Vitamins and Cancer

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There is a large body of evidence suggesting a strong correlation between vitamin intake as well as vitamin blood concentrations with the occurrence of certain types of cancer. The direction of association between the concentration of a given vitamin and cancer risk is tumor specific.

Vitamin cancer Biomarkers

1. Vitamin A

The link between vitamin A and oncogenesis is complex. Animal models have demonstrated the anticancer activity of vitamin A [1][2], a feature backed up by epidemiological studies indicating how vitamin A deficiency was associated with a higher risk of cancer [3]. Thus, vitamin A has been the subject of extensive research in chemoprevention. Apart from the effects on immune cells, it has been shown that this micronutrient is involved in the structure of the cellular membrane, in the process of protein glycosylation, and in the regulation of the cell-to-cell adhesion [3]. Vitamin A also stimulates RNA transcription and DNA replication [4][5], and it has been suggested that retinoic acid binds to a complex containing the transcription factor p300 and the histone acetyltransferase p300/CBP-associated factor (pCAF) [6]. Unsurprisingly, then, the dysfunction of vitamin A is associated with the dysregulation of cellular differentiation [3].

A study of 966 prostate cancer cases and 1064 healthy controls did not show any significant differences in the blood concentrations of carotenes and retinol between these groups [7]. A case-control study with 142 prostate cancer patients and 142 controls reported an OR of 0.8 (0.4–1.5) related to blood concentrations of β-carotene, but without statistical significance (test for trends p-value = 0.33) [8]. However, the blood concentrations of vitamin A were reported to be in median 59.4 µg/dL in 84 prostate cancer cases compared to matched healthy controls (65.1 µg/dL), determining a relative risk (RR) of 2.4 for the ratio lower over the upper quartile of blood vitamin A in cancer cases [9]. A survey of 278 lung cancer cases and 483 matched healthy controls reported a significantly lower concentration of α-carotene in the former group (t-test p-value = 0.03) [10]. A longitudinal study reported that the blood concentration of β-carotene was 7.2 µg/dL in the cases of any cancer compared to 8.4 µg/dL in the controls (t-test p-value < 0.001) [11].

For retinol, a case-control study reported that the OR between the lower and upper quartiles was 0.4 for the development of prostate cancer, albeit with a slightly nonsignificant association (test for trends p-value = 0.07) [12]. Similarly, a study on 975 prostate cancer cases showed an OR of 1.30 (1.00–1.68) for the development of cancer and 1.74 (1.14–2.68) for the development of aggressive cancer when compared to people in the upper and lower quartiles of blood retinol concentrations [13]. The blood concentrations of retinol in 692 cases of prostate cancer and 844 matched controls did not show an increased risk of developing cancer (OR = 0.80, 95% CI: 0.57–1.11; test for trends p-value = 0.11) but higher concentrations of retinol were linked to a reduced risk of developing aggressive cancer (OR = 0.52, 95% CI: 0.32–0.84; test for trends p-value = 0.01) [14].

A comparison of prostate cancer cases (n = 1433) and controls (n = 1433) did not show any relation between blood concentrations of retinol and cancer [15]. A longitudinal study reported that the blood concentration of retinol at baseline was 64.5 µg/dL in 453 males who developed any type of cancer over eight years than the 66.7 µg/dL of 1419 matched healthy controls (t-test p-value < 0.01) [11]. Another longitudinal study reported the opposite trend, where higher retinol concentrations at baseline were observed in subjects who developed prostate cancer within three years than in healthy controls (HR = 1.19, 95% CI: 1.03–1.36, test for trends p-value = 0.009) [16].

2. Vitamin B Complex

The B vitamins represent a complex of water-soluble vitamins—thiamine (B_1), riboflavin (B_2), niacin (B_3), pantothenic acid (B_5), pyridoxine and pyridoxal (B_6), biotin (B_7), folic acid (B_9), and cobalamins (B_{12})—that are present in a wide variety of animal and plant foods [17]. Specific receptors under the control of heterogeneous nuclear ribonucleoprotein E1 (hnRNP-E1) mediate cellular folate intake [18]. Tetrahydrofolate (THF) is the bioactive derivative of folic acid, which can transfer C1 units (methyl, methylene, formyl, formimino, and methenyl groups) with different oxidation states. First, dihydrofolate reductase (DHFR) catalyzes the two-fold reduction of folate via dihydrofolate (DHF) to THF. For example, thymidylate synthase (TS) is a highly conserved enzyme that transfers a methyl group from THF to deoxyuridine monophosphate (dUMP) to produce methylated deoxy-thymidine monophosphate (dTMP) and DHF [19]. Folate deficiency can affect the stability of the DNA by shifting the biochemical reactions carried out by TS toward an excess of dUMP, resulting in its incorporation into strands of DNA under replication or repair reactions [20]. Since uridine is more susceptible to chemical insult than thymidine, the affected DNA chains are prone to single and double-strand breaks, increasing the risk of mutagenesis and oncogenesis [21].

The increased DNA damage induced by folate depletion is applied in cancer therapy. Antifolate drugs are administered purposely to induce DNA insult in the fast-replicating cancer cells [22], highlighting the importance of this micronutrient for the chromosomal stability of the cells. On the other hand, the depletion of methylcytosine (C^{me}) triggered by the depletion of vitamin B_9 induces a global DNA demethylation that can foster oncogenesis [23]. It has been estimated that about 70% of human oncogenes are repressed by the presence of CG islands (CGI), a region of a high density of the duplex $C^{me}G$ [24]. Transposons are also highly methylated [25]. Therefore, a general demethylation status can promote the expression of both oncogenes and endogenous retroviruses, fostering genetic recombination and chromosomal instability. Instead, pantothenate (vitamin B_5) is a constituent of coenzyme A, which is necessary for the synthesis and oxidation of fatty acids and the oxidation of pyruvate in the Krebs cycle [26].

Folate can also affect the cell environment indirectly by altering the infective process and, consequently, modulating the risk of cancer. For instance, cervical carcinoma is one of the most common causes of death and morbidity, ranking fourth among the causes of cancer-related deaths in industrialized countries and second in developing countries, respectively [27]. HPV is recovered in 99.7% of the carcinoma lesions, a feature that demonstrates the unique importance of this virus in the genesis of cervical carcinoma [28][29]. Folate deficiency reduces the translation of HPV's minor capsid protein L2 through the action of hnRNP-E1 [30][31]. Consequently, the encapsidation phase of the HPV infection cycle cannot be completed, resulting in an accumulation of free viral genomes that increases the risk of viral integration and virus-driven oncogenesis [32].

A recent meta-analysis reported that high folate reduced the risk of lung cancer: the odds ratios of cases over healthy controls was 0.82 (0.74–0.90) in men, 0.70 (0.62–0.79) in former smokers, and 0.86 (0.75–1.00) in nonsmokers [33]. Low blood folate concentrations increased the cervical cancer risk (OR = 9.0) [34], while blood folate was lower in women with high-grade cervical lesions (14.3 nmol/L) than in women with low-grade lesions (15.9 nmol/L) and in healthy controls (18.2 nmol/L, 10.3–26.1); thus, folate concentrations below 14.1 nmol/L corresponded to an OR of 2.3 for developing low-grade lesions and 5.3 for the high-grade lesions [35]. Others have shown an OR of 2.7 for developing high-grade cervical lesions [36] and 1.68 for cervical cancer development in the presence of plasma folate below 3.19 ng/mL [37].

However, low folate concentrations were also associated with better prognostic value in B-cell lymphoma [38]. A comparison of 322 patients indicated that people in the lower tertile of blood folate concentration had lower overall survival than people in the upper tertile (HR = 0.181, 95% CI: 0.075–0.437; *t*-test *p*-value < 0.001). Vitamin B_2, followed a similar trend: HR = 0.258 (0.117–0.569), *p*-value < 0.001. High folate concentrations, combined with methylation of the HPV-16 early promoter, were associated with reduced risk of developing cervical lesions. Folate concentrations above 14.3 ng/mL combined with viral methylation above 11% resulted in an OR of 0.3 for the development of high-grade cervical lesions [39].

High vitamin B_{12} concentrations were associated with a higher risk of myeloid leukemia (*n* = 308, OR = 19.2, 95% CI: 13.1–28.0; *t*-test *p*-value < 0.0001) and malignant lymphoid tumors (*n* = 1658, OR = 6.0, 95% CI: 4.7–7.6; *t*-test *p*-value < 0.0001) when compared to healthy controls (*n* = 136 and *n* = 970, respectively) [40]. Conversely, high vitamin B_{12} blood concentrations, combined with methylation of the HPV-16 early promoter, were associated with a reduced risk of developing cervical lesions. B_{12} concentrations above 406.6 pg/mL combined with viral methylation above 11% resulted in an OR of 0.4 for the development of high-grade cervical lesions [39].

Measurement of vitamin B_6 in a cohort of 549 volunteers indicated that people with concentrations above 52.4 nmol/L were at lower risk of pancreatic cancer than people with concentrations below 20 nmol/L (OR = 0.46, 95% CI: 0.23–0.92; test for trends *p*-value = 0.048) [41].

3. Vitamin C

Cancer tissues accumulate higher amounts of vitamin C than normal cells, a feature that is exploited as an anticancer treatment [42]. The mechanism by which vitamin C damages cancer cells is two-fold [43][44]: first, cancer cells have a reduced capacity to remove H_2O_2 and ROS; second, high concentrations of vitamin C boosts the production of ROS that, in turn, increases the redox activity of iron. Nevertheless, our group has demonstrated that the anticancer activity of vitamin C is dependent on the oxygen concentration, thus strengthening its link with the oxygen biochemistry [45]. We also demonstrated that the cytotoxicity of vitamin C requires high doses of this micronutrient (corresponding to the intravenous administration of grams of this vitamin) [46]. In addition, high physiological doses (200 µM), and especially pharmacological doses (8 mM), of vitamin C could profoundly alter the expression profile of interfering RNAs, an outcome whose impact on the affected cells is yet to be fully established [46][47].

The simultaneous administration of vitamin C and K_3 induces cell death in a peculiar fashion that is distinguished from both necrosis and apoptosis [48]. Such an atypical cell death has been first described in the 1990s and has been named autoschizis [49][50]. The main features of autoschizis are the expulsion of the cytoplasm through organelles-free vesicles (unlike apoptosis) and the concentration of damaged organelles around the nucleus [48]. At the molecular level, there is no activation of caspases, as occurs during apoptosis, and the DNA fragmentation produces neither internucleosomal fragments (180–220 bp in length), as in apoptosis, nor a smear, as in necrosis, but rather random pieces cut by the DNAse II [51]. Unlike in apoptosis, autoschizis induces local inflammation and is believed to be an aberrant form of apoptosis [48].

It has been proposed that vitamin C, in the form of ascorbate, might have a protective value at low concentrations but enhance oxidative stress at high concentrations [52]. In the mitochondria, AFR accepts an electron from the reduced form of nicotinamide adenine dinucleotide (NADH) through the action of NADH-cytochrome b5 oxidoreductase 3 (Cyb5R3), becoming ascorbate. AFR is part of the normal aerobic respiration process at low doses but in cancerous cells there is the concomitant increased expression of vitamin C transporters and oxidative processes. The result is the accumulation of AFR with the consequent unbalance of the mitochondrial activity and production of reactive oxygen species (ROS). Apart from causing damage to the DNA and biological membranes, the ROS boosts the biosynthesis of 8-oxo-deoxy-guanosine (oxo-dG) [53], which recruits ten-eleven translocation (TET) proteins that induce demethylation by base excision repair [54][55]. It has been shown that the resulting demethylation inhibits cancer proliferation and boosts apoptosis [56]. Since vitamin C can be involved in the generation of the ROS via H_2O_2 production and its simultaneous reaction with Fe^{2+} during the Fenton reaction, while also counteracting the ROS, this vitamin can generate a dynamic equilibrium in the oxidative status of the cell.

Vitamin C up-regulates the tumor suppressors p53 and p21 so that the expression of these proteins balance demethylation [57]. Vitamin C is also linked to histone demethylation [46][58] and the targeting of the hypoxia inducible factor (HIF) proteins used by cancer to thrive in the oxygen-depleted environment of tumor masses for proteasomal degradation via proline and asparaginyl hydroxylases (HIF hydroxylases, HIFH), which belong to the family of iron-containing dioxygenases [59]. In the gastric tract, vitamin C prevents the development of N-nitroso compounds [60]. Vitamin C is also paramount in the biosynthesis of collagen, whose acute depletion leads to scurvy [61].

The quantification of vitamin C intake in African Americans (*n* = 17) and Native Americans (*n* = 18) indicated a significantly (*t*-test *p*-value < 0.005) higher value in the former group (198 mg daily) than in the latter (48 mg daily) [62]. Other markers were significantly higher in African Americans than in Native Americans (total fat, cholesterol, folate, iron, vitamin A, and zinc). Since African Americans have a 60 times higher risk of colorectal cancer than Native Americans, these micronutrient discrepancies strengthened the epidemiological link between diet and the risk of cancer. However, the overlap between different micronutrients impaired the assessment of specific vitamins or minerals to the oncogenesis.

The blood vitamin C was significantly lower (*t*-test *p*-value < 0.05) in prostate cancer patients (*n* = 32, mean concentratio*n* = 4 µg/mL) than in healthy controls (*n* = 40, mean concentratio*n* = 13 µg/mL) [63]. The quantification of blood vitamin C concentration in gastric cancer patients (*n* = 16, mean value 3.8 µg/mL) and healthy controls (*n* = 12, mean value 7.1 µg/mL) also showed a significant decrease (*t*-test *p*-value = 0.01) [64]. Vitamin C concentration also reflected such a decrease in gastric juice (3.2 µg/mL in gastric cancer patients compared to 18.2 µg/mL in healthy controls, *t*-test *p*-value = 0.001). Since the patients were concomitantly infected with *Helicobacter pylori*, it was proposed that the vitamin C depletion was due to this bacterium. *H. pylori* toxin can disrupt the transport of vitamin C in the gastric lumen [65], and the resolution of the infection is followed by the recovery of vitamin levels [66].

4. Vitamin D

Vitamin D is a group of sterol derivatives which have hormone-like functions. In humans, the most important members of this group are vitamin D_2 (ergocalciferol), which is nonenzymatically formed in the skin by ultraviolet irradiation of 7-dehydrocholesterol, and vitamin D_3 (cholecalciferol), which is also formed by ultraviolet irradiation of the plant sterol ergosterol [67]. The hormonally active forms result from dual hydroxylation in the liver and the kidney to form 1,25-dihydrocholecalciferol (calcitriol) and 1.25-dihydroxyergocalciferol (ergocalciferol), respectively. The final conversion to its active form can further occur in other loci such as the brain, the pancreas, in adipose tissue, the heart, the colon, and in immune cells (such as monocytes and macrophages) [68]. Vitamin D is required for proper bone formation via the pronounced generation of osteoclasts and increasing plasma Ca^{2+} concentrations but has also shown antitumoral and antimetastatic capabilities [69]. Conversely, a reduced vitamin D intake has been linked to a higher risk of developing cancer, particularly hepatocellular carcinomas [70]. Interestingly, it has been estimated that about nine-tenths of the tissue macrophages are present in the liver [71], suggesting that the macrophages might be heavily modulated by vitamin D. Moreover, vitamin D has been shown to reduce the expression of IL-6 in hepatocytes [72].

Vitamin D is carried in the bloodstream attached either to vitamin D binding proteins (VDBPs) or albumin. Then it is transported actively into the cells where it can reach the nucleus, acting as a transcription factor on promoters containing the vitamin D response element (VDRE) [73]. It has been estimated that the human genome contains

2776 VDREs spread across 229 genes [74], including important signal pathways components like signal transducer and activator of transcription (STAT) 1 and nuclear factor κ-B (NF-κB) kinase. As a result, vitamin D is involved in regulating the cell cycle [75], which explains its participation in oncogenesis. Experimental models in vitro and in vivo have suggested a possible anticancer activity for vitamin D, but the translation into clinical practice has given suboptimal results [76].

A case-cohort study of 547 colorectal, 634 breast, and 824 prostate cancer patients reported a significant decrease in colorectal cancer risk in people having high blood concentrations of vitamin D compared with those with the lowest concentrations (HR for the upper quintile over the lowest quintile was 0.71, 95% CI: 0.51–0.98) but not for breast cancer (HR = 0.98, 95% CI: 0.70–1.36) or prostate cancer (HR = 1.11, 95% CI: 0.82–1.48) [77]. A study of 95 healthy volunteers did not find any association between the blood concentrations of vitamin D and either prostate cancer antigen or total antioxidant concentrations [78]. Conversely, a comparison of 60 prostate cancer patients and 120 age-matched healthy controls showed a reduced risk of cancer in the presence of high concentrations of vitamin D (OR = 0.785, 95% CI: 0.718–0.858, *t*-test p-value < 0.05) [79]. A study of 1000 cases of prostate cancer and 1000 healthy controls reported an increased risk of cancer (OR = 1.56, 95% CI: 1.15–2.12, test for trends p-value = 0.01) in people with high blood vitamin D [80]. These results confirmed a previous survey of 234 cases and 234 healthy controls reporting that vitamin D not bound to DBP increased the risk of prostate cancer (OR = 5.01, 95% CI: 2.33–10.78, test for trends p-value < 0.0001) [81]. In pancreatic cancer, people with blood concentrations of vitamin D above 100 nmoL/L had an OR of 2.12 (1.23–3.64) compared to people with low concentrations [82]. Women in the upper tertile of vitamin D_3 blood concentration (≥98 nmoL/L) had a higher risk of breast cancer than those with a concentration in the lowest tertile (≤76 nmoL/L), with an OR of 0.97 (0.75–1.25) [83]. Conversely, a study of 195 postmenopausal breast cancer patients indicated that women with low concentrations of blood vitamin D (<30 ng/mL) had a higher rate of high-grade tumors and metastases than women with higher concentrations [84]. The study also reported that low vitamin D was associated with the overexpression of the proliferation marker Ki-67. Similarly, a study of 50 breast cancer patients highlighted how women with vitamin D blood concentrations below 20 ng/mL had a higher risk of developing larger tumors (*t*-test p-value < 0.001) and worse overall survival (p-value = 0.026) than women with higher vitamin concentrations [85].

A survey of 5313 lung cancer cases and 5313 matched healthy controls did not show any increased risk of cancer (OR = 0.98, 95% CI: 0.91–1.06) [86]. Vitamin D was instead shown to be protective against thyroid cancer: a survey of 506 cases reported OR = 0.63 (0.40–1.00) with a test for trends p-value = 0.046 when comparing patients in the upper quartile (cut points for season-specific quartile: darker months December–May, above 39.0 nmoL/L; sunnier months June–November, above 58.6 nmoL/L) of blood vitamin D concentration with those of the lowest quartile (cut points for season-specific quartile: December–May, less or equal to 23.9 nmoL/L; June–November, less or equal to 36.1 nmoL/L) [87]. The significance was even higher when comparing the vitamin D binding protein concentrations (OR = 0.49, 95% CI: 0.32–0.77, p-value = 0.001).

The concentration of vitamin D was not directly associated with an increased risk of renal cancer, but people with higher concentrations of 25-OH-D_3 not bound to the carrier protein DBP showed a slightly higher risk of cancer than people with lower concentrations of unbound vitamin 25-OH-D_3 (OR = 1.61, 95% CI: 0.95–2.73, test for trends *p*-value = 0.09) [88]. The role of free vitamin D was also observed in bladder cancer [89]. These results contrast to previous analysis showing that high vitamin D blood concentrations were not associated with pancreatic cancer (OR = 1.45, 95% CI: 0.66–3.15) [90].

Vitamin D showed not only diagnostic but prognostic value. For example, in a cohort of 1666 breast cancer patients, women with vitamin D blood concentrations in the lowest tertile (≤16.8 ng/mL) had lower overall survival (HR = 0.54, 95% CI: 0.40–0.72, test for trends *p*-value < 0.001) than women in the upper tertile (≥25.1 ng/mL) [91]. The studies described make it clear that it depends on the type of cancer whether too low or too high blood levels of vitamin D are problematic.

5. Vitamin E

Vitamin E is a set of related isoforms (α-, β-, γ-, and δ-tocopherols, and α-, β-, γ-, and δ-tocotrienol) with antioxidant activities and present in seeds and vegetable oils [92]. Vitamin E acts as a scavenger protecting biological membranes from ROS insults, but it is also involved in immune regulation by inhibiting the NF-kB and STAT3 signal pathways [93], cell proliferation via the phosphoinositide 3-kinase (PI3K) pathway [94], and apoptosis [95]. In addition, like vitamin C, vitamin E reduces the accumulation of N-nitroso compounds in the intestine [60].

A case-control study with 142 prostate cancer patients and 142 controls reported an OR of 0.7 (0.3–1.5) related to blood γ-tocopherol but without statistical significance (test for trends *p*-value = 0.27) [8]. A comparison of prostate cancer cases (*n* = 1433) and controls (*n* = 1433) did not show any relation between blood vitamin E and cancer [15]. Conversely, two separate cohorts (one carried out in the period 1974–1996 and the other in the period 1989–1996) in the U.S. showed significantly lower blood γ-tocopherol in prostate cancer cases [96]. In the first cohort (CLUE I), the median γ-tocopherol blood concentration was 0.20 mg/dL in cases (*n* = 182) and 0.24 mg/dL in the controls (*n* = 364) (Wilcoxon signed-rank test *p*-value of 0.02), whereas in the second cohort (CLUE II) the values where 0.25 mg/dL in the cases (*n* = 142) and 0.29 mg/dL for the controls (*n* = 284) (*p*-value < 0.001). The blood vitamin E was shown to be significantly lower (*t*-test *p*-value < 0.05) in prostate cancer patients (*n* = 32, mean concentratio*n* = 5.2 μg/mL) than in healthy controls (*n* = 40, mean concentratio*n* = 14.2 μg/mL) [63]. A survey of 278 lung cancer cases and 205 prostate cancer cases, matched to 483 controls, reported a significantly lower concentration of α-tocopherol in lung (*p*-value = 0.02) and prostate (*p*-value = 0.03) cancer than in the control group [10].

6. Vitamin K

Vitamin K is a fat-soluble vitamin that is naturally available in dietary fat in two forms, K_1 (phylloquinone, enriched in leafy vegetables) and K_2 (menaquinone, present mostly in liver, milk, and fermented soy products), whereas a synthetic chemical analogue (K_3, menadione) has been used as an antitumoral molecule [69][97]. The cytotoxic properties of vitamin K_3 are due to the reactivity of the quinone moiety of this molecule, which generates ROS [98]. In combination with vitamin C, K_3 induces autoschizis [48]. Even vitamin K_2 shows antitumoral activity [99] but the process is understood to be linked to the alteration of the cell cycle at the transcriptional level and to disruption of the biochemistry of carboxylation [100]. In particular, vitamin K enhances the expression of protein kinase A (which in turn inhibits the factor Rho) and the inhibition of NF-κB by suppressing IκB kinase (IKK), thus affecting cell proliferation [101][102][103][104].

Vitamins K_1/K_2 take part in the carboxylation of glutamic acid to generate γ-carboxylglutamic acid, which is incorporated in the blood clotting factors II, VII, IX, X, protein Z, protein S, and protein C [105]. Deficiency in vitamin K fosters abnormal carboxylation of prothrombin generating des-gamma-carboxy prothrombin (DCP)—also known as prothrombin induced by vitamin K absence or antagonist-II (PIVKA-II))—which has been identified as a prognostic marker of HCC [106]. The increased expression of des-γ-carboxyl-glutamic acid in HCC is not directly due to a deficiency of vitamin K because these cells showed the same concentrations of this micronutrient as normal cells [107]. It has been proposed that the incapability of HCC cells in completing the carboxylation is not due to deficiency in vitamin K but rather to mutations in the receptors recognizing the complex vitamin K/lipoprotein that reduce the concentrations of this micronutrient in cancer cells, which can be restored by supplementation with vitamin K [108].

Serum DCP has been regarded as a useful HCC marker because it can be observed at a higher frequency in patients than α-fetoprotein (AFP), which is used historically as a diagnostic endpoint [109][110]. For instance, DCP above 0.1 µg/mL was observed in 48.2% of 112 HCC patients compared to 40.2% having AFP above 200 ng/mL [111], and 94.7% of 38 HCC patients had DCP above 0.1 µg/mL compared to 51.4% of 35 patients with AFP above 100 ng/mL [112]. Other surveys showed that 48% of 120 HCC patients had DCP above 0.1 µg/mL [113], 67% of 76 HCC patients had DCP above 300 ng/mL [114], and 74% of 70 HCC patients above 20 mU/mL [115]. DCP provided a risk ratio of 5.653 (95% CI: 2.015–15.861, p-value 0.001) for the insurgence of HCC compared to 3.159 (95% CI: 1.028–9.709, p-value 0.0447) provided by AFP [116]. The blood concentrations of DPC were measured at 64 arbitrary optical density units per liter (U/L) in 100 HCC patients and 3 U/L in 59 healthy controls [117].

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