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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)<sup>1</sup>. However, an association between *CYP2R1* SNPs and fatal PCa is found<sup>1</sup>. *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)D into 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 inputs and 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 systems in many tissues<sup>2</sup>. This autocrine/paracrine signaling ensures 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<sup>3</sup>. 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, namely non-hydroxylated vitamin D. There is very little circulating non-hydroxylated vitamin D in the body, but storage can occur. This requires large inputs and is mainly observed in fat tissues when circulating 25(OH)D concentrations exceed 90 nmol/L<sup>4</sup>. 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)<sup>5</sup>. 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<sup>6</sup>. 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 of non-hydroxylated vitamin D in studies investigating relationships between vitamin D and cancer.

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