2022**, *36*, e22082. [CrossRef] [PubMed]
265. Shang, J.; Zhu, Z.; Chen, Y.; Song, J.; Huang, Y.; Song, K.; Zhong, J.; Xu, X.; Wei, J.; Wang, C.; et al. Small-molecule activating SIRT6 elicits therapeutic effects and synergistically promotes anti-tumor activity of vitamin D3 in colorectal cancer. *Theranostics* **2020**, *10*, 5845–5864. [CrossRef] [PubMed]
266. McCray, T.; Pacheco, J.V.; Loitz, C.C.; Garcia, J.; Baumann, B.; Schlicht, M.J.; Valyi-Nagy, K.; Abern, M.R.; Nonn, L. vitamin D sufficiency enhances differentiation of patient-derived prostate epithelial organoids. *iScience* **2021**, *24*, 101974. [CrossRef] [PubMed]
267. Shan, N.L.; Minden, A.; Furmanski, P.; Bak, M.J.; Cai, L.; Wernyj, R.; Sargsyan, D.; Cheng, D.; Wu, R.; Kuo, H.D.; et al. Analysis of the Transcriptome: Regulation of Cancer Stemness in Breast Ductal Carcinoma In Situ by vitamin D Compounds. *Cancer Prev. Res.* **2020**, *13*, 673–686. [CrossRef] [PubMed]
268. So, J.Y.; Wahler, J.; Das Gupta, S.; Salerno, D.M.; Maehr, H.; Uskokovic, M.; Suh, N. HES1-mediated inhibition of Notch1 signaling by a Gemini vitamin D analog leads to decreased CD44(+)/CD24(-/low) tumor-initiating subpopulation in basal-like breast cancer. *J. Steroid Biochem. Mol. Biol.* **2015**, *148*, 111–121. [CrossRef]
269. Wahler, J.; So, J.Y.; Cheng, L.C.; Maehr, H.; Uskokovic, M.; Suh, N. vitamin D compounds reduce mammosphere formation and decrease expression of putative stem cell markers in breast cancer. *J. Steroid Biochem. Mol. Biol.* **2015**, *148*, 148–155. [CrossRef]
270. Ferronato, M.J.; Nadal Serrano, M.; Arenas Lahuerta, E.J.; Bernado Morales, C.; Paolillo, G.; Martinez-Sabadell Aliguer, A.; Santalla, H.; Mascaro, M.; Vitale, C.; Fall, Y.; et al. vitamin D analogues exhibit antineoplastic activity in breast cancer patient-derived xenograft cells. *J. Steroid Biochem. Mol. Biol.* **2021**, *208*, 105735. [CrossRef] [PubMed]
271. Ao, T.; Kikuta, J.; Ishii, M. The Effects of vitamin D on Immune System and Inflammatory Diseases. *Biomolecules* **2021**, *11*, 1624. [CrossRef] [PubMed]
272. Hanel, A.; Neme, A.; Malinen, M.; Hamalainen, E.; Malmberg, H.R.; Etheve, S.; Tuomainen, T.P.; Virtanen, J.K.; Bendik, I.; Carlberg, C. Common and personal target genes of the micronutrient vitamin D in primary immune cells from human peripheral blood. *Sci. Rep.* **2020**, *10*, 21051. [CrossRef]
273. Chun, R.F.; Liu, P.T.; Modlin, R.L.; Adams, J.S.; Hewison, M. Impact of vitamin D on immune function: Lessons learned from genome-wide analysis. *Front. Physiol.* **2014**, *5*, 151. [CrossRef] [PubMed]
274. Catala-Moll, F.; Ferrete-Bonastre, A.G.; Godoy-Tena, G.; Morante-Palacios, O.; Ciudad, L.; Barbera, L.; Fondelli, F.; Martínez-Cáceres, E.M.; Rodriguez-Ubreva, J.; Li, T.; et al. vitamin D receptor, STAT3, and TET2 cooperate to establish tolerogenesis. *Cell Rep.* **2022**, *38*, 110244. [CrossRef] [PubMed]
275. Korf, H.; Wenes, M.; Stijlemans, B.; Takiishi, T.; Robert, S.; Miani, M.; Eizirik, D.L.; Gysemans, C.; Mathieu, C. 1,25-Dihydroxyvitamin D3 curtails the inflammatory and T cell stimulatory capacity of macrophages through an IL-10-dependent mechanism. *Immunobiology* **2012**, *217*, 1292–1300. [CrossRef]
276. Zhang, X.; Zhou, M.; Guo, Y.; Song, Z.; Liu, B. 1,25-Dihydroxyvitamin D(3) Promotes High Glucose-Induced M1 Macrophage Switching to M2 via the VDR-PPARgamma Signaling Pathway. *BioMed Res. Int.* **2015**, *2015*, 157834. [CrossRef]
277. Von Essen, M.R.; Kongsbak, M.; Schjerling, P.; Olgaard, K.; Odum, N.; Geisler, C. vitamin D controls T cell antigen receptor signaling and activation of human T cells. *Nat. Immunol.* **2010**, *11*, 344–349. [CrossRef] [PubMed]
278. El-Sharkawy, A.; Malki, A. vitamin D Signaling in Inflammation and Cancer: Molecular Mechanisms and Therapeutic Implications. *Molecules* **2020**, *25*, 3219. [CrossRef]
279. Dankers, W.; Colin, E.M.; van Hamburg, J.P.; Lubberts, E. vitamin D in Autoimmunity: Molecular Mechanisms and Therapeutic Potential. *Front. Immunol.* **2016**, *7*, 697. [CrossRef] [PubMed]
280. Karkeni, E.; Morin, S.O.; Bou Tayeh, B.; Goubard, A.; Josselin, E.; Castellano, R.; Fauriat, C.; Guittard, G.; Olive, D.; Nunes, J.A. vitamin D Controls Tumor Growth and CD8+ T Cell Infiltration in Breast Cancer. *Front. Immunol.* **2019**, *10*, 1307. [CrossRef] [PubMed]
281. Fleet, J.C.; Burcham, G.N.; Calvert, R.D.; Elzey, B.D.; Ratliff, T.L. 1alpha, 25 Dihydroxyvitamin D (1,25(OH)2D) inhibits the T cell suppressive function of myeloid derived suppressor cells (MDSC). *J. Steroid Biochem. Mol. Biol.* **2020**, *198*, 105557. [CrossRef] [PubMed]
282. Sun, D.; Luo, F.; Xing, J.C.; Zhang, F.; Xu, J.Z.; Zhang, Z.H. 1,25(OH)2 D3 inhibited Th17 cells differentiation via regulating the NF-kappaB activity and expression of IL-17. *Cell Prolif.* **2018**, *51*, e12461. [CrossRef] [PubMed]
283. Cohen-Lahav, M.; Shany, S.; Tobvin, D.; Chaimovitz, C.; Douvdevani, A. vitamin D decreases NFkappaB activity by increasing IkappaBalpha levels. *Nephrol. Dial. Transpl.* **2006**, *21*, 889–897. [CrossRef]
284. Tse, A.K.; Zhu, G.Y.; Wan, C.K.; Shen, X.L.; Yu, Z.L.; Fong, W.F. 1alpha,25-Dihydroxyvitamin D3 inhibits transcriptional potential of nuclear factor kappa B in breast cancer cells. *Mol. Immunol.* **2010**, *47*, 1728–1738. [CrossRef] [PubMed]
285. Krishnan, A.V.; Feldman, D. Mechanisms of the anti-cancer and anti-inflammatory actions of vitamin D. *Annu. Rev. Pharmacol. Toxicol.* **2011**, *51*, 311–336. [CrossRef]
286. Moreno, J.; Krishnan, A.V.; Swami, S.; Nonn, L.; Peehl, D.M.; Feldman, D. Regulation of prostaglandin metabolism by calcitriol attenuates growth stimulation in prostate cancer cells. *Cancer Res.* **2005**, *65*, 7917–7925. [CrossRef] [PubMed]

287. Gibbs, D.C.; Fedirko, V.; Baron, J.A.; Barry, E.L.; Flanders, W.D.; McCullough, M.L.; Yacoub, R.; Raavi, T.; Rutherford, R.E.; Seabrook, M.E.; et al. Inflammation Modulation by vitamin D and Calcium in the Morphologically Normal Colorectal Mucosa of Patients with Colorectal Adenoma in a Clinical Trial. *Cancer Prev. Res.* **2021**, *14*, 65–76. [CrossRef]
288. Bruns, H.; Buttner, M.; Fabri, M.; Mougiakakos, D.; Bittenbring, J.T.; Hoffmann, M.H.; Beier, F.; Pasemann, S.; Jitschin, R.; Hofmann, A.D.; et al. vitamin D-dependent induction of cathelicidin in human macrophages results in cytotoxicity against high-grade B cell lymphoma. *Sci. Transl. Med.* **2015**, *7*, 282ra247. [CrossRef] [PubMed]
289. Min, D.; Lv, X.B.; Wang, X.; Zhang, B.; Meng, W.; Yu, F.; Hu, H. Downregulation of miR-302c and miR-520c by 1,25(OH)2D3 treatment enhances the susceptibility of tumour cells to natural killer cell-mediated cytotoxicity. *Br. J. Cancer* **2013**, *109*, 723–730. [CrossRef]
290. Neumann, F.; Acker, F.; Schormann, C.; Pfreundschuh, M.; Bittenbring, J.T. Determination of optimum vitamin D3 levels for NK cell-mediated rituximab- and obinutuzumab-dependent cellular cytotoxicity. *Cancer Immunol. Immunother.* **2018**, *67*, 1709–1718. [CrossRef] [PubMed]
291. Bittenbring, J.T.; Neumann, F.; Altmann, B.; Achenbach, M.; Reichrath, J.; Ziepert, M.; Geisel, J.; Regitz, E.; Held, G.; Pfreundschuh, M. vitamin D deficiency impairs rituximab-mediated cellular cytotoxicity and outcome of patients with diffuse large B-cell lymphoma treated with but not without rituximab. *J. Clin. Oncol.* **2014**, *32*, 3242–3248. [CrossRef] [PubMed]
292. Mortara, L.; Gariboldi, M.B.; Bosi, A.; Bregni, M.; Pinotti, G.; Guasti, L.; Squizzato, A.; Noonan, D.M.; Monti, E.; Campiotti, L. vitamin D Deficiency has a Negative Impact on Cetuximab-Mediated Cellular Cytotoxicity against Human Colon Carcinoma Cells. *Target. Oncol.* **2018**, *13*, 657–665. [CrossRef] [PubMed]
293. Lipplaa, A.; Fernandes, R.; Marshall, A.; Lorigan, P.; Dunn, J.; Myers, K.A.; Barker, E.; Newton-Bishop, J.; Middleton, M.R.; Corrie, P.G. 25-hydroxyvitamin D serum levels in patients with high risk resected melanoma treated in an adjuvant bevacizumab trial. *Br. J. Cancer* **2018**, *119*, 793–800. [CrossRef] [PubMed]
294. Dimitrov, V.; Bouttier, M.; Boukhaled, G.; Salehi-Tabar, R.; Avramescu, R.G.; Memari, B.; Hasaj, B.; Lukacs, G.L.; Krawczyk, C.M.; White, J.H. Hormonal vitamin D up-regulates tissue-specific PD-L1 and PD-L2 surface glycoprotein expression in humans but not mice. *J. Biol. Chem.* **2017**, *292*, 20657–20668. [CrossRef] [PubMed]
295. Bendix, M.; Greisen, S.; Dige, A.; Hvas, C.L.; Bak, N.; Jorgensen, S.P.; Dahlerup, J.F.; Deleuran, B.; Agnholt, J. vitamin D increases programmed death receptor-1 expression in Crohn's disease. *Oncotarget* **2017**, *8*, 24177–24186. [CrossRef]
296. Stucci, L.S.; D'Oronzo, S.; Tucci, M.; Macerollo, A.; Ribero, S.; Spagnolo, F.; Marra, E.; Picasso, V.; Orgiano, L.; Marconcini, R.; et al. vitamin D in melanoma: Controversies and potential role in combination with immune check-point inhibitors. *Cancer Treat. Rev.* **2018**, *69*, 21–28. [CrossRef] [PubMed]
297. Kutuzova, G.D.; DeLuca, H.F. 1,25-Dihydroxyvitamin D3 regulates genes responsible for detoxification in intestine. *Toxicol. Appl. Pharmacol.* **2007**, *218*, 37–44. [CrossRef]
298. Lindh, J.D.; Bjorkhem-Bergman, L.; Eliasson, E. Vitamin D and drug-metabolising enzymes. *Photochem. Photobiol. Sci.* **2012**, *11*, 1797–1801. [CrossRef] [PubMed]
299. Chatterjee, B.; Echchgadda, I.; Song, C.S. Vitamin D receptor regulation of the steroid/bile acid sulfotransferase SULT2A1. *Methods Enzymol.* **2005**, *400*, 165–191. [CrossRef] [PubMed]
300. Wang, Z.; Schuetz, E.G.; Xu, Y.; Thummel, K.E. Interplay between Vitamin D and the drug metabolizing enzyme CYP3A4. *J. Steroid Biochem. Mol. Biol.* **2013**, *136*, 54–58. [CrossRef] [PubMed]
301. Ajouz, H.; Mukherji, D.; Shamseddine, A. Secondary bile acids: An underrecognized cause of colon cancer. *World J. Surg. Oncol.* **2014**, *12*, 164. [CrossRef]
302. Peterlik, M. Role of bile acid secretion in human colorectal cancer. *Wien. Med. Wochenschr.* **2008**, *158*, 539–541. [CrossRef] [PubMed]
303. Makishima, M.; Lu, T.T.; Xie, W.; Whitfield, G.K.; Domoto, H.; Evans, R.M.; Haussler, M.R.; Mangelsdorf, D.J. vitamin D receptor as an intestinal bile acid sensor. *Science* **2002**, *296*, 1313–1316. [CrossRef]
304. Matsunawa, M.; Akagi, D.; Uno, S.; Endo-Umeda, K.; Yamada, S.; Ikeda, K.; Makishima, M. vitamin D receptor activation enhances benzo[a]pyrene metabolism via CYP1A1 expression in macrophages. *Drug Metab. Dispos.* **2012**, *40*, 2059–2066. [CrossRef] [PubMed]
305. Chen, G.Y. The Role of the Gut Microbiome in Colorectal Cancer. *Clin. Colon Rectal Surg.* **2018**, *31*, 192–198. [CrossRef] [PubMed]
306. Zhou, X.; Chen, C.; Zhong, Y.N.; Zhao, F.; Hao, Z.; Xu, Y.; Lai, R.; Shen, G.; Yin, X. Effect and mechanism of vitamin D on the development of colorectal cancer based on intestinal flora disorder. *J. Gastroenterol. Hepatol.* **2020**, *35*, 1023–1031. [CrossRef] [PubMed]
307. Malaguarnera, L. vitamin D and microbiota: Two sides of the same coin in the immunomodulatory aspects. *Int. Immunopharmacol.* **2020**, *79*, 106112. [CrossRef]
308. Wang, J.; Thingholm, L.B.; Skieceviciene, J.; Rausch, P.; Kummen, M.; Hov, J.R.; Degenhardt, F.; Heinsen, F.A.; Ruhlemann, M.C.; Szymczak, S.; et al. Genome-wide association analysis identifies variation in vitamin D receptor and other host factors influencing the gut microbiota. *Nat. Genet.* **2016**, *48*, 1396–1406. [CrossRef]
309. Lu, R.; Shang, M.; Zhang, Y.G.; Jiao, Y.; Xia, Y.; Garrett, S.; Bakke, D.; Bauerl, C.; Martinez, G.P.; Kim, C.H.; et al. Lactic Acid Bacteria Isolated From Korean Kimchi Activate the vitamin D Receptor-autophagy Signaling Pathways. *Inflamm. Bowel Dis.* **2020**, *26*, 1199–1211. [CrossRef]

310. Zhang, Y.G.; Lu, R.; Wu, S.; Chatterjee, I.; Zhou, D.; Xia, Y.; Sun, J. vitamin D Receptor Protects Against Dysbiosis and Tumorigenesis via the JAK/STAT Pathway in Intestine. *Cell. Mol. Gastroenterol. Hepatol.* **2020**, *10*, 729–746. [CrossRef] [PubMed]
311. Madden, J.M.; Murphy, L.; Zgaga, L.; Bennett, K. De novo vitamin D supplement use post-diagnosis is associated with breast cancer survival. *Breast Cancer Res. Treat.* **2018**, *172*, 179–190. [CrossRef]
312. Carlberg, C.; Haq, A. The concept of the personal vitamin D response index. *J. Steroid Biochem. Mol. Biol.* **2018**, *175*, 12–17. [CrossRef]
313. Dimitrov, V.; Barbier, C.; Ismailova, A.; Wang, Y.; Dmowski, K.; Salehi-Tabar, R.; Memari, B.; Groulx-Boivin, E.; White, J.H. vitamin D-regulated Gene Expression Profiles: Species-specificity and Cell-specific Effects on Metabolism and Immunity. *Endocrinology* **2021**, *162*, bqaa218. [CrossRef]