Study of The Relationship between Colorectal Cancer and Vitamin D Deficiency

Thesis

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بسم الله الرحمن الرحيم

وقُلِ اعْمَلُوا فَسَيَرَى اللَّهُ عَمَلَكُمْ ورَسُولُهُ والْمُؤْمِنُونَ

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List of Abbreviations

$1,25(OH)_2D$:		1, 25-dihydroxyvitamin D3
ALP	:	Alkaline phosphatase
ALT	:	Alanine aminotransferase
APC	:	Adenomatous polyposis coli
AST	:	Aspartate aminotransferase
ATP	:	Adenosine triphosphate
CEA	:	Carcinoembryonic antigen
CF	:	Cystic fibrosis
CI	:	Confidence Interval
CRC	:	Colo-rectal carcinoma
CT	:	Computed tomography
CVD	:	Cardio vascular disease
CYP	:	Cytochrome P
DBP	:	Vitamin D binding protein
DNA	:	Deoxyribonucleic acid
EGF	:	Epidermal growth factor
EGFR	:	Epidermal growth factor receptor
EMT	:	Epithelial-mesenchymal transition
ESCC	:	Esophygeal squamous cell carcinoma
FAP	:	Familial adenomatous polyposis
FGF23	:	Fibroblast growth factor 23
FOBT	:	Fecal occult bloodtesting
Hb	:	Hemoglobin
HIF	:	Hypoxia-inducible factor
HNPCC	:	Hereditary nonpolyposis colon cancer
HPFS	:	Health Professionals Follow-up study
HS	:	Highly significant
IBD	:	Inflammatory bowel disease

List of Abbreviations (Cont.)

IGF	:	Insulin growth factor
IGFBP	:	Insulin growth factor binding protein
IL	:	Interleukin
IU	:	International unit
MDR	:	Multidrug resistance protein
MMR	:	Mismatch repair
MRI	:	Magnetic Resonance Imaging
MRP	:	Multidrug resistance-associated protein
MS	:	Multiple sclerosis
NHS	:	Nurses' Health Study
NS	:	Non significant
NSAIDS	:	Nonsteroidal anti-inflammatory drugs
OH	:	Hydroxy
OPG	:	Osteoprotegerin
OR	:	Odds ratio
PTH	:	Parathyroid hormone
r	:	Pearson correlation coefficient
RA	:	Rheumatoid arthritis
RANK	:	Receptor activator of NF-κB
RANKL	:	Receptor activator of NF-κB ligand
RAS	:	Renin-angiotensin system
RDA	:	Recommended Dietary Allowance
RIF	:	Rifampcin
ROC	:	Receiver Operating Characteristic
RR	:	Relative risk
RXR	:	Retinoic acid X receptor
SD	:	Standard deviation
Sig	:	Significant
t	:	Student t
T1DM	:	Type 1 diabetes mellitus

List of Abbreviations (Cont.)

T2DM	:	Type 2 diabetes mellitus
TGF	:	Transforming growth factor
TGFBR	:	Transforming growth factor receptor
TNF	:	Tumour necrosis factor
TSP-1	:	Thrombospondin-1
UVR	:	Ultra violet rays
VDDR	:	Vitamin D deficiency rickets
VDI	:	Vitamin D intoxication
VDR	:	Vitamin D receptor
VDREs	:	Vitamin D response elements
VEGF	:	Vascular endothelial growth factor
WHS	:	Women's Health Study
ZO	:	Zonula occludens

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Introduction

Colorectal cancer is a major cause of morbidity and mortality throughout the world, It is the third most common cancer worldwide, and the fourth most common cause of death which is more common in males rather than in females **(Boyle, 2000).**

Most colorectal cancers are due to lifestyle factors and increasing age, with only a small number of cases due to underlying genetic disorders. Risk factors include: diet, obesity, smoking and not enough physical activity. Dietary factors that increase the risk include: red and processed meat as well as alcohol. Another risk factor is inflammatory bowel disease, which includes Crohn's disease and ulcerative colitis. Some of the inherited conditions that can cause colorectal cancer include: familial adenomatous polyposis and hereditary non-polyposis colon cancer; however, these represent less than 5% of cases. It typically starts as a benign tumor which over time becomes cancerous (**World Cancer Report, 2014).**

Colorectal cancer survival is highly dependent upon stage of disease at diagnosis, and typically ranges from a 90% 5-year survival rate for cancers detected at the localized stage; 70% for regional; to 10% for people diagnosed for distant metastatic cancer., In general, the earlier the stage at diagnosis, the higher the chance of survival **(Jemal et al., 2004).**

Vitamin D is a fat-soluble vitamin that is naturally present in very few foods, and available as a dietary supplement. It is also produced endogenously when ultraviolet rays from sunlight strike the skin and trigger vitamin D synthesis (**Holick et al., 2006).**

In addition to the known role of vitamin D in promoting calcium absorption in the gut and maintaing adequate serum calcium and phosphate mineralization of bone and preventing hypocalcemic tetany **(Norman et al., 2006).** Vitamin D is being increasingly recognized as an important immunomodulator and low vitamin D has been prospectively associated with disease onset for many autoimmune diseases such as multiple sclerosis, type 1 diabetes mellitus and rheumatoid arthritis (**Mathieu et al., 2004)**

Vitamin D might also play an important part in cancer control by modulating cellular growth and apoptosis and by reducing angiogenesis **(Deeb et al., 2007)**.The hypothesis that vitamin D status is related to colorectal cancer has received strong experimental support over the past two decades, based on the expression in colon cancer cells of the vitamin D receptor (VDR) and 1-a-hydroxylase (CYP27B1), which converts plasma 25-hydroxyvitamin D3[25(OH)D] into 1, 25-dihyroxycholecalciferol [1, 25(OH)2D], the active metabolite. Binding of VDR by 1, 25(OH)2D leads to transcriptional control of target genes, resulting in induction of differentiation and apoptosis, and inhibition of proliferation, angiogenesis, and metastatic potential (**Diaz et al., 2007).**

Aim of The Work

To study the relationship between Vitamin D level and the risk of colorectal cancer.

Vitamin D

Introduction:

Vitamin D is a fat-soluble vitamin which is different from all other fat soluble vitamins, in that the body can synthesise it with the help of sunlight from a precursor that the body makes from cholesterol **(Holick et al., 2006).**

The main biological function of vitamin D is to maintain normal blood levels of calcium and phosphate. This in turn sustains the normal mineralisation of bone, muscle contraction, nerve conduction and general cellular function in all cells of the body. The active form of vitamin D, 1, 25-dihydroxyvitamin D or calcitriol, also regulates the transcription of a number of vitamin D-dependent genes coding for calcium transporting proteins and bone matrix proteins **(Norman et al., 2008).**

It also seems to have some anti-inflammatory and immune-modulating properties. In addition, recent epidemiologic studies have observed relationships between low vitamin D levels and multiple disease states. Low vitamin D levels are associated with increased overall and cardiovascular mortality, cancer incidence and mortality, and autoimmune diseases such as Rheumatoid arthritis, Inflammatoy bowel disease and multiple sclerosis. Although it is well known that the combination of vitamin D and calcium is necessary to maintain bone density as people age, vitamin D may also be an independent risk factor for falls among the elderly **(Brannon et al., 2008)**

Structure and Forms of vitamin D:

Table (1): Forms of vitamin D:

Name	Chemical composition
Vitamin D_1	Molecular compound of ergocalciferol with lumisterol
Vitamin D_2	Ergocalciferol (made from ergosterol)
Vitamin D_3	Cholecalciferol (made from 7-Dehydrocholesterol in the skin).
Vitamin D_4	22-dihydroergocalciferol
Vitamin D_5	Sitocalciferol (made from 7-dehydrositosterol)

Several forms (vitamers) of vitamin D exist (see table 1). The two major forms are vitamin D_2 or ergocalciferol, and vitamin D_3 or cholecalciferol, vitamin D without a subscript refers to either D_2 or D_3 or both. These are known collectively as calciferol **(Hodgkin, 1957).**

Chemically, the various forms of vitamin D are secosteroids, i.e., steroids in which one of the bonds in the steroid rings is broken. The structural difference between vitamin D_2 and vitamin D_3 is the side chain of D_2 contains a double bond between carbons 22 and 23, and a methyl group on carbon 24 **(Hodgkin et al., 1957).**

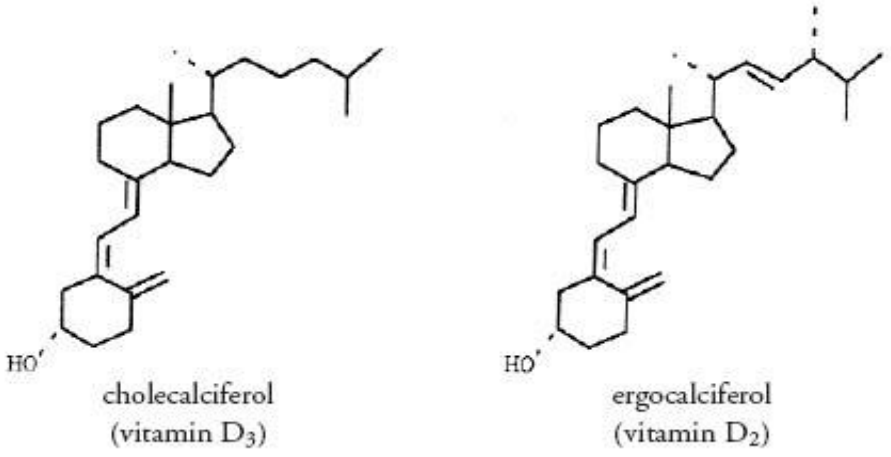

Figure 1: The two major forms of vitamin D (Ikekawa et al., 1993).