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Mendelian randomization studies of cancer risk: a literature review

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Abstract

Purpose of review—In this paper, we summarize prior studies that have used Mendelian Randomization (MR) methods to study the effects of exposures, lifestyle factors, physical traits, and/or biomarkers on cancer risk in humans. Many such risk factors have been associated with cancer risk in observational studies, and the MR approach can be used to provide evidence as to whether these associations represent causal relationships. MR methods require a risk factor of interest to have known genetic determinants that can be used as proxies for the risk factor (i.e., “instrumental variables” or IVs), and these can be used to obtain an effect estimate that, under certain assumptions, is not prone to bias caused by unobserved confounding or reverse causality. This review seeks to describe how MR studies have contributed to our understanding of cancer causation.

Recent findings—We searched the published literature and identified 76 MR studies of cancer risk published prior to October 31, 2017. Risk factors commonly studied included alcohol consumption, Vitamin D, anthropometric traits, telomere length, lipid traits, glycemic traits, and markers of inflammation. Risk factors showing compelling evidence of a causal association with risk for at least one cancer type include alcohol consumption (for head/neck and colorectal), adult body mass index (increases risk for multiple cancers, but decreases risk for breast), height (increases risk for breast, colorectal, and lung; decreases risk for esophageal), telomere length (increases risk for lung adenocarcinoma, melanoma, renal cell carcinoma, glioma, B-cell lymphoma subtypes, chronic lymphocytic leukemia, and neuroblastoma), and hormonal factors (affects risk for sex-steroid sensitive cancers).

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Compliance with Ethical Standards

Conflict of Interest

Brandon L. Pierce, Peter Kraft, and Chenan Zhang declare no conflicts of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Summary—This review highlights alcohol consumption, body mass index, height, telomere length, and the hormonal exposures as factors likely to contribute to cancer causation. This review also highlights the need to study specific cancer types, ideally subtypes, as the effects of risk factors can be heterogeneous across cancer types. As consortia-based genome-wide association studies increase in sample size and analytical methods for MR continue to become more sophisticated, MR will become an increasingly powerful tool for understanding cancer causation.

Keywords

Mendelian randomization; causal inference; cancer risk; instrumental variable

INTRODUCTION

There are many risk factors with well-established associations with cancer risk, but for most, it is unclear whether a causal relationship underlies the observed association. While cancer prevention trials (i.e., randomized controlled trials) have been used to estimate the causal effects of modulating several specific risk factors (e.g., aspirin and chronic inflammation), it is not feasible to study most risk factors in this way due to lack of effective interventions, high costs, and/or ethical reasons.

For a subset of cancer-associated risk factors, it is possible to gain insights into causality using Mendelian randomization (MR). MR is a method used to test or estimate a causal effect of an exposure on a disease outcome using known genetic determinants of the exposure. These genetic determinants are used as instrumental variables (IVs) to determine whether an observed exposure–disease association may be due to a causal relationship, as opposed to unobserved confounding or reverse causation.

A valid MR analysis requires that the IVs are: 1) associated with the exposure, 2) independent of factors that confound the exposure–outcome relationship; and 3) independent of the outcome, given the exposure and confounders of the exposure–outcome relationship. These assumptions are coded on the following directed acyclic graph (Figure 1) showing an exposure (X), and outcome (Y), and multiple valid IVs ($G_1, G_2, \dots, G_n$). To make causal inference for the effect of X on Y we must additionally assume that intervening on X cannot affect the distributions of U , Y , or G , conditional on X as set by the intervention [1]. Inference regarding the causal association between X and Y depends on these assumptions; violations of these assumptions can lead to both false positives or false negatives [2, 3] (see Discussion).

MR has become commonplace in genetic epidemiology, with >1,000 MR studies published since 2005. Most early MR studies were conducted using individual-level data on SNPs, risk factors, and outcomes. These studies used either single SNPs or scores composed of multiple SNP scores as IVs for the exposure. It is now common to use two-sample approaches for MR [4] in which information on the SNP–exposure associations and SNP–outcome associations are obtained from different datasets, and these analyses often rely on summary statistics [5] from genome-wide association (GWA) studies. In this review, we summarize MR studies investigating the potential effects of risk factors on cancer risk. We also discuss

methodological developments in the area of Mendelian randomization, as well as future directions for MR studies of cancer risk.

METHODS FOR LITERATURE REVIEW

To identify primary research studies using MR to study cancer risk, we conducted a PubMed Search using the search terms “Mendelian randomization” and “cancer” (also using the alternative spelling “Mendelian Randomisation”), restricting to English language articles in peer-reviewed journals. We are aware of several studies that do not use the MR terminology but employ similar methods and draw causal conclusions; therefore, we used the search terms “polygenic risk score” (OR “polygenic score” OR “genetic risk score” OR “genetic score” OR “allele score” OR “allele sum” OR “weighted linear combination”) AND “cancer” to identify papers conducting MR-like analyses without explicitly using MR terminology. Our search reflects studies indexed in PubMed as of October 31, 2017. We read the titles and abstracts of all papers to determine if they were eligible to be included in this review. We classified the MR studies identified according to the type of risk factor studied. All studies we identified are shown in Table 1. Evidence of an effect was defined as a MR P-value <0.05.

RESULTS

Diet and Lifestyle Factors

Alcohol Consumption—We identified three MR studies examining the effect of alcohol consumption on cancer risk, and all three used a variant at ALDH2 as an IV. These studies provided evidence of an effect of alcohol consumption on increased risk for esophageal [6], head and neck [7], and colorectal cancer [8].

Vitamins D and B12—We identified five MR studies of vitamin D and cancer risk. Most used a set of 3–4 SNPs that are known to associate with circulating vitamin D as IVs, but one study used 8–12 for constructing polygenic scores for tanning, skin color, and freckling as a proxy for vitamin D exposure [9]. These studies found no evidence for a causal relationship between vitamin D and colorectal [10] or breast cancer [11]. A large multi-cancer MR study provided no evidence for a causal effect of MR on risk for prostate, breast, ovarian, colorectal, or lung cancer [12]. However, evidence of a causal relationship between low vitamin D and increased risk was reported for prostate cancer [9] and ovarian cancer [13]. There has been a single study of plasma vitamin B(12) (cobalamin) and total transcobalamin, which focused on prostate cancer [14]; but this study provided no evidence of a causal relationship.

Fatty Acids—Three MR studies estimated the effect of fatty acid intake on cancer risk, using a set of 1–5 SNPs that predict fatty acid concentrations in blood. Khankarai, *et al.* found no evidence of an overall effect of polyunsaturated fatty acids (PUFA) on prostate cancer risk; however, a potential association for linoleic, alpha-linolenic, and long chain PUFAs was observed among subgroups defined by age [15]. Wang, *et al.* reported evidence of an effect of increased PUFA on increased lung cancer risk [16]. May-Wilson, *et al.* reported that oleic and palmitoleic MUFAs (monounsaturated FAs) and linoleic PUFA

reduced colorectal cancer risk, while arachidonic PUFA and steric saturated FAs increased colorectal cancer risk [17].

Other dietary factors—Other dietary factors studied using MR include a study of coffee consumption and prostate cancer [18] and studies of the effect of milk consumption on renal cell carcinoma [19] and overall cancer mortality [20]. In these studies, no evidence of causal relationship was reported.

Anthropometric traits

BMI/obesity—We identified 15 MR studies of BMI and cancer risk. These studies used between 1 and 84 SNPs as IVs for BMI. Higher BMI was reported to be associated with increased risk for colorectal [21–23]; ovarian [22], particularly non-high grade serous [24]; lung [22], including squamous and small cell carcinoma [25, 26]; endometrial [27, 28]; kidney [29]; gastric [30]; pancreatic [31]; and esophageal cancer [32]. Two studies provided evidence of a causal relationship between high BMI and decreased breast cancer risk [22, 33]. A single study provided evidence of an effect of high BMI on decreased risk for lung cancer [29], but this study was based on a single SNP/IV. No association was shown for prostate cancer [34] or for an “all cancer” phenotype [35].

Height—We identified six MR studies of height and cancer risk, and these studies used up to 567 SNPs as IVs for height. Evidence of a causal relationship between increasing height and cancer risk was reported for breast [36], colorectal [37, 38], and lung cancer [38]. Evidence of a protective effect of height on esophageal adenocarcinoma and Barrett’s esophagus was also reported [39]. For prostate and pancreatic cancer, no evidence of a causal relationship was observed [34, 31].

Other anthropometric traits—We identified five MR studies that examined the effect of waist to hip ratio (WHR) on cancer risk. For colorectal cancer, results for WHR were consistent with the BMI results, with both increasing risk [23]. However, studies of endometrial [27], breast [22], pancreatic [31], and lung [26] cancer do not show clear evidence of causal effect. In these studies, results for WHR were often directionally consistent with BMI, suggesting that lack of statistical significance could potentially be due to low power (i.e., weak IVs). Several MR studies also examined birthweight and childhood BMI [22, 23], with one providing evidence that high childhood BMI decreases breast cancer risk [22].

Telomere length

We identified 13 MR studies of telomere length (TL) and cancer risk, and these studies used between 3 and 16 SNPs that predict leukocyte TL as IVs. These studies provided compelling evidence that longer telomeres increase risk for several cancer types, including lung adenocarcinoma [40–42], melanoma [43, 42], renal cell carcinoma [44], glioma [45], B-cell lymphoma subtypes [46], chronic lymphocytic leukemia [47], as well as neuroblastoma and other childhood cancers [48]. There was also MR evidence that long TL increases breast cancer risk among Chinese women [49], but this finding has not yet been observed in studies of women of European ancestry [40, 50]. A recent paper reported that both longer and

shorter telomere length increase risk for HBV-related HCC (i.e., U-shared association) [51]. A recent meta-analysis of MR studies of TL summarized many of the effects reported above [50]. There are cancer types for which MR studies have not identified such an association, including gastric cancer [52], as well as prostate, colorectal, ovarian cancer [40, 50]. This lack of association could be due to either lack of a true effect of TL on those cancer types, a weak effect not detectable using current sample sizes, or poor instruments for tissue-specific TL (IVs obtained from studies of TL in blood cells).

Lipid Traits

We identified eight MR studies of lipid traits and cancer risk, and these studies used between 1 and 67 SNPs as IVs for one or more of the following blood lipid phenotypes: total cholesterol (TC), low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), and triglycerides (TG). Among four studies which used “any cancer” as an outcome, no association was detected for TC [53] or LDL [54]. However, one study reported a relationship between reduced HDL and increased cancer risk [55], while another identified an inverse relationship for both LDL and TG with cancer risk that the authors attributed to pleiotropy [56]. Rodriguez-Broadbent et al. [57] reported that higher TG increases colorectal cancer risk (but not LDL or HDL), while Bull et al. reported no association for LDL, HDL, or TG with prostate cancer risk [58]. Carreras-Torres and colleagues observed no effect of various lipid traits on pancreatic cancer [31], but found evidence of an effect of high LDL on decreased lung cancer risk [26].

Glycemic traits

We identified six MR studies of glycemic traits. Three of these studies focused on adiponectin, with two studies reporting no association with colorectal cancer risk [59, 60] and one reporting a positive association with colorectal cancer risk and an inverse association with lung cancer risk [61]. Neale, *et al.* found evidence that higher fasting insulin and post-challenge insulin levels increased endometrial cancer risk, while fasting glucose did not [28]. Studies of pancreatic cancer and lung cancer from Carreras-Torres, *et al.* found evidence that higher fasting insulin increases risk for pancreatic [31] and overall lung cancer [26].

Inflammation and infection

We identified five studies of the effect of inflammatory markers/processes on cancer risk. Among these studies, higher IL-10 was linked to increased risk for HPV- and EBV-associated cancers [62] as well as digestive cancers [63], while high IL-6 was linked to liver cancer [64]. Studies of C-reactive protein (CRP) suggested that increased CRP increases colorectal cancer risk [65], but did not show an association with overall cancer [66]. A single MR study examined the effect of malarial infection on endemic Burkitt Lymphoma and found evidence that infection increases risk [67].

Hormonal factors

We identified four studies of the effects of hormonal factors on hormone-related cancers. Evidence suggested that later age at menopause increases breast cancer risk [68], while later

age at menarche reduces risk of breast and endometrial cancer [69]. Similarly, MR studies suggested that later age at puberty onset decreases prostate cancer risk [70, 69]. One MR study of circulating estradiol found that high levels increase endometrial cancer risk [71].

Other biomarkers

A variety of circulating biomarkers have been investigated in MR studies of cancer risk, including circulating microRNA miR-34b [72], plasma Fetuin-A [73], cardiovascular disease marker YKL-40 [74], insulin-like growth factors [75], transforming growth factor beta (TGF-beta1) [76], homocysteine [77], sRAGE (soluble form of receptor for advanced glycation end products) [78], and plasma urate [79]. These studies have linked several of these biomarkers to cancer risk (see Table 1).

DISCUSSION

Summary

This review of MR studies of cancer risk highlights a number of risk factors likely to have causal relationships with multiple cancer types. The MR-estimated effects of alcohol consumption and obesity on increased risk for multiple cancer types are largely consistent with observational studies. In contrast, the MR evidence supporting an effect of Vitamin D on cancer risk is rather weak, despite associations observed in prior observational studies [80]. The estimated effect of longer TL on increased risk for multiple cancers is contradictory to numerous prior observational studies which suggested that short TL increases cancer risk. This highlights the limitations of these prior studies, including non-prospective TL measurement. [81, 82]. This review also highlights the need to study specific cancer types, ideally subtypes, as the effects of risk factors can be heterogeneous across cancer types. Studying an “all cancer” phenotype will mask such heterogeneous effects.

Statistical Power

The primary determinants of power for MR studies are sample size, instrument strength, and effect size (of the risk factor on cancer risk) [83–85]. Using a larger number of SNPs in the context of a SNP/allele score can increase IV strength, thereby increasing power/precision [83, 86, 87], although most genetic IVs explain <5% of the variability of the risk factor. Very recent MR studies tend to use larger sample sizes and more SNPs/IVs (Table 1), and this is because the sample sizes of cancer GWA studies are increasing (i.e., the typical data source for MR studies) and new SNPs that affect risk factors of interest are being discovered over time, providing more IVs for MR. Consequently, recent studies tend to provide stronger evidence, in terms of both the precision of MR estimates, as well as the number of SNP/IVs that can potentially provide complementary evidence supporting an effect or lack thereof. For some MR studies, very weak effects of risk factors on cancer may be present (a parameter which investigators cannot control), so we must keep in mind that a null result does not rule out the existence of an effect too weak to be detected.

Study Design

Many recent MR studies use two-sample approaches [4] and MR methods that utilize SNP summary statistics [5], which can enable highly-efficient MR study designs while boosting

sample size. For two-sample approaches, SNP-risk factor associations and SNP-cancer associations are obtained from different datasets (ideally from the same source population). This allows one to use large samples from existing GWA studies, rather than collect risk factor and outcome data on a single sample. Furthermore, MR methods that use summary statistics enable the use of meta-analysis of results from multiple individual studies and avoid the need for individual-level data. These developments enable larger, more powerful studies to be conducted in a highly efficient manner for large numbers of cancer risk factors. However, bias can arise in the two-sample setting when the samples share common participants [88]

Violations of MR assumptions and sensitivity analyses

Many of the very recent MR studies reported here have used newly-developed approaches for sensitivity analyses that assess potential violations of MR assumptions (described in the introduction) using SNP summary statistics. This includes Egger regression [89] as well as weighted median estimators [90] for obtaining MR estimates that are robust to pleiotropy (under some assumptions). In addition, methods have been developed for individual-level (i.e., one-sample) data that estimate effects for multiple interrelated exposures and allow for analysis of mediation [91, 92]. While MR research is currently shifting to two-sample approaches that use summary statistics to increase power, individual-level one-sample data may prove useful for mediation and multivariate analyses, as well as validation of MR assumptions [93]. However, weak IV bias is a more prominent concern for one-sample as compared to two-sample MR analyses [5].

Violations of MR assumptions may be of particular concern for MR studies of the effect of molecular/cellular phenotypes on cancer risk. Most recent MR studies use IVs with well-validated associations with the risk factor in interest (X). However, this assumption might be of concern with “transcriptome-wide association studies,” where X is (tissue-specific) gene expression. In such studies, liberal significance thresholds and small sample sizes for identifying eQTLs (expression quantitative trait loci) may lead to false positive associations between the IVs ($G_1, \dots, G_n$) and X . [94–96]. Absence of a true association between the IV(s) and X makes any inference about the X - Y relationship impossible. In addition, the “exclusion restriction” assumption—that the genetic IV(s) have no association with Y conditional on X —can be violated by pleiotropy or co-localization due to linkage disequilibrium. Under pleiotropy, the IV(s) is/are causally related to Y through a causal pathway that is not mediated by X . Under co-localization, the IV(s) may not be causally related to Y (except perhaps through X), but they are in linkage disequilibrium with other variants that are causally related to Y through a mechanism that does not involve X . This is also a concern for transcriptome-wide association studies, as eQTLs for different genes often co-localize. Methods to alleviate concerns regarding violations of MR assumptions are currently an active area of investigation [3].

Future Directions

In the coming years, MR is likely to become an increasingly powerful tool for understanding cancer causation. GWA studies of cancer risk factors will identify new variants that can be used as IVs, increasing power for MR and enabling additional risk factors to be studied.

GWA studies of cancer risk will continue to increase in size and focus on cancer subtypes, and the availability of summary statistics from these studies will enable powerful MR studies that are subtype-specific. Furthermore, tissue- and cell type-specific studies of molecular QTLs (quantitative trait loci), such as expression QTLs, DNA methylation QTLs, and protein QTLs, will enable genetic prediction of tissue specific molecular phenotypes, enabling MR-like studies of cell-type specific molecular phenotypes [94–98].

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Figure 1.

A directed acyclic graph showing a scenario in which multiple genetic variants ($G_1, G_2, \dots, G_n$) are valid IVs for estimating the effect of a risk factor (X) on a health outcome (Y), such as cancer status. The observational association between X and Y is potentially confounded by both observed and unobserved factors, represented by U .

Table 1

Summary of Mendelian randomization studies of cancer risk published prior to October 31, 2017.

Exposure	Cancer Type(s)	SNPs/IVs	Result ¹	Sample Size	Lead Author (Year)	PMID
<i>Dietary/lifestyle</i>						
Alcohol consumption	Esophageal	1 variant	Alcohol consumption increases risk	905 cases, 2078 controls	Lewis (2005)	16103445
Alcohol consumption	Head and neck	1 variant	Alcohol consumption increases risk	945 cases, 2,917 controls	Boccia (2009)	19124505
Alcohol consumption	Colorectal neoplasia	1 variant	Alcohol increases risk	1960 cases, 3163 controls	Wang (2011)	21114754
Vitamin D	Colorectal cancer	4 SNPs	No association	2,001 cases, 2,237 controls	Theodoratou (2012)	22701574
Vitamin D	Prostate	8–12 SNPs	Less sun/vitamin D increases risk	1,136 cases, 1,791 controls	Bonilla (2013)	23441100
Vitamin D	Ovarian cancer	3 SNPs	Lower vitamin D concentrations increases risk of ovarian cancer risk	10,065 cases, 21,654 controls	Ong (2016)	27594614
Vitamin D	Breast cancer	4 SNPs	No association	1,657 cases, 2029 controls	Wang (2017)	28891071
Vitamin D	Breast, lung, colorectal, ovarian, pancreatic, and neuroblastoma	4 SNPs	No association	70,563 cases, 84,418 controls	Dimitrakopoulou (2017)	29089348
Vitamin B12	Prostate	2 SNPs	No association	913 cases, 895 controls	Collin (2011)	22199995
PUFAs	Prostate cancer	1–4 SNPs	No overall association. Results suggest ω -3 and ω -6 PUFAs have different effects in early- vs. late-onset disease	22,721 cases, 23,034 controls	Khankari (2016)	27490808
PUFAs	Lung cancer	1 SNP	PUFAs increase risk	2331 cases, 3077 controls, Replication: 13,945 cases, 12,939 controls	Wang (2017)	28968813
PUFAs, MUFAs, and SFAs	Colorectal cancer	1–5 SNPs	MUFAs (oleic and palmitoleic) and linoleic PUFAs reduce risk, PUFA (arachidonic) and SFA (stearic) increase risk	9254 cases, 18,386 controls	May-Wilson (2017)	28829991
Coffee consumption	Prostate cancer	2 SNPs	No association	2,131 cases, 2,591 controls	Taylor (2017)	27741566
Milk intake	Renal cell carcinoma	1 SNP	No association	915 cases, 2,346 controls	Timpson (2010)	20447925
Milk intake	All cancers (deaths)	1 SNP	No association	2822 cases among 82,964	Bergholdt (2017)	29071499
<i>Anthropometric</i>						
BMI	Lung, kidney and upper-aerodigestive cancers	1 SNP	Higher BMI decreases lung cancer risk, increases kidney cancer risk	4000 cases, 3000 controls	Brennan (2009)	19542184
BMI	Endometrial cancer	32 SNP	Higher BMI increases risk	1287 cases, 8273 controls	Nead (2015)*	26134033

Exposure	Cancer Type(s)	SNPs/IVs	Result ¹	Sample Size	Lead Author (Year)	PMID
BMI	Esophageal adenocarcinoma and Barrett's esophagus	29 SNPs	Higher BMI increases risk of esophageal adenocarcinoma and Barrett's esophagus	999 EAC cases, 2061 BE cases, 2169 controls	Thrift (2014)	25269698
BMI	Colorectal cancer	77 SNPs	Higher BMI increases risk in women	10,226 cases, 10,286 controls	Thrift (2015)	25976416
BMI, height	Prostate cancer	32 (BMI) 179 (height)	No association	20,848 cases, 20,214 controls	Davies (2015)	26387087
BMI	Any cancer and multiple cancer types	5 SNPs	No association	11,349 total cases among 108,812	Benn (2016)	27061578
BMI	Ovarian cancer	87 SNPs	Higher BMI increases risk of non-high grade serous ovarian cancers	14,047 cases, 23,003 controls	Dixon (2016) (20)	27401727
BMI, WHR, childhood obesity	Colorectal cancer	76 (BMI) 14 (WHR) 9 (child obesity)	Obesity increases risk	9254 cases, 18,386 controls	Jarvis (2016)	27336604
BMI	Lung cancer	97 SNPs	Higher BMI increases risk of squamous cell and small cell; decreases risk of overall lung cancer (in non-smokers)	16,572 cases, 21,480 controls	Carreras-Torres (2016)	27487993
BMI (adulthood), childhood BMI, birthweight, WHR	Breast, lung, colorectal, ovarian and prostate cancer	15 (child BMI) 77 (adult BMI) 7 (BW) 14 WHR	Higher childhood BMI decreases breast cancer risk; high adult BMI decreases breast cancer risk, increases ovarian, lung, and colorectal cancer.	51 537 cases, 61,600 controls	Gao (2016)	27427428
BMI, WHR	Endometrial cancer	77 (BMI) 47 (WHR)	High BMI (but not WHR) increases risk for endometrial cancer	6,609 cases, 37,926 controls	Painter (2016)	27550749
BMI	Breast cancer	84 SNPs	High BMI decreases breast cancer risk	46,325 cases, 42,482 controls replicated in 16,003 cases, 41,335 controls	Guo (2016)	27551723
BMI	Gastric cancer	37 SNPs	High BMI increases risk	26,31 cases, 4373 controls	Mao (2017)	28635950
BMI, WHR	Different histological types of lung cancer	73 (BMI) 32 (WHR)	Higher BMI increases risk for squamous cell and small cell cancer, not adenocarcinoma.	29,266 cases, 56,450 controls	Carreras-Torres (2017)*	28594918
BMI, WHR, height	Pancreatic cancer	96 (BMI) 567 (height) 34 (WHR)	Higher BMI increases risk	7,110 cases, 7,264 controls	Carreras-Torres (2017)*	28954281
Height	Esophageal adenocarcinoma and Barrett's esophagus	243 SNPs	Greater height reduces risk of esophageal adenocarcinoma and Barrett's esophagus	3,060 cases, 2,169 controls	Thrift (2014)	24530603
Height	Colorectal cancer	696 SNPs	Greater height increases risk in women	10,226 cases, 10,286 controls	Thrift (2015)	25997436
Height	Breast cancer	168 SNPs	Greater height increases risk	46,325 cases, 42,482 controls, replicated in 16,003 cases, 41,335 controls	Zhang (2015)	26296642

Exposure	Cancer Type(s)	SNPs/IVs	Result ¹	Sample Size	Lead Author (Year)	PMID
Height	Colorectal, lung, prostate	423 SNPs	Greater height increases risk of colorectal and lung cancer	47,800 cases, 81,353 controls	Khankari (2016)	27598322
Telomere length						
Telomere length	Melanoma	7 SNPs	Longer telomere length increases risk	11,108 cases, 13,933 controls	Iles (2014)	25231748
Telomere length	Lung cancer	7 SNPs	Longer telomere length increases risk among never-smoking women	5,457 cases, 4,493 controls	Machiela (2015)	25516442
Telomere length	Gastric cancer	8 SNPs	No association	1,136 cases, 1,012 controls	Du (2015)	26025910
Telomere length	Breast, lung, colorectal, ovarian, prostate	9 SNPs	Longer telomere length increases risk for lung adenocarcinoma	51,725 cases, 62,035 controls	Zhang (2015)	26138067
Telomere length	Glioma	8 SNPs	Longer telomere length increases risk	1,130 cases; 6,294 controls	Walsh (2015)	26646793
Telomere length	B-cell lymphoma subtypes	9 SNPs	Longer telomere length increases risk	10,102 cases, 9,562 controls	Machiela (2016)	27008888
Telomere Length	Chronic lymphocytic leukemia	8 SNPs	Longer telomere length increases risk	273 cases, 5,725 controls	Ojha (2016)	27197291
Telomere Length	Neuroblastoma and other childhood cancers	8 SNPs	Longer telomere length increases risk of neuroblastoma, osteosarcoma and leukemia.	1516 NB, 958 ALL, 660 osteosarcoma, 6892 controls	Walsh (2016)	27207662
Telomere length	Any cancer, 25 cancer types	3 SNPs	Longer telomere length increases risk of any cancer and specifically melanoma and lung	10,895 cases among 95,568 subjects	Rode (2016)	27498151
Telomere length	Breast cancer	6 SNPs	Longer telomere length increases risk	2,865 cases, 2,285 controls	Luu (2016)	27581250
Telomere length	35 cancer types	16 SNPs	Longer telomere length increases risk for several cancers	420,081 cases, 1,093,105 controls	Haycock (2017)	28241208
Telomere length	HBV-related hepatocellular carcinoma risk	9 SNPs	Longer and shorter telomere length increases risk in a U-shared manner	1538 HBV positive HCC cases, 1,465 controls	Cheng (2017)	28797893
Telomere length	Renal Cell Carcinoma	9 SNPs	Longer telomere length increases risk	10,784 cases and 20,406 controls	Machiela (2017)	28797570
Lipid traits						
TC	Any cancer	ApoE genotype	No association	199 cases, 2536 controls	Trompet (2009)	19889709
LDL	Any cancer	4 SNPs	No association	6816 cases in cohort of 70,179	Benn (2011)	21285406
HDL	Any cancer	1 variant	Reduced HDL increases risk	13,478 cases, 77,592 controls	Yang (2015)	25820350
LDL, HDL, TG	Prostate cancer	11 (LDL) 36 (HDL)	No association	22,249 cases, 22,133 controls	Bull (2016)	26992435

Exposure	Cancer Type(s)	SNPs/IVs	Result ¹	Sample Size	Lead Author (Year)	PMID
HDL, LDL, TG, TC	Colorectal cancer	15 (TG) 58 (HDL) 29 (LDL) 26(TG) 38 (TC)	Higher TG increases risk	9,254 cases, 18,386 controls	Rodriguez-Broadbent (2017)	28340513
LDL, TG	Any cancer (excluding skin cancer)	42 (LDL) 67 (TG)	LDL and TG inversely associated with risk (pleiotropy likely)	27,820 total subjects	He (2017)	28964830
HDL, LDL, TG, TC	Pancreatic cancer	70 (HDL) 54 (LDL) 39 (TG) 72 (TC)	No association	7110 cases, 7264 controls	Carreras-Torres (2017)*	28954281
HDL, LDL, TG, TC	Lung cancer subtypes	70 (HDL) 54 (LDL) 45 (TG) 65 (TC)	Higher LDL decreases risk of overall lung cancer	29,266 cases, 56,450 controls	Carreras-Torres (2017)*	28594918
Glycemic traits						
Adiponectin	Any cancer, multiple cancer types	1 SNP	Adiponectin reduces lung cancer risk, increases colorectal cancer risk	11,982 cases, 14,337 controls	Pei (2015)	25273172
Adiponectin	Colorectal cancer	19 SNPs	No association	7,020 cases, 7,631 controls	Song (2015)	25431318
Adiponectin	Colorectal cancer	8 SNPs	No association	1,253 cases, 1,627 controls	Nimpisch (2017)	28350647
T2D, FG, FI, 30mPCI	Endometrial cancer	49 (T2D) 36 (FG) 18 (FI) 17 (30mPCI)	Higher FI and 30mPCI increase risk, no association for T2D or FG	1,287 cases, 8,273 controls	Nead (2015)	26134033
FG, FI, 2hPGC, T2D	Pancreatic cancer	37 (FG) 17 (FI) 9 (2h PGC) 43 (T2D)	Higher FI increases risk, no association for T2D	7,110 cases, 7,264 controls	Carreras-Torres (2017)*	28954281
FI, FG, 2hPGC	Lung cancer subtypes	24 (FG) 11 (FI) 6 (2h PGC)	Higher FI increases risk of overall lung cancer	29,266 cases, 56,450 controls	Carreras-Torres (2017)*	28594918
Inflammation						
CRP	Any cancer	4 SNPs	No association	5921 cases among 46,618	Allin (2010)	20056955
CRP	Colorectal cancer	4 SNPs	Higher CRP increases risk	727 cases, 727 controls	Nimpisch (2015)	25043606
IL-6	Multiple cancer types	1 variant	Reduced IL-6 reduces risk of liver cancer	45,569 cases, 57,990 controls	Tian (2015)	26096712
IL-10	Digestive cancers	3 SNPs	Higher IL-10 increases risk of gastric cancer	Meta-analysis of 29,307 subjects	Niu (2016)	26886630

Exposure	Cancer Type(s)	SNPs/IVs	Result ¹	Sample Size	Lead Author (Year)	PMID
IL-10	HPV- and EBV-associated cancers	1 SNP	Higher IL-10 levels increases risk	5,390 cases, 5,780 controls	Qu (2016)	27022283
Malaria infection	Endemic Burkitt Lymphoma	6 variants	Malaria infection increases risk	202 cases, 624 controls	Legason (2017)	29033373
Hormonal						
Age of natural menopause	Breast cancer	56 SNPs	Later menopause increases risk	46,347 cases, 41,736 controls	Day (2015)	26414677
Estradiol	Endometrial cancer	1 SNP	Estradiol increases risk	6,608 cases, 37,925 controls	Thompson (2016)	26574572
Pubertal development	Prostate cancer	13 SNPs	Later puberty onset decreases risk	23,296 cases, 23,368 controls	Bonilla (2016)	27044414
Age at menarche	breast, endometrial, ovarian, prostate	375 SNPs	Later puberty onset reduces risk of breast, endometrial, and prostate cancer	>90,000 cases >115000 controls across 4 cancers	Day (2017)	28436984
Other Biomarkers						
miR-34b	Osteosarcoma	1 SNP	Lower plasma miR-34b increases risk	133 cases, 133 controls	Tian (2014)	24063968
Fetuin-A	Colorectal cancer	5 SNPs	No association	1,367 cases, 1,367 controls	Nimptsch (2015)	25611809
YKL-40	Multiple cancer types	1 SNP	No association	>12,000 cases in cohort of 96,099	Kjaergaard (2015)	26095694
Insulin-like growth factors and binding proteins	Prostate cancer	1 SNP	Higher IGF-II increases risk of high vs. low grade disease	22,992 cases, 22,936 controls	Bonilla (2016)	27225428
Transforming growth factor β 1	Hepatocellular carcinoma	1 SNP	Higher TGF- β 1 increases risk	2809 cases, 4802 controls	Lu (2016)	27835897
Homocysteine (blood)	Gastic cancer	1 SNP	Higher homocysteine levels increases risk	7566 cases, 10,640 controls	Xu (2016)	27196483
Circulating sRAGE	Any cancer	1 variant	Reduced circulating sRAGE increases risk	4346 cases, 4777 controls	Huang (2016)	26857858
Malaria infection	Endemic Burkitt Lymphoma	6 variants	Malaria infection increases risk	202 cases, 624 controls	Legason (2017)	29033373
Plasma urate	Any cancer risk	1 variant	Higher plasma urate increases risk	3243 cases in cohort of 86,210	Kobylecki (2017)	28428355

For some studies, the sample size includes the replication sample.

¹ Evidence of an effect was defined as a MR P-value <0.05.

² Indicates a study of multiple risk factors that is included in the table more than once

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Abbreviations: 2h PCG, 2-hour post-challenge glucose; 30mPCI, 30-minute post-challenge insulin; BMI, Body mass index; CRP, C-reactive protein; EIS, early insulin secretion; FG, fasting glucose; FI, fasting insulin; HDL, high-density lipoprotein cholesterol; IL, interleukin; LDL, low-density lipoprotein cholesterol; MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids; SFAs, saturated fatty acids; sRAGE, soluble form of receptor for advanced glycation end products; T2D, type 2 diabetes; TC, total cholesterol; TG, triglycerides; WHR, waist-to-hip ratio.