Dig Dis Sci (2015) 60:2488–2494
DOI 10.1007/s10620-015-3644-6

ORIGINAL ARTICLE

Vitamin D Deficiency Adds an Element of Risk to Insulin Resistance in Colorectal Neoplasms

Myong Ki Baeg[1] · Myung-Gyu Choi[1] · Sun-Hye Ko[2] · Bo-Geun Park[1] · Kyung-Do Han[3] · Jae Myung Park[1] · Bo-In Lee[1] · In-Seok Lee[1] · Sang-Woo Kim[1]

Received: 2 December 2014 / Accepted: 26 March 2015 / Published online: 4 April 2015

Abstract

Background Both insulin resistance (IR) and vitamin D deficiency (VitDdef) have been suggested as risk factors for colorectal neoplasms (CRNs). However, the associations between the two with regard to CRNs are unclear.

Aims To determine whether IR is a risk factor for CRNs and whether VitDdef confers an additive risk of CRNs.

Methods Colonoscopy-naïve asymptomatic women undergoing a routine health screening program were analyzed. IR was defined as homeostatic model assessment of IR >3 and VitDdef set as <20 ng/mL. Multivariable logistic regression was performed between women with and without CRNs, matched for age and body mass index, to investigate associations with CRNs in IR, VitDdef, and VitDdef combined with IR.

Results We analyzed 216 women with CRNs and 216 without CRNs. A significant association was found between IR and CRNs (OR 1.838, 95 % CI 1.029–3.285, $P = 0.040$) but not with VitDdef. IR conferred a higher risk in advanced CRNs (OR 3.244, 95 % CI 1.588–6.631, $P = 0.001$) than CRNs. When VitDdef was combined with IR, risks of both CRNs and advanced CRNs increased (OR 2.131, 95 % CI 1.077–4.216, $P = 0.030$ and OR 4.438, 95 % CI 2.058–9.571, $P < 0.001$, respectively).

Conclusions IR increases the risk of CRNs, and a combination of IR and VitDdef further increases this risk. As both VitDdef and IR are modifiable risk factors, such associations may have important clinical implications in the prevention of CRNs.

✉ Myung-Gyu Choi
choim@catholic.ac.kr

Myong Ki Baeg
baegmk@catholic.ac.kr

Sun-Hye Ko
dr.ksh@catholic.ac.kr

Bo-Geun Park
reme21@hanmail.net

Kyung-Do Han
hkd917@naver.com

Jae Myung Park
parkjerry@catholic.ac.kr

Bo-In Lee
gidoc4u@gmail.com

In-Seok Lee
isle@catholic.ac.kr

Sang-Woo Kim
viper@catholic.ac.kr

[1] Division of Gastroenterology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, 222 Banpodaero, Seocho-Gu, Seoul 137-701, Republic of Korea

[2] Division of Endocrinology and Metabolism, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, 222 Banpodaero, Seocho-Gu, Seoul 137-701, Republic of Korea

[3] Department of Biostatistics, College of Medicine, The Catholic University of Korea, 222 Banpodaero, Seocho-Gu, Seoul 137-701, Republic of Korea

Keywords Colorectal neoplasm · Colorectal adenoma · Colorectal carcinoma · Insulin resistance · Vitamin D deficiency

Introduction

Metabolic risk factors have been implicated in the formation of colorectal cancer (CRC) [1–3]. Insulin resistance and its associated pathological conditions, such as elevated levels of fasting glucose, insulin, and insulin-like growth factor-1 (IGF-1), have been reported to play a role in colorectal carcinogenesis [4]. IGF-1 plays various roles in colorectal carcinogenesis such as proliferation, differentiation, and antiapoptosis [4, 5]. IGF-1 may also have a role in the development of colorectal neoplasms (CRNs) and advanced CRNs [6]. Although the association between CRC risk and insulin resistance has been well-documented, the relationship between insulin resistance and colorectal adenomas is still controversial [7, 8].

Serum vitamin D level has also been reported to be associated with the risk of CRC [9, 10]. Vitamin D induces antiproliferative, prodifferentiating, and growth inhibitory effects on colorectal carcinogenesis, primarily by acting on the WNT–β-catenin pathway [11, 12]. However, as with insulin resistance, the association between vitamin D deficiency and the risk of colorectal adenomas is less clear [13–18].

Diabetes, metabolic syndrome, insulin resistance, and vitamin D deficiency have close associations [19]. Vitamin D deficiency reportedly increases insulin resistance, although this also remains controversial and vitamin D deficiency should not be regarded as a cause of insulin resistance per se [19–21]. The effect of an association between vitamin D deficiency and insulin resistance on carcinogenesis has not been fully investigated, although one study has suggested additive associations in prostate cancer [22]. However, the effect of this relationship on colorectal carcinogenesis has not been explored. One recent study suggested that CRC patients with a polymorphism of the FokI vitamin D receptor gene had increased CRC risk [23]. Another study speculated that increased vitamin D levels may be associated with a decreased risk of CRCs associated with higher IGF-1 levels [24]. The aim of this study was therefore to investigate the association between insulin resistance and the risk of CRNs and to determine whether vitamin D deficiency confers an added risk in subjects with insulin resistance.

Materials and Methods

Study Population

We conducted a cross-sectional study of women who had routine colonoscopies performed during health screening examinations at the Center for Health Promotion of Seoul St. Mary's Hospital (Seoul, South Korea) between October 2008 and December 2013. Colonoscopy-naïve patients with insulin and 25-hydroxyvitamin D (25-(OH)-D) values were included in this study. Only women were included in this study as women were more likely to have vitamin D deficiency and our center's routine health check-up program recommends checking vitamin D levels for primarily women [25]. Subjects were divided into two groups. The CRN group was comprised of subjects who had histologically confirmed CRNs during colonoscopy. The control group, which was also from the routine, asymptomatic health check-up population and did not have CRNs discovered during colonoscopy, was selected by systematic random sampling after being matched for age and body mass index to those in the CRN group.

Subjects with (1) missing colonoscopy or laboratory records; (2) incomplete colonoscopic examination because of poor bowel preparation or incomplete insertion; (3) any symptom of colorectal disease (abdominal pain, bowel habit change, hematochezia); (4) a history of malignant neoplasm or inflammatory bowel disease; (5) a family history of cancer syndromes or polyposis; (6) previous colectomy; (7) previous colonoscopy or colorectal polypectomy history; or (8) abnormal findings or medical history from the health screening in sites other than the colon were excluded.

Periodic routine health screening is very common in South Korea because of the Industrial Safety and Health Law. This study used medical records that did not include any identifying features. This study was approved by the Institutional Review Board of Seoul St. Mary's Hospital, which waived the informed consent because of the retrospective use of data lacking any identifying features (KC14RISI0564).

Data Collection

All subjects completed a standardized self-administered questionnaire during the screening program. The questionnaire asked about smoking, alcohol consumption, and exercise; and medical history regarding prior malignancies, surgery, diabetes, hypertension, dyslipidemia, cardiovascular and cerebrovascular diseases, previous colonoscopy, previous colon polypectomy, and pregnancy. Medication history included current and regular use of aspirin,

nonsteroidal anti-inflammatory drugs, antidiabetic medication, antihypertensives, and medication for dyslipidemia. Trained nurses took anthropometric measurements including weight, height, waist circumference, and blood pressure (BP). Waist circumference was taken at the midpoint of the lowest rib and the iliac crest in a horizontal plane. BP was measured using a mercury sphygmomanometer in the right arm, using an adequate cuff in a seated position after at least 10 min of rest. Body mass index was calculated as weight in kilograms divided by the square of height in meters (kg/m^2).

Fasting venous blood samples were taken in the morning after an overnight fasting period of at least 12 h. Fasting plasma glucose, glycated hemoglobin (HbA1c), total cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol levels were measured by the Hitachi 7150 Autoanalyzer (Hitachi Ltd., Tokyo, Japan). Serum calcium and phosphate levels were measured using the Hitachi 7600 Autoanalyzer. Fasting serum insulin level was measured by using radioimmunoassay kits (Insulin RIA beads; TFB-Japan Co. Ltd., Tokyo, Japan). Serum 25-(OH)-D concentration was measured with the Liaison® TOTAL chemiluminescent immunoassay (DiaSorin, Stillwater, MN, USA). Serum carcinoembryonic antigen level was checked using an Architect i2000 chemiluminescent microparticle immunoassay (Abbott Laboratories, Abbott Park, IL, USA).

Definition

Individuals with type 2 diabetes were defined as those with an HbA1c level ≥6.5 %, a previous diagnosis of type 2 diabetes, or those taking antidiabetic medication. Metabolic syndrome was defined according to the American Heart Association and the National Heart, Lung and Blood Institute, along with the International Diabetes Federation, if they had at least three of the following: (1) waist circumference ≥90 cm in men and ≥80 cm in women, which is the modified criteria for the Asian population; (2) triglyceride level ≥150 mg/dL or triglyceride-lowering medication; (3) low HDL cholesterol level (<50 mg/dL); (4) systolic BP ≥130 mmHg, diastolic BP ≥85 mmHg, or antihypertensive medication use; and (5) fasting glucose level ≥100 mg/dL or use of antidiabetic medication, or previously diagnosed type 2 diabetes [26]. Homeostatic model of insulin resistance (HOMA-IR; fasting blood insulin (mlU/ml) × fasting glucose (mg/dl)/405) was used to assess insulin resistance and the cutoff value for insulin resistance set at 3 [27]. Vitamin D deficiency was defined as subjects having a serum level of 25-(OH)-D of <20 ng/mL [28].

Colonoscopic Examinations and Definition of Colorectal Neoplasms

Colonoscopic examination was carried out by endoscopists certified as experts by the Korean Society of Gastrointestinal Endoscopy in the standard manner after routine preparation with 4 L of polyethylene glycol. Small polyps (<0.5 cm) were removed via biopsy forceps, and large polyps (≥0.5 cm) were removed by snare polypectomy or endoscopic mucosal resection. Polyp size was endoscopically measured by both visual estimation and comparison with biopsy forceps.

All retrieved polyps were reviewed by an experienced gastrointestinal pathologist. CRN was defined as the presence of adenoma or adenocarcinoma components. Non-neoplastic polyps such as inflammatory, lymphoid, hyperplastic polyps, or mucosal tags were excluded. Patients were classified into the advanced CRN group if they met either the high-risk adenoma category of the 2012 American Gastroenterological Association guidelines or had an adenocarcinoma component [29]: (1) ≥3 adenomas; (2) high-grade dysplasia; (3) villous features; (4) ≥1 cm in size; or (5) adenocarcinoma.

Statistical Analysis

Categorical variables were examined through Pearson's Chi-squared test, and continuous variables were assessed by the Student's *t* test. Two multivariable models were constructed to determine whether there was an added element of risk in CRN and advanced CRN subjects with vitamin D deficiency, HOMA-IR > 3, and those with both vitamin D deficiency and HOMA-IR > 3. Model 1 included adjustment for age; model 2 added adjustments for smoking and alcohol history in addition to model 1. Odds ratios (ORs) and 95 % confidence intervals (CIs) were calculated for each variable in the multivariable analysis. Multicollinearity was determined for all multiple regression models by calculating the tolerance and variance inflation factors. Any regression model with a variance inflation factor >5 was excluded on the basis of significant multicollinearity. *P* values <0.05 were accepted to be statistically significant. All tests were two-sided and performed at the 5 % level of significance by calculation via SAS software (SAS; SAS Institute, Cary, NC, USA).

Results

A total of 4576 women who underwent health screening at the Center for Health Promotion of Seoul St. Mary's Hospital between October 2008 and December 2013 had both colonoscopies and fasting insulin levels examined. Of

these subjects, 796 elected to have serum 25-(OH)-D levels checked. Excluded from the analysis were 62 subjects with a history of previous polypectomy or colonoscopy, 35 with poor colonoscopic preparation, 26 with a previous history of malignancy, and nine with incomplete medical records. Of the 664 subjects analyzed, 216 were found to have CRNs and compared with a control group of 216 non-CRN subjects matched for age and body mass index.

Of the 216 subjects with CRNs, 42 had advanced CRNs, and five of these were CRCs. The mean (±SD) number of CRNs per subject was 1.5 ± 1.0. The baseline characteristics of the non-CRN and CRN groups can be seen in Table 1. The CRN group had a significantly higher number of subjects with alcohol consumption and higher HOMA-IR levels. There was no significant difference in the level of serum 25-(OH)-D or prevalence of vitamin D deficiency between the two groups.

The association between CRNs and vitamin D deficiency, HOMA-IR, and vitamin D deficiency combined with HOMA-IR is shown in Table 2. HOMA-IR > 3 was a significant risk factor for both CRNs and advanced CRNs (OR 1.838, 95 % CI 1.029–3.285, $P = 0.040$ and OR 3.244, 95 % CI 1.588–6.631, $P = 0.001$). Although vitamin D deficiency was not a significant risk factor for either CRNs or advanced CRNs in both models, vitamin D deficiency combined with HOMA-IR > 3 significantly increased the risk of CRNs and advanced CRNs (OR 2.131, 95 % CI 1.077–4.216, $P = 0.030$ and OR 4.438, 95 % CI 2.058–9.571, $P < 0.001$).

Discussion

Our study demonstrates that there is a clear association between insulin resistance and the risk of CRNs and advanced CRNs. However, both CRNs and advanced CRNs were not associated with vitamin D deficiency. When vitamin D deficiency was combined with insulin resistance, the risk of CRNs and advanced CRNs was elevated further than with insulin resistance alone. These results suggest that while insulin resistance is part of the CRN formation pathway, vitamin D deficiency adds an element of risk to CRN formation.

Diabetes has been established as a risk factor for the development of CRC [1, 30], but the association between glucose metabolism and the development of colorectal adenomas is less clear [7, 8]. A recent large, cross-sectional study comparing 5900 adenoma patients with 13,000 controls reported that markers of glucose metabolism such as fasting glucose levels, insulin levels, HbA1c, HOMA-IR, and C-peptide levels were significantly associated with the overall presence of colorectal adenomas. These associations were even stronger for advanced adenomas than for any adenomas, which is similar to the results of our study [7]. This finding is supported by previous studies reporting a positive association between insulin levels and advanced adenomas or early CRCs [6, 31].

Serum vitamin D level has been reported to be inversely associated with the risk of CRC [9, 10]. However, the association between vitamin D deficiency and the risk of colorectal adenomas is less clear. Several studies have reported a significant inverse association similar to that for CRC [13–15]. However, other studies have found that this association exists only in women and is U-shaped or nonsignificant [16–18, 32]. The results of our study are in contrast to those of a recent meta-analysis, which has reported an inverse association between vitamin D deficiency and the risk of CRN [33]. However, the added element of risk conferred by vitamin D deficiency in our study, especially in advanced CRNs, may be corroborated by reports suggesting that vitamin D deficiency is related to different stages of adenoma development [34]. Our finding is also supported by papers reporting that vitamin D deficiency is related to an increased risk of larger adenomas or those with villous histology [32, 33].

Vitamin D deficiency is associated with insulin-resistant states such as metabolic syndrome, nonalcoholic fatty liver disease, and diabetes [19, 35, 36]. Vitamin D has been reported to enhance insulin sensitivity by stimulating insulin receptor expression, promoting pancreatic beta cell function, lessening the effects of systemic inflammation, and improving insulin resistance by improving the uptake of glucose by peripheral tissues [36, 37]. However, whether vitamin D deficiency can be regarded as another manifestation of insulin resistance, or vice versa, remains questionable. Although epidemiologic, cross-sectional, and longitudinal studies have reported associations between metabolic syndrome, diabetes, and vitamin D deficiency, other studies have failed to find any relationship [16, 21, 37]. With regard to carcinogenesis, one study has reported an additive effect between vitamin D deficiency and insulin resistance, which is similar to our results. This study investigated the association between metabolic syndrome factors and prostate cancer risk. It reported that subjects with both metabolic syndrome and vitamin D deficiency were at an increased risk of prostate cancer, whereas subjects with either metabolic syndrome or vitamin D deficiency were not at an increased risk. The authors theorized that common putative pathways between vitamin D deficiency and metabolic syndrome exist [22]. As prostate cancers are associated with precancerous prostatic intraepithelial neoplasia [38], which may be considered analogous to colorectal adenomas, a stepwise pathway may indeed exist.

One possible pathway is the relationship between IGF binding proteins (IFGBP) and vitamin D analogues, which

Table 1 Baseline characteristics of the groups with and without colorectal neoplasms

	Non-CRN group ($n = 216$)	CRN group ($n = 216$)	P
Age	56.8 ± 8.5	56.8 ± 8.7	0.930
Diabetes mellitus, *n* (%)	21 (9.7)	27 (12.5)	0.358
Hypertension, *n* (%)	46 (21.3)	61 (28.2)	0.095
Metabolic syndrome, *n* (%)	63 (29.2)	80 (37.0)	0.082
Body Mass Index (kg/m^2)	23.7 ± 3.0	23.7 ± 3.3	0.725
Waist circumference, cm	84.0 ± 8.0	85.2 ± 8.7	0.137
Alcohol consumption, *n* (%)	71 (32.9)	97 (44.9)	0.010
History of smoking, *n* (%)	24 (11.1)	37 (17.1)	0.072
Aspirin/NSAID use, *n* (%)	28 (13.0)	27 (12.5)	0.885
Regular calcium use, *n* (%)	23 (10.6)	29 (13.4)	0.375
Total cholesterol (mg/dL)	206.1 ± 39.6	209.3 ± 40.4	0.395
Triglyceride (mg/dL)	89.7 ± 57.8	93.8 ± 61.6	0.484
HDL cholesterol (mg/dL)	55.3 ± 12.6	55.3 ± 12.5	0.991
LDL cholesterol (mg/dL)	126.8 ± 35.2	129.1 ± 35.0	0.485
Fasting glucose (mg/dL)	95.4 ± 20.5	98.9 ± 23.6	0.102
Fasting insulin (mIU/mL)	6.4 ± 5.0	7.3 ± 5.7	0.074
HbA1c (%)	5.7 ± 0.7	5.7 ± 0.9	0.371
HOMA-IR[a]	1.6 ± 1.5	1.9 ± 1.9	0.051
HOMA-IR[a] > 3, *n* (%)	21 (9.7)	37 (17.1)	0.034
HOMA-B[b]	83.8 ± 73.8	79.7 ± 76.9	0.566
CEA (ng/mL)	1.4 ± 1.0	1.6 ± 1.3	0.087
25-hydroxyvitamin D (ng/mL)	16.9 ± 8.9	16.0 ± 8.8	0.510
Vitamin D <20 ng/mL, *n* (%)	154 (71.3)	160 (74.1)	0.517
Ca (mg/dL)	9.2 ± 0.4	9.2 ± 0.4	0.434
P (mg/dL)	3.8 ± 0.6	3.8 ± 0.5	0.978

Data presented as mean ± standard deviation or as proportion

CEA carcinoembryonic antigen, *CRN* colorectal neoplasm, *HDL* high-density lipoprotein, *HOMA-B* homeostatic model assessment of beta cell function, *HOMA-IR* homeostatic model assessment of insulin resistance, *LDL* low-density lipoprotein, *NSAID* nonsteroidal anti-inflammatory drug

[a] HOMA-IR = (fasting glucose × fasting insulin)/405

[b] HOMA-B = (360 × fasting insulin)/(fasting glucose − 63)

has been reported in breast, colon, prostate, and osteosarcoma cancer cell lines [39–42]. Vitamin D and its analogues have been reported to inhibit the secretion of IGFs and stimulate production of IGFBPs, which mostly inhibit IGF action [40–43]. The insulin resistance states of our subjects would lead to increased IGF levels, whose carcinogenic effects would be even more augmented by the lack of IGFBPs caused by vitamin D deficiency. However, as our study was a cross-sectional study that did not investigate the mechanisms between CRC, insulin resistance, and vitamin D deficiency, further studies will be needed.

In the CRN group, there was a tendency for higher prevalence of hypertension, metabolic syndrome, history of smoking, and fasting insulin. These findings imply that the CRN patients may have a more unhealthy lifestyle which may have contributed as risk factors for CRNs.

In conclusion, our study demonstrates that there is a significant association between insulin resistance and the risk of CRNs. CRNs were not associated with vitamin D deficiency, but when vitamin D deficiency was combined with insulin resistance, the risk of CRNs was increased further than with insulin resistance alone. These associations were even more prominent when only advanced CRNs were considered. Whether checking and correcting vitamin D deficiency in subjects with insulin resistance states as well as increasing colon screening in such subjects leads to CRN prevention need more investigation. Also, the stepwise progression in the CRC pathway suggested by our study may lead to new areas of research and treatment.

Table 2 Analysis of patients with colorectal neoplasms and advanced colorectal neoplasms according to vitamin D deficiency, HOMA-IR > 3, and vitamin D deficiency combined with HOMA-IR > 3

	Colorectal neoplasms			Advanced neoplasms		
	Odds Ratio	95 % CI	*P*	Odds Ratio	95 % CI	*P*
Model 1						
Vitamin D Def	1.159	0.754–1.783	0.501	1.134	0.558–2.305	0.729
HOMA-IR > 3	1.925	1.083–3.421	0.026	3.385	1.666–6.874	0.001
Vitamin D Def + HOMA-IR > 3	2.062	1.049–4.054	0.036	4.388	2.045–9.415	<0.001
Model 2						
Vitamin D Def	1.144	0.741–1.765	0.545	1.122	0.550–2.288	0.751
HOMA-IR > 3	1.838	1.029–3.285	0.040	3.244	1.588–6.631	0.001
Vitamin D Def + HOMA-IR > 3	2.131	1.077–4.216	0.030	4.438	2.058–9.571	<0.001

Model 1: age

Model 2: model 1 + smoking + alcohol

HOMA-IR homeostatic model of insulin resistance, *Vitamin D Def* vitamin D deficiency

Acknowledgments This research was supported by program of Global Research and Development Center through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT, and Future Planning (NRF-2011-0031644).

Conflict of interest None.

References

1. Yuhara H, Steinmaus C, Cohen SE, Corley DA, Tei Y, Buffler PA. Is diabetes mellitus an independent risk factor for colon cancer and rectal cancer? *Am J Gastroenterol*. 2011;106:1911–1921; quiz 1922.
2. Garland C, Shekelle RB, Barrett-Connor E, Criqui MH, Rossof AH, Paul O. Dietary vitamin D and calcium and risk of colorectal cancer: a 19-year prospective study in men. *Lancet*. 1985;1:307–309.
3. Bardou M, Barkun AN, Martel M. Obesity and colorectal cancer. *Gut*. 2013;62:933–947.
4. Sandhu MS, Dunger DB, Giovannucci EL. Insulin, insulin-like growth factor-I (IGF-I), IGF binding proteins, their biologic interactions, and colorectal cancer. *J Natl Cancer Inst*. 2002;94:972–980.
5. Sax AT, Jenkins DG, Devin JL, Hughes GI, Bolam KA, Skinner TL. The insulin-like growth factor axis: a biological mechanism linking physical activity to colorectal cancer survival. *Cancer Epidemiol*. 2014;38:455–459.
6. Schoen RE, Weissfeld JL, Kuller LH, et al. Insulin-like growth factor-I and insulin are associated with the presence and advancement of adenomatous polyps. *Gastroenterology*. 2005;129:464–475.
7. Rampal S, Yang MH, Sung J, et al. Association between markers of glucose metabolism and risk of colorectal adenoma. *Gastroenterology*. 2014;147:78–87 e73.
8. Tsilidis KK, Brancati FL, Pollak MN, et al. Metabolic syndrome components and colorectal adenoma in the CLUE II cohort. *Cancer Causes Control*. 2010;21:1–10.
9. Ma Y, Zhang P, Wang F, Yang J, Liu Z, Qin H. Association between vitamin D and risk of colorectal cancer: a systematic review of prospective studies. *J Clin Oncol*. 2011;29:3775–3782.
10. Lee JE, Li H, Chan AT, et al. Circulating levels of vitamin D and colon and rectal cancer: the Physicians' Health Study and a meta-analysis of prospective studies. *Cancer Prev Res (Phila)*. 2011;4:735–743.
11. Giovannucci E. The epidemiology of vitamin D and cancer incidence and mortality: a review (United States). *Cancer Causes Control*. 2005;16:83–95.
12. Feldman D, Krishnan AV, Swami S, Giovannucci E, Feldman BJ. The role of vitamin D in reducing cancer risk and progression. *Nat Rev Cancer*. 2014;14:342–357.
13. Hong SN, Kim JH, Choe WH, et al. Circulating vitamin D and colorectal adenoma in asymptomatic average-risk individuals who underwent first screening colonoscopy: a case–control study. *Dig Dis Sci*. 2012;57:753–763.
14. Peters U, McGlynn KA, Chatterjee N, et al. Vitamin D, calcium, and vitamin D receptor polymorphism in colorectal adenomas. *Cancer Epidemiol Biomark Prev*. 2001;10:1267–1274.
15. Fedirko V, Bostick RM, Goodman M, Flanders WD, Gross MD. Blood 25-hydroxyvitamin D3 concentrations and incident sporadic colorectal adenoma risk: a pooled case–control study. *Am J Epidemiol*. 2010;172:489–500.
16. Platz EA, Hankinson SE, Hollis BW, et al. Plasma 1,25-dihydroxy- and 25-hydroxyvitamin D and adenomatous polyps of the distal colorectum. *Cancer Epidemiol Biomark Prev*. 2000;9:1059–1065.
17. Jacobs ET, Alberts DS, Benuzillo J, Hollis BW, Thompson PA, Martinez ME. Serum 25(OH)D levels, dietary intake of vitamin D, and colorectal adenoma recurrence. *J Steroid Biochem Mol Biol*. 2007;103:752–756.
18. Zheng XE, Lipka S, Li T, et al. The relationship of vitamin D status, smoking, and colorectal adenoma: a retrospective study in an ethnically diverse community. *J Steroid Biochem Mol Biol*. 2013;136:280–283.
19. Ford ES, Ajani UA, McGuire LC, Liu S. Concentrations of serum vitamin D and the metabolic syndrome among U.S. adults. *Diabetes Care*. 2005;28:1228–1230.
20. Amirbaigloo A, Hosseinpanah F, Sarvghadi F, Tohidi M, Eskandary PS, Azizi F. Absence of association between vitamin D deficiency and incident metabolic syndrome: tehran lipid and glucose study. *Metab Syndr Relat Disord*. 2013;11:236–242.
21. Al-Shoumer KA, Al-Asoosi AA, Ali AH, Nair VS. Does insulin resistance in type 2 diabetes alter vitamin D status? *Prim Care Diabetes*. 2013;7:283–287.
22. Tuohimaa P, Tenkanen L, Syvala H, et al. Interaction of factors related to the metabolic syndrome and vitamin D on risk of

prostate cancer. *Cancer Epidemiol Biomark Prev*. 2007;16:302–307.
23. Murtaugh MA, Sweeney C, Ma KN, et al. Vitamin D receptor gene polymorphisms, dietary promotion of insulin resistance, and colon and rectal cancer. *Nutr Cancer*. 2006;55:35–43.
24. Wu K, Feskanich D, Fuchs CS, Willett WC, Hollis BW, Giovannucci EL. A nested case control study of plasma 25-hydroxyvitamin D concentrations and risk of colorectal cancer. *J Natl Cancer Inst*. 2007;99:1120–1129.
25. Choi EY. 25(OH)D status and demographic and lifestyle determinants of 25(OH)D among Korean adults. *Asia Pac J Clin Nutr*. 2012;21:526–535.
26. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009;120:1640–1645.
27. Lee S, Choi S, Kim HJ, et al. Cutoff values of surrogate measures of insulin resistance for metabolic syndrome in Korean nondiabetic adults. *J Korean Med Sci*. 2006;21:695–700.
28. Rosen CJ, Gallagher JC. The 2011 IOM report on vitamin D and calcium requirements for north America: clinical implications for providers treating patients with low bone mineral density. *J Clin Densitom*. 2011;14:79–84.
29. Lieberman DA, Rex DK, Winawer SJ, Giardiello FM, Johnson DA, Levin TR. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology*. 2012;143:844–857.
30. Deng L, Gui Z, Zhao L, Wang J, Shen L. Diabetes mellitus and the incidence of colorectal cancer: an updated systematic review and meta-analysis. *Dig Dis Sci*. 2012;57:1576–1585.
31. Yamamoto S, Nakagawa T, Matsushita Y, et al. Visceral fat area and markers of insulin resistance in relation to colorectal neoplasia. *Diabetes Care*. 2010;33:184–189.
32. Peters U, Hayes RB, Chatterjee N, et al. Circulating vitamin D metabolites, polymorphism in vitamin D receptor, and colorectal adenoma risk. *Cancer Epidemiol Biomark Prev*. 2004;13:546–552.
33. Wei MY, Garland CF, Gorham ED, Mohr SB, Giovannucci E. Vitamin D and prevention of colorectal adenoma: a meta-analysis. *Cancer Epidemiol Biomark Prev*. 2008;17:2958–2969.
34. Jacobs ET, Hibler EA, Lance P, Sardo CL, Jurutka PW. Association between circulating concentrations of 25(OH)D and colorectal adenoma: a pooled analysis. *Int J Cancer*. 2013;133:2980–2988.
35. Seo JA, Eun CR, Cho H, et al. Low vitamin D status is associated with nonalcoholic fatty liver disease independent of visceral obesity in Korean adults. *PLoS ONE*. 2013;8:e75197.
36. Mitri J, Pittas AG. Vitamin D and diabetes. *Endocrinol Metab Clin N Am*. 2014;43:205–232.
37. Gulseth HL, Gjelstad IM, Birkeland KI, Drevon CA. Vitamin D and the metabolic syndrome. *Curr Vasc Pharmacol*. 2013;11:968–984.
38. Merrimen JL, Evans AJ, Srigley JR. Preneoplasia in the prostate gland with emphasis on high grade prostatic intraepithelial neoplasia. *Pathology*. 2013;45:251–263.
39. Mitri J, Dawson-Hughes B, Hu FB, Pittas AG. Effects of vitamin D and calcium supplementation on pancreatic beta cell function, insulin sensitivity, and glycemia in adults at high risk of diabetes: the Calcium and Vitamin D for Diabetes Mellitus (CaDDM) randomized controlled trial. *Am J Clin Nutr*. 2011;94:486–494.
40. Colston KW, Perks CM, Xie SP, Holly JM. Growth inhibition of both MCF-7 and Hs578T human breast cancer cell lines by vitamin D analogues is associated with increased expression of insulin-like growth factor binding protein-3. *J Mol Endocrinol*. 1998;20:157–162.
41. Brosseau C, Pirianov G, Colston KW. Role of insulin-like growth factor binding protein-3 in 1, 25-dihydroxyvitamin-d 3-induced breast cancer cell apoptosis. *Int J Cell Biol*. 2013;2013:960378.
42. Oh YS, Kim EJ, Schaffer BS, et al. 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.
43. Martin JL, Baxter RC. Signalling pathways of insulin-like growth factors (IGFs) and IGF binding protein-3. *Growth Factors*. 2011;29:235–244.