



BRIEF ARTICLES

No association between cyclooxygenase-2 and uridine diphosphate glucuronosyltransferase 1A6 genetic polymorphisms and colon cancer risk

Cheryl L Thompson, Sarah J Plummer, Alona Merkulova, Iona Cheng, Thomas C Tucker, Graham Casey, Li Li

Cheryl L Thompson, Li Li, Departments of Family Medicine and Epidemiology and Biostatistics, Case Center for Transdisciplinary Research on Energetics and Cancer, Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH 44106-7136, United States

Sarah J Plummer, Graham Casey, Department of Preventive Medicine, University of Southern California, Los Angeles, CA 90033-1006, United States

Alona Merkulova, Department of Cancer Biology, Cleveland Clinic Foundation, Cleveland, OH 44195-0001, United States

Iona Cheng, Department of Epidemiology and Biostatistics and Institute for Human Genetics, University of California San Francisco, San Francisco, CA 94143-0644, United States

Thomas C Tucker, Markey Cancer Center, University of Kentucky, Lexington, KY 40504-3381, United States

Author contributions: Thompson CL performed the statistical analyses, assisted with the subject recruitment and data collection and drafted the manuscript; Plummer SJ conducted some of the genotyping and assisted with the manuscript preparation; Merkulova A performed some of the genotyping; Tucker TC assisted with patient referrals and recruitment; Casey G coordinated the lab work and assisted with manuscript preparation; Li L led the study design and data collection and assisted with the manuscript preparation; Cheng I selected the SNPs for inclusion in the study and reviewed the manuscript.

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Correspondence to: Li Li, MD, PhD, Department of Family Medicine, Research Division, Case Western Reserve University, 11001 Cedar Ave., Suite 306, Cleveland, Ohio 44106-7136, United States. li.li@case.edu

Telephone: +1-216-3685437 Fax: +1-216-3684348

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METHODS: NSAIDs, which are known to reduce the risk of colon cancer, act directly on COX2 and reduce its activity. Epidemiological studies have associated variations in the *COX2* gene with colon cancer risk, but others were unable to replicate this finding. Similarly, enzymes in the *UGT1A6* gene have been demonstrated to modify the therapeutic effect of NSAIDs on colon adenomas. Polymorphisms in the *UGT1A6* gene have been statistically shown to interact with NSAID intake to influence risk of developing colon adenomas, but not colon cancer. Here we examined the association of tagging single nucleotide polymorphisms (SNPs) in the *COX2* and *UGT1A6* genes, and their interaction with NSAID consumption, on risk of colon cancer in a population of 422 colon cancer cases and 481 population controls.

RESULTS: No SNP in either gene was individually statistically significantly associated with colon cancer, nor did they statistically significantly change the protective effect of NSAID consumption in our sample. Like others, we were unable to replicate the association of variants in the *COX2* gene with colon cancer risk ($P > 0.05$), and we did not observe that these variants modify the protective effect of NSAIDs ($P > 0.05$). We were able to confirm the lack of association of variants in *UGT1A6* with colon cancer risk, although further studies will have to be conducted to confirm the association of these variants with colon adenomas.

CONCLUSION: Our study does not support a role of COX2 and UGT1A6 genetic variations in the development of colon cancer.

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Key words: Uridine diphosphate glucuronosyltransferase 1A6; Cyclooxygenase-2; Non-steroidal anti-inflammatory drugs; Colon cancer; Genetic association studies; Single nucleotide polymorphisms

Peer reviewer: Alessandro Fichera, MD, FACS, FASCRS, Assistant Professor, Department of Surgery, University of Chicago, 5841 S. Maryland Ave, MC 5031, Chicago, IL 60637, United States

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Abstract

AIM: To investigate the association of variations in the cyclooxygenase-2 (COX2) and uridine diphosphate glucuronosyltransferase 1A6 (UGT1A6) genes and non-steroidal anti-inflammatory drugs (NSAIDs) use with risk of colon cancer.

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INTRODUCTION

Almost 150 000 new colorectal cancer cases are estimated to be diagnosed in 2008, resulting in almost 50 000 deaths (National Cancer Institute-www.cancer.gov). Colon adenomas (polyps) are a well established precursor of colon cancer. The genetic and environmental factors that cause the development of colon adenomas or their subsequent progression into cancer are not entirely known. Genetics are known to be a large risk factor for colon cancer, and indeed having a family history of colon cancer increases your risk of developing it yourself substantially. However, the known genetic susceptibility loci for colon cancer make up only a small fraction of this risk.

Cyclooxygenase-2 (COX-2) is a pro-inflammatory enzyme that converts arachidonic acid to prostaglandins. COX2 has been shown to be upregulated in a high proportion (about 86%) of human colorectal cancer^[1]. Numerous additional findings have indicated a likely role for the cyclooxygenases and inflammation in the development of colon cancer^[2].

Non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin and ibuprofen, act directly on COX2 as well as other targets to reduce activity. A substantial body of epidemiologic and randomized clinical trial evidence suggests that regular NSAID use and selective COX-2 inhibitors reduce the risks of colorectal cancer or the recurrence of adenomatous polyps^[3], which is, at least in part, attributed to their known anti-inflammatory effects. The COX-2 gene is thus a good candidate gene for colorectal carcinogenesis and its genetic variants may affect the susceptibility to the development of this colorectal cancer by altering the effects of this enzyme on the inflammatory response. To date, a few studies have evaluated a limited number of polymorphisms in the COX2 gene in relation to risk of colorectal cancer and adenomatous polyps^[4-7]. The findings have yielded inconsistent results, with some^[4-6], but not all^[7], reporting an association with the risk of colorectal cancer or polyps. Additionally, a sib-pair study of colon neoplasia with relatively small sample size found no linkage to the COX2 locus^[8].

Furthermore, genetic variation in the uridine diphosphate glucuronosyltransferase 1A6 (UGT1A6) gene have been associated with differences in aspirin metabolism, and those with the less frequent variants have a 30%-50% lower enzyme activity^[9]. Additionally, a few studies have examined the association of genetic polymorphisms in UGT1A6, a rate-limiting enzyme directly involved in aspirin metabolism, and their interactions with aspirin or NSAIDs in relation to colorectal cancer and polyps^[10-13]. Although two studies

of colon cancer observed no association with genetic variants in UGT1A6^[12,13], two studies of colon adenomas identified variants in UGT1A6 that modified the protective effect of aspirin^[10,11]. Others have identified variants that influence the risk of adenoma recurrence^[14]. To further investigate the role of COX2 and UGT1A6 in relation to the risk of colon cancer, we tested nine tag single nucleotide polymorphisms (SNPs) in COX2 and two functional SNPs in UGT1A6^[13] in a population-based case-control study of colon cancer.

MATERIALS AND METHODS

Study population

The details of the present study have been described elsewhere^[15]. Briefly, colon cases ($n = 422$) were identified through the population-based Surveillance, Epidemiology and End Results (SEER) Kentucky Cancer Registry, and 481 population controls living in Kentucky were recruited *via* random digit dialing. Participants donated a blood sample for genetic analyses and completed a detailed self-administered lifestyle risk factor questionnaire that included information on NSAID use. Participation rates were 72.2% for cases and 62.5% for controls. All participants provided written informed consent. The study was approved by the Institutional Review Boards of the University of Kentucky, Lexington, and Case Western Reserve University/University Hospitals Case Medical Center.

Genotyping

We assessed the common genetic variation (SNPs with minor allele frequencies > 5%) of COX-2 that spanned about 2 kb upstream of the transcription start site and about 1 kb downstream of the 3' untranslated region. Seven tag SNPs for COX-2 were selected to predict unmeasured SNPs ($r^2 > 0.8$) using publicly available genotype data for European populations from the International HapMap project (www.hapmap.org) and the Perlegen and Seattle SNP projects (<http://gvs.gs.washington.edu/GVS>). One common SNP, -899 G/C (rs20417), that was previously associated with colorectal cancer^[9], and rs689470, which was previously associated with prostate cancer^[16], were also included. Two functional non-synonymous SNPs [rs1105879 (R184S) and rs2070959 (T181A)] in UGT1A6^[13] were selected. Genotyping was performed using the Taqman allelic discrimination assay with genotyping error < 0.1%, as described previously^[15].

Statistical analyses

We evaluated the association between COX-2 and UGT1A6 genotypes and colon cancer risk using multivariate unconditional logistic regression models. Each SNP was evaluated assuming dominant, additive and recessive modes of inheritance. For all SNPs, the allele with the lower frequency was coded as the risk allele. For the dominant model, individuals with at least one copy of the risk allele were coded as 1, others were

coded as 0. For the recessive model, only those with two copies of the risk allele were coded as 1. In the additive model, individuals were coded with the number of risk alleles they possessed (0, 1 or 2). In our base models, we adjusted for age, gender, and race. For these analyses, age was defined as age at diagnosis for cases and age at recruitment for controls. We further controlled for family history of colorectal cancer, body mass index (BMI), regular NSAID use, alcohol consumption, smoking, and intensity of recreational physical activity in the 20 s, for those with available data. Regular NSAID use was defined as having reported intake of at aspirin or ibuprofen at least twice a week for a period of one month or longer.

To evaluate potential effect modification of NSAID use, we tested for multiplicative interaction by including the main effects and a cross-product term of SNP \times NSAID use in the logistic regression models. All *P*-values were two-sided, and all analyses were undertaken with SAS software (version 9.1; SAS Institute, Inc., Cary, North Carolina).

RESULTS

The characteristics and genotypic distributions of this predominantly Caucasian study population are summarized in Table 1. All SNPs were found to be in Hardy-Weinberg equilibrium both in controls alone and in the entire sample. We found no statistically significant association between any of the nine *COX2* SNPs and two functional *UGT1A6* SNPs and colon cancer risk, regardless of the mode of inheritance (Table 2).

We further explored potential effect modification of the association by regular NSAID use, and found no evidence for interaction of any SNP (Table 2) in either gene ($P > 0.05$).

Since others^[10] have reported that *UGT1A6* variants modify the therapeutic effects of aspirin in a population of women only, we stratified our analyses by gender. We found very little differences in results with nothing significant in females or males only as well (results not shown).

DISCUSSION

In our analysis, we examined potential effect modification by regular NSAID use rather than aspirin alone, as other groups have done, due to the smaller number of aspirin alone users. To account for this, we repeated our analysis using aspirin use only (115 cases and 157 controls), and the results did not change materially (not shown), with no significant findings. However, the lack of association with aspirin alone may be due to the small sample size and thus lack of statistical power.

Our study had over 90% power to detect an OR \geq 1.75 at a two-sided $\alpha = 0.05$ for the polymorphisms studied here, and over 80% power to detect an OR \geq 1.60, assuming a dominant model of inheritance and

Table 1 Population characteristics *n* (%)

	Case (<i>n</i> = 422)	Control (<i>n</i> = 481)	<i>P</i> ¹
Age (mean \pm SD) (yr) ²	62.9 \pm 10.6	57.9 \pm 11.1	< 0.0001
Gender			0.0002
Female	203 (50.5)	304 (64.1)	
Male	199 (49.5)	178 (35.9)	
Race			0.35
Caucasian	378 (93.6)	449 (93.2)	
African-American	21 (4.4)	21 (5.2)	
Other	12 (2.5)	5 (1.2)	
BMI (mean \pm SD) (kg/m ²)	29.2 \pm 6.2	28.1 \pm 6.1	< 0.0001
Family history ³			0.0011
Yes	94 (24.0)	71 (15.2)	
No	297 (76.0)	395 (84.8)	
NSAID use			0.14
Regular	235 (64.2)	306 (69.1)	
Irregular/none	131 (35.8)	137 (30.9)	
Physical activity			0.008
None/low	111 (29.1)	113 (24.7)	
Moderate	106 (27.8)	98 (21.4)	
High	165 (43.2)	246 (53.8)	
Regular alcohol use			0.04
Ever	134 (34.8)	191 (41.7)	
Never	251 (65.2)	267 (58.3)	
Smoking			0.88
Ever	207 (53.6)	248 (54.2)	
Never	179 (46.4)	210 (45.9)	

¹*P*-value of significance difference between cases and controls in χ^2 test (discrete variables and genotypes) or *t*-test (continuous); ²Age at diagnosis for cases, and age at questionnaire completion for controls; ³Family history of first-degree relatives with colorectal cancer.

allele frequency of 0.1. While we did comprehensively capture the common genetic variation across the *COX2* gene, we only evaluated two putative functional SNPs in *UGT1A6*, and were limited in our ability to make direct conclusions about the effect of other genetic variants in *UGT1A6*. It is possible that these variants have smaller effects on colorectal cancer susceptibility or the therapeutic effects of NSAID use that we were unable to detect with this study.

It is important to note that NSAID use was based on self-report. Individuals may not accurately recall duration or frequency of NSAID intake. Nevertheless, our finding of a protective effect of NSAID use (OR = 0.69, 95% CI = 0.50-0.96, $P = 0.02$) is in agreement with its well-documented association with colon cancer^[17], lending credibility to our questionnaire data.

In conclusion, this moderately large population-based case-control study did not detect a direct association between variants in the *UGT1A6* and *COX2* genes and risk of colon cancer nor an effect modification by NSAIDs. The results of our study are in line with the two studies of colon cancer showing null results^[12,13]. Taken together with the studies showing an association with polyps^[10,11], our results suggest genetic variation of *UGT1A6* may affect the early stages of colon tumorigenesis, but has little influence on the progression from adenomatous polyps to colon cancer, although we are unable to test that hypothesis directly.

Table 2 Odds ratios for individual SNPs and SNP by NSAID use interactions

SNP	Case/control	Crude		Adjusted		Stratified by NSAID use		
		OR (95% CI)	P ¹	OR (95% CI)	P ²	Regular	None	P ³
COX2								
rs2066826			0.45		0.34			0.41
GG	314/370	Ref		Ref		Ref	Ref	
AG	98/99	1.17 (0.85, 1.60)		1.23 (0.88, 1.72)		1.05 (0.68, 2.64)	1.52 (0.82, 2.83)	
AA	8/12	0.79 (0.32, 1.95)		1.06 (0.41, 2.73)		0.52 (0.10, 2.64)	1.96 (0.30, 12.62)	
rs2206593			0.049		0.25			0.47
GG	382/417	Ref		Ref		Ref	Ref	
AG	39/63	0.68 (0.44, 1.03)		0.69 (0.44, 1.07)		0.64 (0.36, 1.13)	0.89 (0.42, 1.90)	
AA	0/2	----		----		----	----	
rs5277			0.97		0.58			0.76
CC	310/353	Ref		Ref		Ref	Ref	
CG	104/119	1.00 (0.73, 1.35)		0.90 (0.65, 1.25)		0.90 (0.59, 1.36)	0.86 (0.48, 1.54)	
GG	7/8	1.00 (0.36, 2.78)		0.80 (0.27, 2.36)		0.52 (0.09, 2.95)	1.85 (0.32, 10.56)	
rs689470			0.87		0.79			> 0.99
GG	380/440	Ref		Ref		Ref	Ref	
AG	35/36	1.13 (0.69, 1.83)		1.15 (0.66, 2.02)		1.13 (0.54, 2.35)	1.59 (0.60, 4.22)	
AA	4/4	1.16 (0.29, 4.66)		1.60 (0.26, 9.70)		----	2.38 (0.13, 43.43)	
rs4648310			0.95		0.67			0.50
AA	405/462	Ref		Ref		Ref	Ref	
AG	17/19	1.08 (0.55, 2.12)		1.07 (0.53, 2.19)		1.25 (0.48, 3.23)	0.69 (0.21, 2.27)	
GG	0/1	----		----		----	----	
rs5275			0.34		0.51			0.89
AA	176/216	Ref		Ref		Ref	Ref	
AG	189/199	1.17 (0.88, 1.55)		1.17 (0.87, 1.58)		1.14 (0.78, 1.67)	1.04 (0.60, 1.79)	
GG	56/65	1.06 (0.70, 1.59)		1.22 (0.79, 1.88)		0.98 (0.57, 1.71)	1.79 (0.78, 4.12)	
rs689466			0.46		0.69			0.99
AA	275/297	Ref		Ref		Ref	Ref	
AG	138/168	0.89 (0.67, 1.17)		0.86 (0.64, 1.15)		0.91 (0.62, 1.33)	0.83 (0.48, 1.42)	
GG	9/15	0.65 (0.28, 1.51)		0.65 (0.26, 1.60)		0.75 (0.26, 2.17)	0.69 (0.11, 4.45)	
rs20417			0.41		0.20			0.44
GG	291/343	Ref		Ref		Ref	Ref	
CG	119/121	1.16 (0.86, 1.56)		1.25 (0.91, 1.71)		1.17 (0.78, 1.74)	1.39 (0.78, 2.47)	
CC	11/15	0.86 (0.39, 1.91)		0.97 (0.43, 2.20)		0.46 (0.14, 1.54)	3.12 (0.57, 17.15)	
rs2745557			0.61		0.41			0.18
GG	287/321	Ref		Ref		Ref	Ref	
AG	120/141	0.95 (0.71, 1.27)		0.93 (0.69, 1.27)		1.04 (0.70, 1.54)	0.77 (0.43, 1.38)	
AA	13/19	0.76 (0.37, 1.58)		1.01 (0.48, 2.14)		1.49 (0.60, 3.67)	0.34 (0.07, 1.68)	
UGT1A6								
rs1105879			0.46		0.28			0.93
AA	191/206	Ref		Ref		Ref	Ref	
AC	167/209	0.86 (0.65, 1.14)		0.84 (0.63, 1.14)		0.84 (0.57, 1.23)	0.86 (0.50, 1.48)	
CC	64/66	1.05 (0.70, 1.55)		1.07 (0.71, 1.64)		1.20 (0.70, 2.06)	1.07 (0.50, 2.32)	
rs2070959			0.21		0.21			0.93
AA	208/207	Ref		Ref		Ref	Ref	
AG	154/206	0.78 (0.59, 1.03)		0.78 (0.58, 1.04)		0.76 (0.52, 1.12)	0.82 (0.48, 1.42)	
GG	59/57	1.08 (0.72, 1.63)		1.11 (0.72, 1.72)		1.26 (0.72, 2.23)	1.04 (0.47, 2.29)	

¹P-value of SNP in best fitting genetic model in the unadjusted logistic regression; ²P-value of SNP in best fitting genetic model in the full multivariate logistic regression; ³P-value of interaction of SNP in best fitting genetic model with regular NSAID use in the logistic regression.

COMMENTS

Background

Colon cancer accounts for almost 150 000 cancer cases and 50 000 deaths in the United States alone. Non-steroidal anti-inflammatory drug (NSAID) use has been well known to reduce the risk of colon cancer.

Research frontiers

It is unclear how individual variation influences the protective effect of NSAIDs. Cyclooxygenase-2 (COX2) and uridine diphosphate glucuronosyltransferase 1A6 (UGT1A6) are two genes that have been proposed to modify the effect of NSAIDs on colon cancer risk. COX2 is a direct target of NSAIDs and UGT1A6 variations have been shown to alter the metabolism of aspirin, a common NSAID.

Innovations and breakthroughs

This study has provided further insight into the role of the COX2 and UGT1A6 genes in colon cancer risk.

Applications

Since genetic variation often accounts for differences in an individual's response to preventive or therapeutic drugs, it is important to understand the relationship between genes, the drugs and the intended outcome. NSAIDs have been suggested as a chemopreventive agent for individuals at high risk of colon cancer. It is thus important to identify those individuals who would most benefit from the use of NSAIDs. This study found that, while other genes may predict enhanced benefit of NSAID use for colon cancer prevention, COX2 and UGT1A6 do not.

Terminology

COX2 and UGT1A6 are two genes involved in NSAID metabolism. Since NSAIDs, including aspirin and ibuprofen, are known to be protective for colon cancer, it has been hypothesized that these genes would influence and individual's response to NSAID use with respect to colon cancer risk.

Peer review

The authors examined the association of COX2 and UGT1A6 polymorphisms

and risk of colon cancer. They also evaluated the effect of variations in these genes on the protective effect of NSAIDs. They did not find an association with any variant examined and risk of colon cancer nor did they find these variants altered NSAID effects. This study gives further evidence that these genes are not directly involved in colon cancer carcinogenesis.

REFERENCES

- 1 Eberhart CE, Coffey RJ, Radhika A, Giardiello FM, Ferrenbach S, DuBois RN. Up-regulation of cyclooxygenase 2 gene expression in human colorectal adenomas and adenocarcinomas. *Gastroenterology* 1994; **107**: 1183-1188
- 2 Williams CS, Mann M, DuBois RN. The role of cyclooxygenases in inflammation, cancer, and development. *Oncogene* 1999; **18**: 7908-7916
- 3 Bosetti C, Gallus S, La Vecchia C. Aspirin and cancer risk: an updated quantitative review to 2005. *Cancer Causes Control* 2006; **17**: 871-888
- 4 Goodman JE, Bowman ED, Chanock SJ, Alberg AJ, Harris CC. Arachidonate lipoxygenase (ALOX) and cyclooxygenase (COX) polymorphisms and colon cancer risk. *Carcinogenesis* 2004; **25**: 2467-2472
- 5 Siezen CL, Bueno-de-Mesquita HB, Peeters PH, Kram NR, van Doeselaar M, van Kranen HJ. Polymorphisms in the genes involved in the arachidonic acid-pathway, fish consumption and the risk of colorectal cancer. *Int J Cancer* 2006; **119**: 297-303
- 6 Ulrich CM, Whitton J, Yu JH, Sibert J, Sparks R, Potter JD, Bigler J. PTGS2 (COX-2) -765G > C promoter variant reduces risk of colorectal adenoma among nonusers of nonsteroidal anti-inflammatory drugs. *Cancer Epidemiol Biomarkers Prev* 2005; **14**: 616-619
- 7 Cox DG, Pontes C, Guino E, Navarro M, Osorio A, Canzian F, Moreno V. Polymorphisms in prostaglandin synthase 2/cyclooxygenase 2 (PTGS2/COX2) and risk of colorectal cancer. *Br J Cancer* 2004; **91**: 339-343
- 8 Wiesner GL, Platzer P, Buxbaum S, Lewis S, MacMillen M, Olechnowicz J, Willis J, Chakravarti A, Elston RC, Markowitz SD. Testing for colon neoplasia susceptibility variants at the human COX2 locus. *J Natl Cancer Inst* 2001; **93**: 635-639
- 9 Ciotti M, Marrone A, Potter C, Owens IS. Genetic polymorphism in the human UGT1A6 (planar phenol) UDP-glucuronosyltransferase: pharmacological implications. *Pharmacogenetics* 1997; **7**: 485-495
- 10 Bigler J, Whitton J, Lampe JW, Fosdick L, Bostick RM, Potter JD. CYP2C9 and UGT1A6 genotypes modulate the protective effect of aspirin on colon adenoma risk. *Cancer Res* 2001; **61**: 3566-3569
- 11 Chan AT, Tranah GJ, Giovannucci EL, Hunter DJ, Fuchs CS. Genetic variants in the UGT1A6 enzyme, aspirin use, and the risk of colorectal adenoma. *J Natl Cancer Inst* 2005; **97**: 457-460
- 12 McGreavey LE, Turner F, Smith G, Boylan K, Timothy Bishop D, Forman D, Roland Wolf C, Barrett JH. No evidence that polymorphisms in CYP2C8, CYP2C9, UGT1A6, PPARGdelta and PPARGgamma act as modifiers of the protective effect of regular NSAID use on the risk of colorectal carcinoma. *Pharmacogenet Genomics* 2005; **15**: 713-721
- 13 Samowitz WS, Wolff RK, Curtin K, Sweeney C, Ma KN, Andersen K, Levin TR, Slattery ML. Interactions between CYP2C9 and UGT1A6 polymorphisms and nonsteroidal anti-inflammatory drugs in colorectal cancer prevention. *Clin Gastroenterol Hepatol* 2006; **4**: 894-901
- 14 Hubner RA, Muir KR, Liu JF, Logan RF, Grainge M, Armitage N, Shepherd V, Popat S, Houlston RS. Genetic variants of UGT1A6 influence risk of colorectal adenoma recurrence. *Clin Cancer Res* 2006; **12**: 6585-6589
- 15 Li L, Plummer SJ, Thompson CL, Tucker TC, Casey G. Association between phosphatidylinositol 3-kinase regulatory subunit p85alpha Met326Ile genetic polymorphism and colon cancer risk. *Clin Cancer Res* 2008; **14**: 633-637
- 16 Shahedi K, Lindström S, Zheng SL, Wiklund F, Adolfsson J, Sun J, Augustsson-Bälter K, Chang BL, Adami HO, Liu W, Grönberg H, Xu J. Genetic variation in the COX-2 gene and the association with prostate cancer risk. *Int J Cancer* 2006; **119**: 668-672
- 17 Potter JD. Colorectal cancer: molecules and populations. *J Natl Cancer Inst* 1999; **91**: 916-932

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