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Investigating the relationship between vitamin D and cancer requires dosing the bio-available non-hydroxylated vitamin D storage in cancer tissues.

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In a recent article published in *Cancer*Shui et al. observed no statistically significant relationship between circulating 25-hydroxyvitamin D (25(OH)D) and fatal prostate cancer (PCa)[1]. However, an association between *CYP2R1* SNPs and fatal PCa is found[1]. CYP2R1 is the hydroxylase involved in the conversion of vitamin D into 25(OH)D. In the classical vitamin D endocrine system,activation of vitamin D into 1,25(OH)2D requires two successive hydroxylation steps. The first one is catalyzed by CYP2R1 in the liver and the second one by CYP27B1 in the kidneys. Then, 1,25D is released in the blood circulation and behaves as an endocrine hormone. The conversion of 25(OH)Dinto the active hormone 1,25(OH)2D by CYP27B1 is under stringent control. However, the first hydroxylation step catalyzed in the liver by CYP2R1 is constitutive and is not believed to be subjected to tight regulation. This has two important consequences: i) the regulation of liver *CYP2R1* has retained little attention, and ii) circulating non-hydroxylated vitamin D is rapidly metabolized by liver CYP2R1. Therefore, 25(OH)D concentrations are considered to reflect vitamin D inputsand are used to determine the vitamin D status.

A major breakthrough in our understanding on the nonskeletal effects of vitamin D is the recent discovery of autocrine/paracrine vitamin D systemsin many tissues[2].This autocrine/paracrine signalingensures the local bioactivation of 25(OH)D into 1,25(OH)2D by extra-renal *CYP27B1*. In autocrine/paracrine vitamin D systems, the vitamin D metabolites are produced, act and are degraded locally without affecting serum 25(OH)D levels. Shui and coll rightly pointed out that local synthesis of 1,25(OH)2D from 25(OH)D can occur,because *CYP27B1* is expressed in the prostate. However, the authors do not mention that *CYP2R1* is also expressed in prostate tissue[3]. The fact that prostate can also perform the conversion of vitamin D into 25(OH)D is critical. Activity of prostate CYP2R1 depends on the local bio-availability of its substrate, namelynon-hydroxylated vitamin D. There is very little circulating non-hydroxylated vitamin D in the body, but storage can occur. Thisrequires large inputs and is mainly observed in fat tissues whencirculating 25(OH)D concentrations exceed 90 nmol/L[4]. This value is higher than the defined physiological levels for 25(OH)D sufficiency (50 nmol/L -75 nmol/L) but is consistent with 25(OH)D concentrations suggested to reduce cancer risk (~150 nmol/L)[5]. The existence of a functional vitamin D autocrine/paracrine system in prostate that depends on the local bio-availability of non-hydroxylated vitamin D explains the findings reported by Shiu et al. that are:i) the lack of significant association between circulating 25(OH)D and fatal Pca, and ii) the association between *CYP2R1* SNPs and fatal PCa.*CYP2R1* and *CYP27B1* expression are regulated by inflammatory stimuli[6]. In the prostate cancer inflammatory microenvironment, locally bioavailable non-hydroxylated vitamin D would be metabolized first by prostate CYP2R1 to generate 25(OH)D and then by CYP27B1 to produce 1,25(OH)D. This prostate autocrine/paracrine vitamin D system is disconnected to the physiological circulating levels of 25(OH)D (50-75 nmol/L) but will depend on local stores of non-hydroxylated vitamin D and of CYP2R1

activity. The co-existence of two vitamin D systems (endocrine and autocrine/paracrine) with different aims and characteristics, including optimal vitamin D requirements, enlightens the complexity of the vitamin D functions. The association between *CYP2R1* SNPs and fatal PCa described by Shui et al points to the importance to include analyses on the bioavailability ofnon-hydroxylatedvitamin D in studies investigating relationships between vitamin D and cancer.

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