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Genetic Susceptibility to Cancer: the Role of Polymorphisms in Candidate Genes

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Abstract

Context—Continuing advances in genotyping technologies and the inclusion of DNA collection in observational studies have resulted in an increasing number of genetic association studies.

Objective—To evaluate the overall progress and contribution of candidate gene association studies to current understanding of the genetic susceptibility to cancer.

Data Sources—We systematically examined the results of meta- and pooled analyses for genetic polymorphisms and cancer risk published through March 2008.

Study Selection—We identified 161 meta- and pooled analyses, encompassing 18 cancer sites and 99 genes. Analyses had to meet the following criteria: 1) at least 500 cases, 2) cancer risk as outcome, 3) not focused on HLA genetic markers, and 4) published in English.

Data Extraction—Information on cancer site, gene name, variant, point estimate and 95% confidence interval, allelic frequency, number of studies and cases, tests of study heterogeneity and publication bias were extracted by one investigator and reviewed by other investigators.

Results—These 161 analyses evaluated 344 gene-variant/cancer associations and included on average 7.3 studies and 3,551 cases (range: 508–19,729 cases) per investigated association. The summary OR for 98 (28%) statistically significant associations (p-value <0.05) were further

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evaluated by estimating the false-positive report probability (FPRP) at a given prior probability and statistical power. At a prior probability level of 0.001 and statistical power to detect an OR of 1.5, thirteen gene-variant/cancer associations remained noteworthy (FPRP<0.2). Assuming a very low prior probability of 0.000001, similar to a probability assumed for a randomly selected SNP in a genome-wide association study, and statistical power to detect an OR of 1.5, four associations were considered noteworthy as denoted by a FPRP value < 0.2: 1) *GSTM1* null and bladder cancer (OR: 1.5, 95% CI: 1.3–1.6, p-value=1.9×10^{-14}), 2) *NAT2* slow acetylator and bladder cancer (OR: 1.46, 95% CI:1.26–1.68, p-value=2.5×10^{-7}), 3) *MTHFR* C677T and gastric cancer (OR: 1.52, 95% CI: 1.31–1.77, p-value=4.9×10^{-8}), and 4) *GSTM1* null and acute leukemia (OR: 1.20, 95% CI: 1.14–1.25, p-value=8.6×10^{-15}). When the OR used to determine statistical power was lowered to 1.2, two of the four noteworthy associations remained so: *GSTM1* null with bladder cancer and acute leukemia.

Conclusions—Phase II enzymes, which are key enzymes involved in the detoxification and excretion of carcinogens (and particularly deletion of *GSTM1*), were among the most consistent and highly significant associations.

Introduction

During the last few decades, extensive effort has been invested in identifying sources of genetic susceptibility to cancer. Both the International Human Genome Sequencing Project and the International HapMap Project have generated a very large amount of data on the location, quantity, type, and frequency of genetic variants in the human genome.[1–4] Facilitated by continuing technological advances that allow faster and cheaper genotyping results, a large and increasing number of observational studies investigating the association between variants in candidate genes and cancer risk have emerged.[5]

This growing number of studies prompted us to assess the overall contribution of these studies to our current understanding of the genetic susceptibility to cancer. One of the main criticisms of genetic epidemiology has been a lack of replication. There are several examples of studies exploring a previously published statistically significant finding for a genetic variant and failing to reproduce those findings, suggesting a large number of "false positive" reports.[6, 7] The size of these genetic association studies is also an important methodologic concern, which has prompted the utilization of meta- and pooled analyses to combine both statistically significant and non-significant results from individual studies and weighting these results by their precision (a function of sample size).[8–10]

To evaluate the overall progress of candidate gene association studies in identifying genetic variants associated with cancer risk, we systematically examined the results of all published meta- and pooled analyses on genetic polymorphisms and risk of cancer and report observed point estimates, 95% confidence intervals and p-values. Just as three parameters are needed to fully evaluate medical diagnostic tests (specificity, sensitivity, and predictive value of a positive test), three analogous parameters are needed to evaluate fully statistical tests of an association (e.g., between a genetic variant and cancer).[11] The p-value, the probability of obtaining a more extreme estimate than the one observed when the null hypothesis of no association (OR=1.0) is true, is analogous to 1 minus specificity (the likelihood of a test classifying a person as having the condition when they truly do not have the condition). Study power, the likelihood of detecting an association when one exists, is analogous to sensitivity (the likelihood of a test classifying someone as having the condition when they truly have it.) However it is well established in medical diagnostics that specificity and sensitivity can be high, but the predictive value of a positive test can still be low. This is because, if the condition is rare, positive diagnostic tests will mostly be false positives. This is less appreciated but also important in evaluating statistical tests of hypothesized associations: when the prior probability

is small that an exposure-disease hypothesis is true, then a statistically significant finding has a high chance of being a false positive. The false-positive report probability (FPRP) is defined as "the probability of no association given a statistically significant finding"[12] and is analogous to 1 minus the predictive value of a positive test. Thus, it is the FPRP rather than the p-value that answers the question of how probable the hypothesis, as tested, actually is.

In this paper, we evaluate the results of candidate gene-cancer association studies by presenting the p-value, power, and FPRP for all statistically significant associations as reported in meta- or pooled analyses. The FPRP is calculated from the statistical power of the test, the observed p-value, and a given prior probability for the association.[12] Because the prior probabilities are not easily determined, we calculated the FPRP for two levels of prior probabilities that are appropriate for a range of hypotheses, from low probabilities, appropriate for polymorphisms with known functional consequences in important candidate genes to very low probabilities, appropriate for randomly selected variants as used in a genome-wide association studies.

This review presents information on knowledge generated thus far by candidate gene association studies conducted to identify cancer susceptibility genes, and can also be used to direct future studies towards areas that remain unclear. Furthermore, results from this analysis provide information on the allelic frequency and expected effect size (strictly speaking, strength of association), which can be helpful for planning (genome-wide) association studies.

Methods

We identified all published meta- and pooled analyses that had evaluated the association between genetic polymorphisms and cancer risk in observational studies (i.e. case-control and nested case-control studies) through March 15, 2008. Meta- and pooled analyses are defined as tools that integrate results from individual studies that, alone, may not have sufficient power to detect a statistically significant association.[8–10] In brief, the data (i.e. crude and adjusted odds ratios) used for a meta-analysis are extracted from published results, whereas original datasets acquired from a number of independent studies are used for a pooled analysis. We performed a literature search of the PubMed database using the following search terms for our literature searches: the keyword combinations of "cancer + meta + gene," "cancer + pooled + gene," "cancer + consortium + gene," and the keyword combinations of "gene + cancer" and "genetic + cancer" restricted to publication type "meta-analysis." We considered 794 articles identified through our search methods, screened in detail 224 articles, for a final 161 articles included (Figure 1). Studies included in our review had to meet all of the following criteria: 1) included at least 500 cases combined from all summarized studies, 2) evaluated cancer risk as the outcome (analyses of survival, neoplastic markers or precursors, such as polyps, were excluded), 3) excluded HLA genetic markers, and 4) published in English. Furthermore, as this review focuses on common variants, meta-and pooled analysis of low-frequency, high-penetrance genes, such as *APC* and *BRCA1/2* were excluded. In addition, although statistically significant associations were reported for *HRAS1* polymorphisms and risks of breast and lung cancer, these associations have been questioned because of flawed genotyping methods. Thus, these are not reported with other statistically significant associations in Table 2. To avoid duplication of results from more than one meta- or pooled analysis addressing the same association, we selected the most recent one, which typically had the largest number of cases (sometimes smaller, due to stricter inclusion criteria). Data extracted from each meta- or pooled analysis included cancer site, gene name, genetic variant, point estimate (i.e. relative risk [RR] or odds ratio [OR]) and 95% confidence interval (CI), allelic frequency (if provided), number of studies, number of cases, test of study heterogeneity (e.g. Q test), and test of publication bias (including Begg's test, Egger's test and funnel plots). Random-effect estimates from meta-analyses were presented, unless only fixed-effect estimates were available.

We calculated summary estimates to describe published reports identified through our search. Differences in the number of studies and cases were evaluated by t-test. Associations were considered statistically significant if the reported p-value was <0.05 or if the 95 % CI excluded 1.0. P-values were determined by first calculating a Z-score based on the reported OR and 95% CI: Z-score= ln(OR)/[(ln(upper CI) − ln(lower CI))/(2*1.96)], and then comparing it to a normal distribution.

For each statistically significant association reported, we estimated the FPRP using methods described by Wacholder et al.[12] The FPRP value is determined by the p-value, the given prior probability for the association, and the statistical power of the test. Assigning a prior probability should be determined before obtaining results from a study and should be independent of any data used in the analysis. Prior probabilities are subjective and are influenced by both previous epidemiologic findings and experimental evidence about known functions of a genetic variant. Therefore, we chose to calculate FPRP values for two levels of prior probabilities: at a low prior that would be similar to what would be expected for a candidate gene (0.001) and at a very low prior that would be similar to what would be expected for a random SNP (0.000001), thus allowing the reader to evaluate the association using their own judgment about the supporting evidence for a given loci. Wacholder et al.[12] suggests estimating statistical power based on the ability to detect an OR of 1.5 (or its reciprocal 0.67=1/1.5 for ORs less than 1.0), with an alpha level equal to the observed p-value.[12] But given the recent attention to much smaller ORs this estimate may be too conservative, thus we have chosen to present results for both an OR of 1.5 and 1.2 (or its reciprocal 0.83=1/1.2). To evaluate whether an association is "noteworthy", we used a FPRP cut-off value of 0.2, as suggested by the authors[12] for summary analyses. Hence, FPRP values less than 0.2 indicate an association that remained robust for a given prior probability and will be referred to as noteworthy in the present paper. Statistical power and FPRP were computed by the Excel spreadsheet provided by Wacholder et al.[12]

Results

We identified 161 published meta- and pooled analyses, encompassing 18 cancer sites and 99 different genes. These 161 meta- and pooled analyses addressed 344 gene-variant/cancer associations with an average of 7.3 studies and 3,551 cases per investigated association (range: 508–19,729 cases). As expected, most analyses were conducted for common cancers, such as breast (n=119), prostate (n=42), and lung (n=34) cancer; there are very few evaluations of genetic associations in rare cancers, such as cervical and esophageal (Table 1). Across all cancer sites, variants in genes involved in DNA repair (e.g. *XRCC1* and *XPD*; n=81) and genes encoding metabolizing enzymes (e.g. cytochrome P450 (*CYP*) variants, n=58; or glutathione S-transferases (*GSTs*), n=31) were most often evaluated. Meta- and pooled analyses that found a statistically significant association evaluated a higher number of studies but included a lower number of cases than those that found a non-significant association (p=0.02 and p=0.05, respectively; Table 1). A complete table that lists all data extracted from each of the 344 associations identified in our search is included in the Appendix (Table A1).

Among the 344 gene-variant/cancer associations evaluated, the summary OR for 98 (28%) associations (excluding those involving *HRAS1*) were statistically significant (p-values between 0.05 to 8.6×10^{-15}; Figure 2a, 2b and Table 2). Thirty of these 98 associations were inverse for the variant, with a mean OR of 0.73 (median: 0.75; range: 0.32–0.92). The other 68 analyses reported ORs above 1.0, with a mean of 1.47 (median: 1.34; range 1.07–3.13). Statistically significant associations were found among 16 cancer sites, predominantly among studies investigating breast, glioma and lung cancer.

In order to evaluate the robustness of these findings, we calculated FPRP values at two levels of prior probabilities (Table 2). Among the 98 associations, 85 gene-variant/cancer associations

had FPRP values *higher* than 0.2 across the pre-specified prior probabilities (0.001 and 0.000001); these results are *not* considered noteworthy. For example, although the summary OR from the pooled analysis for *XRCC1 Arg399Gln* indicated a statistically significant positive association with risk of breast cancer (OR, 1.6; 95% CI, 1.1–2.3), FPRP values were higher than 0.2, at any of the two prior probabilities; hence, the finding is not considered noteworthy.

At a prior probability level of 0.001 and statistical power to detect an OR of 1.5, 13 gene-variant/cancer associations remained noteworthy (FPRP ≤0.2) for: 1) *MDM2* SNP309 and lung cancer (OR, 1.27; p-value=0.0002)[13]; 2) *XPD* Lys751Gln and lung cancer (OR, 1.30; p-value=0.0002)[14]; 3) *RNASEL* Asp541Glu and prostate cancer (OR, 1.27; p-value=0.0001)[15]; 4) *GSTT1* null and colorectal cancer (OR, 1.37; p-value=8.1×10^{-5})[16]; 5) *XRCC1* Arg399Gln and lung cancer (OR, 1.34; p-value=5.2×10^{-5})[17]; 6) *TGFB1* Leu10Pro and breast cancer (OR, 1.16; p-value=6.9×10^{-5})[18]; 7) *CASP8* Asp302His and breast cancer (OR, 0.89; p-value=5.7×10^{-6})[18]; 8) *NAT2* slow acetylator and bladder cancer (OR, 1.46; p-value=2.5×10^{-7})[19]; 9) *MTHFR* C677T and gastric cancer (OR, 1.52; p-value=4.9×10^{-8})[20]; 10) *CHEK2* *1100delC and breast cancer (OR, 2.4; p-value=2.5×10^{-9})[21]; 11) *GSTT1* null and acute leukemia (OR, 1.19; p-value=3.5×10^{-8})[22]; 12) *GSTM1* null and bladder cancer (OR, 1.5; p-value=1.9×10^{-14})[23]; and 13) *GSTM1* null and acute leukemia (OR, 1.20; p-value=8.6×10^{-15}).[22] At a very low prior probability of 0.000001, four of these thirteen gene-variant/cancer associations remained noteworthy: *MTHFR* C677T, *NAT2* slow acetylator, and *GSTM1* null (Table 2). This number further reduced to two (*GSTM1* null with bladder cancer and *GSTM1* null with leukemia) when we calculated statistical power based on a lower OR of 1.2. Consistent with the FPRP, associations noteworthy at a very low prior probability were highly statistically significant (p-values between 10^{-7} to 10^{-15}).

Discussion

Overall, close to one-third of all gene-variant/cancer associations from published meta- and pooled analyses were reported to be statistically significant. Thirteen of these associations were noteworthy at a prior probability of 0.001 and statistical power to detect an OR of 1.5, of which four remained noteworthy at even a lower prior probability similar to one appropriate for a randomly selected SNP in a genome-wide association study (1/1,000,000=0.000001) with p-values between 10^{-7} to 10^{-15}. These associations are thus less likely to be false positives and have a high likelihood of being true associations with cancer risk. Specifically, we observed that, among the noteworthy associations, genes encoding for phase II metabolizing enzymes made up the majority of noteworthy associations.

Continuing advances in genotyping technologies have led to the feasibility of testing a large number of genetic variants; with this has come the potential for the publication of a large number of false positives due to the widely used strategy of declaring significance based on a p-value <0.05. A key feature of the Bayesian approach using the FPRP is that it is based, not only on the observed p-value, but also on both the power and prior probability of the hypothesis, allowing the user to incorporate prior knowledge, including functional information, of the specifically tested variants. Although the FPRP calculation allows an evaluation at different scenarios of prior probability, statistical power, and noteworthiness criterion, the choice for these parameters should be determined *a priori* using empirical evidence from past studies. Accordingly, it may be reasonable to claim that SNPs of relevant candidate genes with known or predicted function (based on experimental studies or *in silico* tests) are more likely to be associated with cancer risk and hence justify higher prior probabilities. However, choice of a single prior probability will be subject to debate; hence, here, we provide readers with the opportunity to use their own judgment about the body of evidence for a given candidate gene or variant. In this paper, we chose a more agnostic approach to evaluating associations by applying two levels of prior probability (0.001 and 0.000001) and statistical power (OR of 1.5,

recommended by Wacholder et al. and similar to the average reported OR in our review; as well as OR of 1.2, close to the median reported OR in our review) to all statistically significant associations. As suggested by Thomas and Clayton [24], the prior probability for studies evaluating candidate genes will usually exceed 1000:1 (or 0.001). Thus, at a prior probability of 0.001, thirteen associations were noteworthy and may plausibly be true associations. The likelihood of being a true association, however, is even greater for the four associations that remain noteworthy at a very low prior probability (0.000001).

GSTM1 and *GSTT1* belong to a family of phase II enzymes, the glutathione *S*-transferases, that are involved in the metabolism and biotransformation of toxic xenobiotics and endobiotics.[25] Deletion of *GSTT1* was associated with an increased risk of colorectal cancer[16] and acute leukemia[22] and the *GSTM1* deletion was statistically significantly associated with risk of bladder cancer[23] and acute leukemia[22]; and the latter two were found to be among the most noteworthy findings across all meta- and pooled analyses. Individual studies conducted subsequent to the meta analyses continue to support findings for *GSTT1*[26–31] and *GSTM1*[32–37], except for one study that reported a statistically significant inverse association between *GSTT1* null and colorectal cancer[38] and a few small studies on *GSTT1* and leukemia providing inconsistent results.[35, 37, 39, 40] The prevalence of *GSTT1* null ranges from 20% in Caucasians to 60% among Asians,[41] and approximately 50% of humans (ranging from 22% in Africa to 62% in Europe) are *GSTM1* null.[42] *GSTT1* and *GSTM1* are involved in the elimination of carcinogens in the body, such as products of oxidative stress and polycyclic aromatic hydrocarbons from tobacco smoke.[43] Deletion of the *GSTT1* and *GSTM1* gene results in the variant called *GSTT1/GSTM1* null and a complete loss of enzymatic activity.[44] An individual with the null variants is thus expected to have an impaired ability to detoxify carcinogens and an increased risk of cancer, potentially affecting multiple cancer sites. This and the fact that *GSTT1* and *GSTM1* result in noteworthy associations with risk of various cancers lends support to the theory that these two variants, in particular *GSTM1* are functional and truly impact cancer risk.

Another finding that was among the most noteworthy was the association between *NAT2* slow acetylator phenotype and bladder cancer.[19] This meta-analysis was published recently, thus no additional studies were identified subsequent to the meta-analysis. *NAT2* is one of two *N*-acetyl transferase isoforms expressed in humans, which are involved in the detoxification of heterocyclic or aromatic amines and their metabolites.[45] *NAT2* is highly polymorphic and several non-synonymous polymorphisms result in poor expression, an unstable protein, or decreased catalytic activity, all of which result in the slow acetylator phenotype.[46] The prevalence of *NAT2* slow acetylators in European whites is about 56% and approximately 11% among Asians.[23] The change in the rate of acetylation is expected to alter the effect of carcinogens on cancer risk, but the effect of this change may differ by cancer site. The *NAT2* slow-acetylator phenotype is associated with an increased risk of bladder cancer (due to decreased detoxification of carcinogens from tobacco smoke), but has been associated with decreased risk of colorectal cancer (due to reduced activation of carcinogens).[45–47] Taken together, the strong evidence supporting a functional effect of the *NAT2* slow acetylator and the highly statistically significant association with bladder cancer supports the hypothesis that this variant is likely to modify cancer risk.

The recently published association between *MTHFR* C677T and gastric cancer was also among the most noteworthy associations.[20] *MTHFR*, 5,10-methyletetetrahydrofolate reductase, plays a key role in the one-carbon metabolism pathway. Specifically, *MTHFR* converts 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate which then allows for the metabolism of homocysteine and the provision of methyl groups. Enzyme activity among individuals homozygous for *MTHFR* C677T is much reduced, approximately 30% of expected enzyme activity, compared with those who are homozygous for the common variant. [48, 49]

Consequently, the reduced ability of *MTHFR* has been associated with alteration in methylation patterns and potentially aberrant DNA synthesis, repair, and chromosomal instability.[50] Due to its role in a key pathway, the *MTHFR* C677T variant may have a true impact on cancer risk.

Among associations noteworthy at prior probabilities of 0.001 were three genes associated with DNA repair (*CHEK2*, *XPD*, and *XRCC1*). Pathways involving these genes are responsible for repairing DNA damage and errors that may occur during DNA replication. There have been no studies published subsequent to the meta-analysis on *CHEK2* *1100delC and breast cancer.[21] Studies conducted subsequent to the meta-analysis on *XPD* Lys751Gln and lung cancer[51, 52] have drawn the same conclusions as our review. The statistically significant finding for *XRCC1* was present among Asians only, and one of the three subsequent studies conducted among Asians[53–55] found a statistically significant association between *XRCC1* Arg399Gln and lung cancer. Overall, it is biologically plausible that genes associated with DNA repair have an impact on the risk of cancer and our review lends support towards the likelihood of these associations.

RNASEL Asp541Glu, *MDM2* SNP309, *TGFB1* Leu10Pro and *CASP8* Asp302His are additional variants identified through our review as being noteworthy; they belong to key pathways plausibly influencing cancer susceptibility. *RNASEL* plays an important role in the inflammatory response pathway and was first identified as a candidate gene for prostate cancer risk due to its location within the hereditary prostate cancer 1 (HPC1) region.[56, 57] As the meta-analysis has been published recently, only three subsequently published studies were identified but with conflicting results for prostate cancer.[58–60] *MDM2* encodes for the human homolog of mouse double minute 2, a nuclear phospholipoprotein that binds and inhibits p53, a tumor suppressor.[61] A further study published after the meta-analysis lend support when analysis was restricted to never smokers.[62] *TGFB1*, which encodes transforming growth factor beta 1, has been implicated as both a tumor suppressor and a tumor promoter.[63, 64] An additional study published subsequent did not find an association.[65] *CASP8* encodes for Caspase 8 which plays a central role in the initiation and activation of a cascade of caspases leading to apoptosis.[66] The decreased risk with *CASP8* Asp302His for breast cancer observed in the pooled analysis is further supported by findings from a recent association study.[67]

Very recently, results from the first genome-wide association studies of cancer have become available, in which hundreds of thousands of variants were genotyped across the entire genome. These studies detected several highly statistically significant variants in the human chromosome 8q24 region that were associated with prostate, colorectal, and breast cancer susceptibility; however, there are no known characterized genes within this region.[68–75] Variants located within *SMAD7*[74], a gene involved with cell signaling, and *DAB2IP*[76], a putative tumor suppressor gene, have also been associated with colorectal and prostate cancer, respectively. Three follow-up genome wide-scans in prostate cancer have confirmed the previously identified loci and identified several additional loci that may be associated with prostate cancer risk.[77–79] The loci which were identified in at least two of the studies were as follows: 8q24, *HNF1B* (17q12), *MSMB* (10q11), *NUDT10/11* (Xp11.22), and 17q24. Six highly statistically significant variants associated with breast cancer susceptibility have also been identified through genome-wide studies, of which three are located within genes associated with control of cell growth or cell signaling (*TNRC9*, *MAP3K1* and *LSP1*).[75, 80, 81] Two variants were located in the 8q24 and 2q35 regions, and the sixth within *FGFR2*, a tumor suppressor gene overexpressed in breast cancer. The substantial evidence supporting these variants, including sizeable power and replication in large samples, indicates that these associations are likely to be true and yet none of the statistically significant variants had been previously identified because most did not reside in “interesting” candidate regions. Genome-wide association studies of cancer have also demonstrated that the effect size of statistically significant genetic variants is overall quite modest (point estimates between 1.1–1.5 for an

additive mode of inheritance), which is consistent with the weak associations found in most meta- and pooled analyses.

We attempted to review all published meta- and pooled analyses covering the topic of genetic variants and cancer risk through several iterations of search criterion; however, it is possible that we have missed some studies. Many of the noteworthy variants identified were deletions (which may not be well captured by genome-wide association studies) and non-synonymous SNPs, but this may be due to the fact that these types of mutations tend to be the most commonly studied. Our focus was strictly on results from candidate-gene association studies and did not take into account results from linkage studies to identify high-penetrance genes. A further potential limitation of this review is that associations were confined to those summarized in a meta- or pooled analysis. We are aware of individual studies with potentially much larger sample sizes and hence more power to find a statistically significant association than some meta- and pooled analyses; some of these studies have been conducted subsequent to the meta- or pooled analyses and some prior. To address this issue in part, we reviewed studies conducted subsequent to the latest meta- or pooled analysis for associations considered noteworthy at a low prior probability to determine whether evidence continued to support the previously observed associations. Another limitation of our review is that our results are susceptible to reduced quality and breadth of the meta- or pooled analysis as a result of publication bias. However, most analyses included here tested for publication bias and heterogeneity, as noted in the accompanying tables. As the power to assess gene-gene and gene-environment interactions is even lower than that to assess main effects and most meta- and pooled analyses focused on main effects, we only reported on main effects of genetic variants. Therefore, we may have missed important subgroup effects, as it is possible that certain genetic variants may only be relevant when “the system is under stress,” e.g. smoking, concurrent illness, or malnutrition. Most analyses evaluated single candidate polymorphisms; however, because genotyping has become increasingly affordable in recent years, this now allows investigators to test for genetic variants across entire candidate genes and pathways and most recently across the entire genome. Although results from single SNPs are easy to compare, this approach is certainly less comprehensive and does not rule out that other SNPs in the same gene may be related to cancer risk. As the number of articles on genetic variants published in the past decade has increased considerably and continues to grow, we accept that this review will not long remain current but does provide a snapshot of progress in the field.

In summary, we observed 98 statistically significant gene-variant/cancer associations, of which thirteen were considered noteworthyat a prior probability of 0.001. At at very low prior probability (0.000001), four remained noteworthy of which all were highly statistically significant (p-values between 10^{-7} to 10^{-15}). A majority of the most noteworthy associations identified are not SNPs but deletions, four involve *GST* variants. Results from meta-and pooled analyses were helpful in synthesizing published results and may guide future genetic studies toward areas that require further clarification and away from those that do not.

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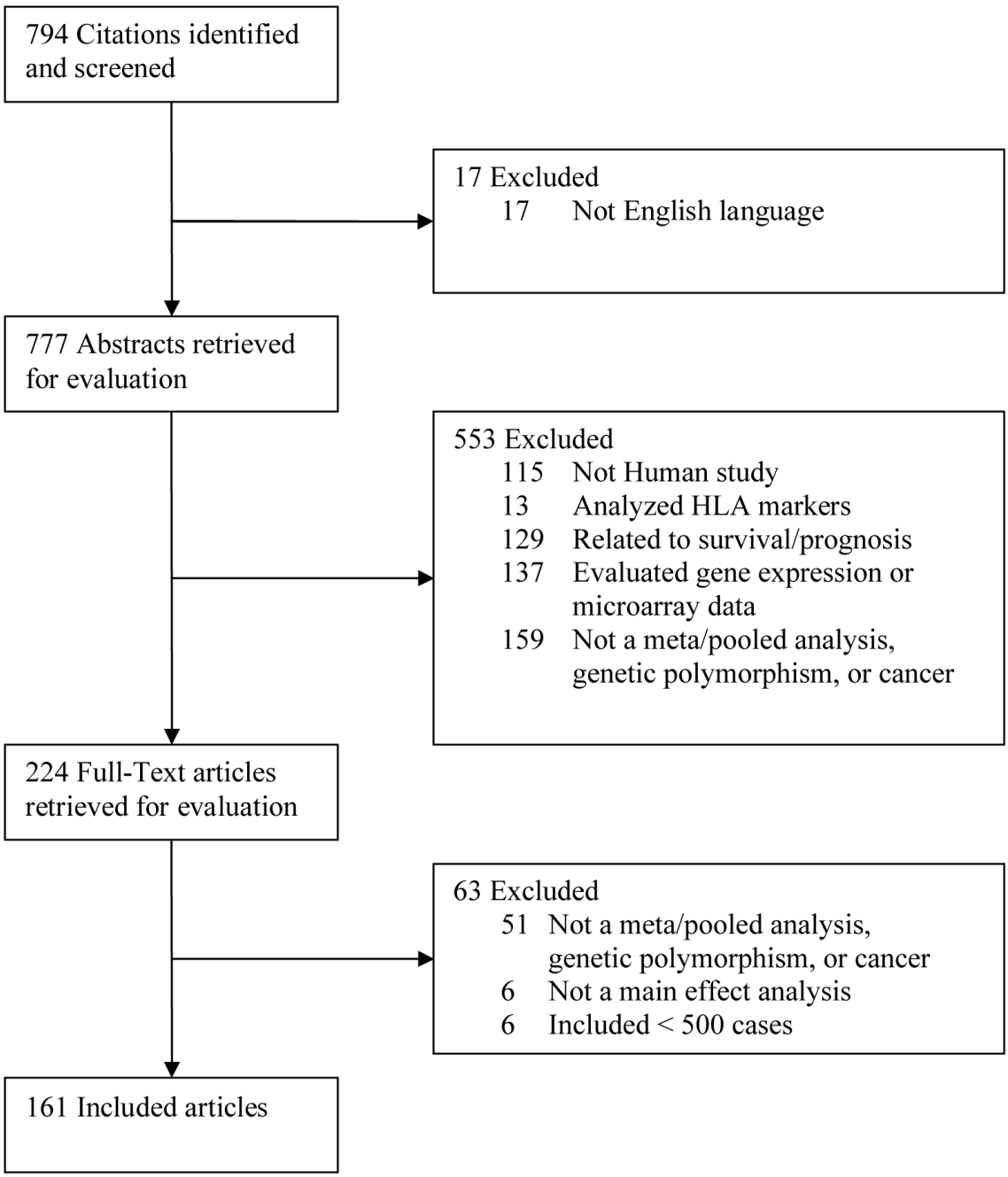
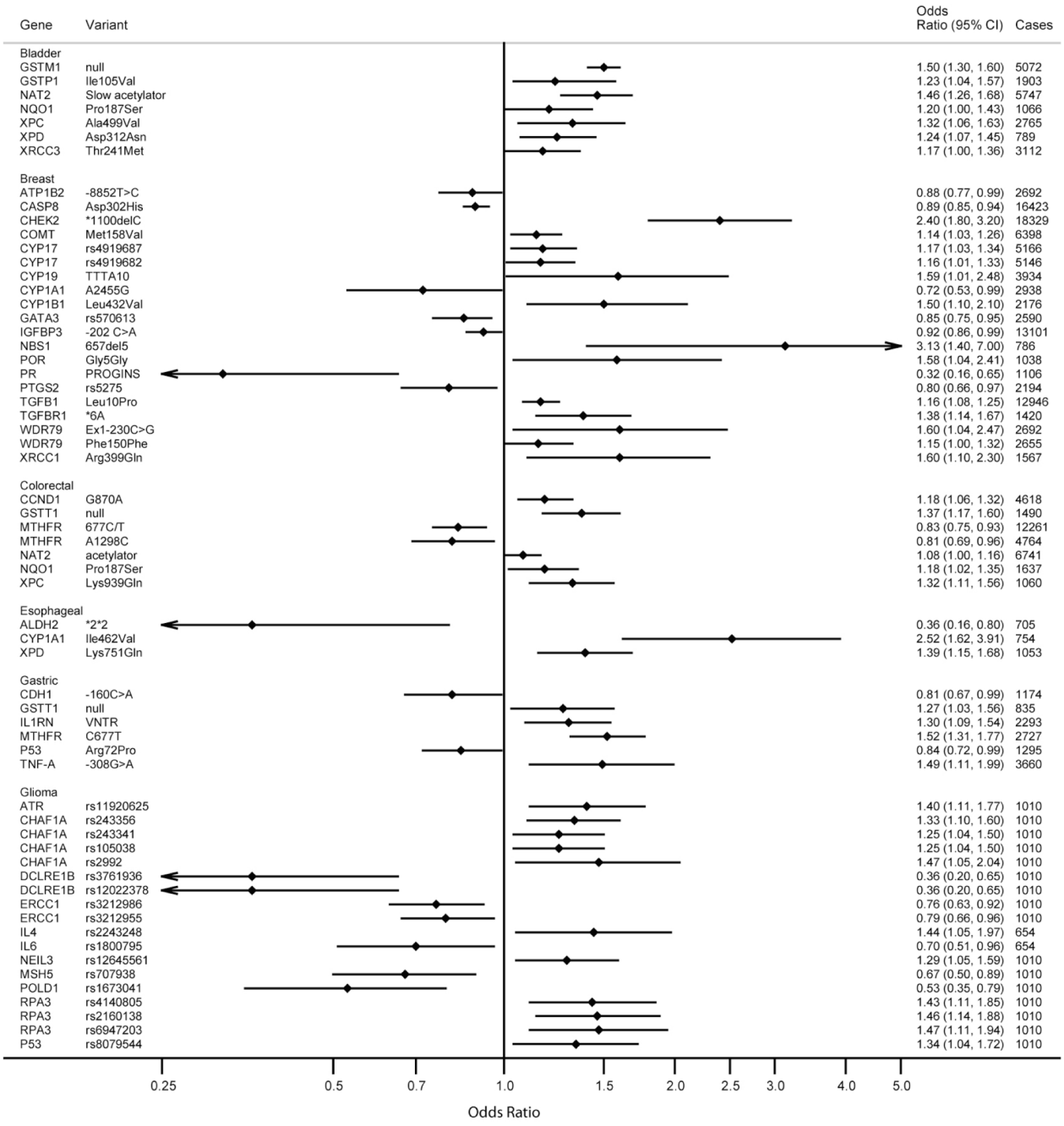


Figure 1.
Selection of Studies



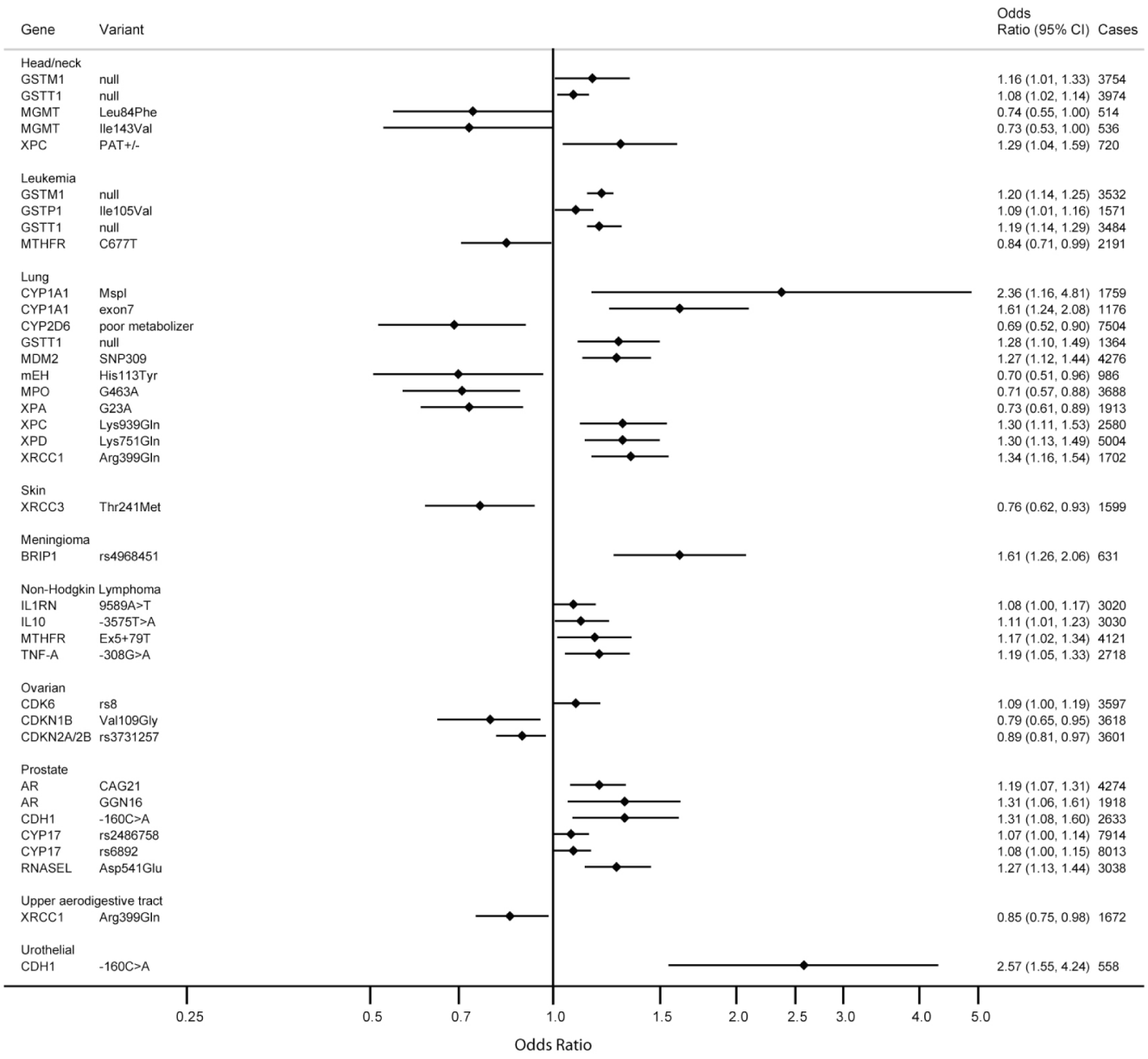


Figure 2.

Figure 2a and Figure 2b. Summary ORs and 95% CIs for Cancer Risk by Genetic Variants – Limited to Meta- and Pooled Analyses With Significant Summary Risk Estimates

Table 1

Significance of Gene-variant/Cancer Associations Demonstrated by Meta- and Pooled Analyses by Cancer Site

Cancer Site	Total			Significant Associations			Non-significant Associations		
	# of associations	Average cases per association	Average studies per association	# of associations	Average cases per association	Average studies per association	# of associations	Average cases per association	Average studies per association
Bladder	13	2574	9.8	7	2922	13	6	2168	6.2
Breast	119	5246	6.0	21	5111	6	98	5275	6.0
Cervical	1	14999	70.0	0	-	-	1	-	70.0
Colorectal	24	2589	7.0	7	4653	12.4	17	1738	4.8
Esophageal	5	839	6.6	3	837	6.0	2	843	7.5
Gastric	18	1559	9.6	6	1997	12.3	12	1339	8.2
Glioma	31	913	3.9	18	970	4.7	13	832	2.8
Head & Neck	12	1582	7.3	5	1900	8.4	7	1356	6.6
Hepatocellular	2	2469	13.5	0	-	-	2	2469	13.5
Leukemia	8	1930	9.8	4	2695	14.3	4	1165	5.3
Lung	34	3073	9.8	12	2738	9.9	22	3256	9.8
Meningioma	1	631	5.0	1	631	5.0	0	-	-
Non-Hodgkin Lymphoma	13	3051	8.2	4	3222	8.8	9	2975	8.0
Ovarian	8	3737	11	3	3605	11.0	5	3815	11.0
Prostate	42	4557	7.1	6	4632	9.5	36	4544	6.7
Skin	8	1599	4.6	1	1599	4.0	7	1599	4.7
Upper digestive tract	4	1364	5.0	1	1672	7.0	3	1261	4.3
Urothelial	1	558	3.0	1	558	3.0	0	-	-
	344	3551	7.3	100	3014	8.4	244	3772	6.8

Table 2

Statistically Significant Gene-variant/Cancer Associations and False Positive Report Probabilities (FPRP)

Cancer Site	Gene	Variant	Comparison	MAF or Freq at Risk[1]	OR	95%CI	p-value	Evid for Pub Bias[2]	Evid for Het[2]	Studies N	Cases	Power[3] OR:1.5	Power[3] OR:1.2	FPRP values at Prior Probability OR:1.5 0.001	OR:1.5 0.000001	OR:1.2 0.001	OR:1.2 0.000001	Ref
Bladder																		
	GSTM1	null	vs. present	0.51[W], 0.53[S]	1.5	1.3–1.6	1.9×10^{-14}	No	No	28	5072	1.0	0.017	<0.001	<0.001	<0.001	<0.001	23
	GSTP1	Ile105Val	GG+GA vs. AA	0.14[W]	1.23	1.04–1.57	0.0488	Yes	No	7	1903	0.944	0.421	0.990	1.000	0.996	1.000	82
	NAT2	acetylator	Slow vs. rapid/intermed	0.56[W]	1.46	1.26–1.68	2.5×10^{-7}	No	No	36	5747	0.647	0.003	<0.001	0.163	0.039	0.976	19
	NQO1	Pro187Ser	CT+TT vs. CC	0.13–.20[W]	1.20[4]	1.00–1.43	0.0457	No	No	6	1066	0.994	0.500	0.977	1.000	0.988	1.000	83
	XPC	Ala499Val	TT vs. CT+CC	0.25[W], 0.31[S]	1.32[4]	1.06–1.63	0.0114	No	No	4	2765	0.883	0.188	0.918	1.000	0.981	1.000	84
	XPD	Asp312Asn	GA+AA vs. GG	0.32–0.71	1.24[4]	1.07–1.45	0.0055	No	No	3	789	0.991	0.341	0.876	1.000	0.954	1.000	85
	XRCC3	Thr241Met	TT vs. CC	0.37	1.17	1.00–1.36	0.0409	No	No	7	3112	0.999	0.629	0.976	1.000	0.985	1.000	86
Breast[6]																		
	ATP1B2	−8852T>C	TC vs. TT	0.23–0.33	0.88	0.77–0.99	0.0462	-	Yes	2	2692	1.0	0.818	0.971	1.000	0.976	1.000	87
	CASP8	Asp302His	GC vs. GG	0.13	0.89	0.85–0.94	5.7×10^{-6}	-	No	14	16423	1.0	0.991	0.028	0.967	0.029	0.967	18
	CHEK2	*1100delC	heterozygotes vs. non-carrier	0.002–0.02[W]	2.4	1.8–3.2	2.5×10^{-9}	No	No	12	18329	0.001	1×10^{-6}	0.004	0.782	0.678	1.000	21
	COMT	Met108/158V al	GG vs. AA	0.45–0.47	1.14[4]	1.03–1.26	0.0108	-	No	11	6398	1.0	0.842	0.911	1.000	0.924	1.000	88
	CYP17	rs4919687	AA vs. GG	0.26	1.17	1.03–1.34	0.0193	-	No	5	5166	1.0	0.643	0.959	1.000	0.973	1.000	89
	CYP17	rs4919682	TT vs. CC	0.25	1.16	1.01–1.33	0.0345	-	No	5	5146	1.0	0.686	0.971	1.000	0.980	1.000	89
	CYP19	$TTTA_{10}$	carrier vs. non-carrier	0.01–0.02[W]	1.59	1.01–2.48	0.0430	-	-	5	3934	0.399	0.107	0.990	1.000	0.997	1.000	90
	CYP1A1	A2455G	GG vs. AA	0.25[S]	0.72	0.53–0.99	0.0393	No	No	3	2938	0.682	0.184	0.984	1.000	0.996	1.000	91
	CYP1B1	Leu432Val	GG +GC vs. CC	0.43[W]	1.5	1.1–2.1	0.0140	No	No	6	2176	0.500	0.097	0.973	1.000	0.995	1.000	92
	GATA3	rs570613	CT vs. TT	0.40–0.45[W]	0.85	0.75–0.95	0.007	-	No	2	2590	1.0	0.636	0.807	1.000	0.868	1.000	93
	IGFBP3	−202 C>A	AA vs. CC	0.45[W]	0.92	0.86–0.99	0.0202	-	No	10	13101	1.0	0.996	0.963	1.000	0.963	1.000	18
	NBS1	657del5	carrier vs. non-carrier	0.02[W]	3.13	1.40–7.00	0.0055	-	-	2	786	0.037	0.010	0.993	1.000	0.998	1.000	94
	POR	Gly5Gly	GG vs. AA	0.21–0.25[A]	1.58	1.04–2.41	0.0329	-	No	4	1038	0.405	0.101	0.988	1.000	0.997	1.000	95
	PR	PROGINS	T2/T2 vs. T1/T1	0.14	0.32	0.16–0.65	0.0014	-	-	4	1106	0.021	0.004	0.987	1.000	0.998	1.000	90
	PTGS2	Ex10+837	CC vs. TT	0.35[W]	0.80	0.66–0.97	0.0231	-	No	3	2194	0.968	0.339	0.960	1.000	0.986	1.000	96
	TGFB1	Leu10Pro	TT vs. CC	0.38[W]	1.16	1.08–1.25	6.9×10^{-5}	-	No	11	12946	1.0	0.813	0.090	0.990	0.108	0.992	18
	TGFBR1	*6A	*9A/*6A + *6A/*6A vs. *9A/*9A	0.12–0.15	1.38	1.14–1.67	0.0009	No	-	7	1420	0.804	0.075	0.537	0.999	0.925	1.000	97
	WDR79	Arg68Gly	GG vs. CC	0.21–0.23[W]	1.60	1.04–2.47	0.0332	-	No	2	2692	0.385	0.097	0.989	1.000	0.997	1.000	87
	WDR79	Phe150Phe	CT vs. CC	0.15–0.16[W]	1.15	1.00–1.32	0.0485	-	No	2	2655	1.0	0.727	0.979	1.000	0.985	1.000	87
	XRCC1	Arg399Gln	AA vs. GG	0.30[S]	1.6	1.1–2.3	0.0125	No	No	4	1567	0.364	0.060	0.968	1.000	0.995	1.000	98
Colorectal																		
	CCND1	G870A	GA vs. GG	0.12–0.64	1.18	1.06–1.32	0.0031	No	No	12	4618	1.0	0.616	0.792	1.000	0.861	1.000	99
	GSTT1	null	null vs. present	0.21[W], 0.44[S]	1.37	1.17–1.60	8.1×10^{-5}	-	-	11	1490	0.874	0.047	0.074	0.988	0.598	0.999	16
	MTHFR	677 C/T	TT vs. CC	0.32[W]0.40[S]	0.83	0.75–0.93	0.0007	No	No	25	12261	1.0	0.472	0.570	0.999	0.737	1.000	100
	MTHFR	A1298C	CC vs. CA+AA	0.29[W], 0.22[S]	0.81	0.69–0.96	0.0124	No	No	14	4764	0.988	0.372	0.938	1.000	0.976	1.000	101
	NAT2	acetylator[5]	rapid vs. slow	0.32–0.77[W], 0.46–0.95[S]	1.08[4]	1.00–1.16	0.0421	-	No	18	6741	1.0	0.998	0.972	1.000	0.972	1.000	47
	NQO1	Pro187Ser	CT+TT vs. CC	0.11–0.23[W]	1.18[4]	1.02–1.35	0.0206	No	No	5	1637	1.0	0.597	0.941	1.000	0.964	1.000	83
	XPC	Lys939Gln	CA vs. AA	0.65[S],0.61[W]	1.32[4]	1.11–1.56	0.0014	No	No	2	1060	0.933	0.132	0.546	0.999	0.895	1.000	102
Esophageal																		
	ALDH2	*2*2	*2*2 vs. *1*1	0.10–0.33[S]	0.36	0.16–0.80	0.0128	No	No	5	705	0.065	0.020	0.995	1.000	0.998	1.000	103
	CYP1A1	Ile462Val	GG vs. AA	0.21–0.25[S]	2.52	1.62–3.91	3.9×10^{-5}	No	No	9	754	0.010	0.0	0.783	1.000	0.988	1.000	104
	XPD	Lys751Gln	AC+CC vs. AA	0.07–0.37	1.39[4]	1.15–1.68	0.0007	No	No	4	1053	0.785	0.064	0.456	0.999	0.911	1.000	85
Gastric																		
	CDH1	-160C>A	CA+AA vs. CC	0.14–0.16[S]	0.81	0.67–0.99	0.0343	No	No	7	1174	0.971	0.391	0.976	1.000	0.990	1.000	105
	GSTT1	null	null vs. present	0.13–0.26[W]	1.27	1.03–1.56	0.0240	No	No	8	835	0.944	0.294	0.960	1.000	0.987	1.000	106
	IL1RN	VNTR	*2 carrier vs. LL	0.22–0.29[W]	1.30	1.09–1.54	0.0029	No	No	16	2293	0.951	0.177	0.716	1.000	0.931	1.000	107

Cancer Site	Gene	Variant	Comparison	MAF or Freq at Risk[1]	OR	95%CI	p-value	Evid for Pub Bias[2]	Evid for Het[2]	Studies N	Cases	Power[3] OR:1.5	Power[3] OR:1.2	FPRP values at Prior Probability OR:1.5 0.001	OR:1.5 0.000001	OR:1.2 0.001	OR:1.2 0.000001	Ref
	MTHFR	C677T	TT vs. CT+CC	0.35–0.57[M]	1.52	1.31–1.77	4.9×10^{-8}	No	No	16	2727	0.432	0.001	<0.001	0.140	0.057	0.984	20
	P53	Arg72Pro	GG vs. CC	0.41–0.49[S]	0.84	0.72–0.99	0.0319	No	-	8	1295	0.997	0.538	0.974	1.000	0.986	1.000	108
	TNF-A	-308G>A	AA vs. GG	0.04–0.16[M]	1.49	1.11–1.99	0.0074	No	No	19	3660	0.518	0.071	0.930	1.000	0.990	1.000	109
Glioma																		
	ATR	rs11920625	AG vs. GG	0.08[W]	1.40	1.11–1.77	0.0047	-	No	5	1010	0.718	0.099	0.873	1.000	0.980	1.000	110
	CHAF1A	rs243356	CT vs. CC	0.21[W]	1.33	1.10–1.60	0.0028	-	No	5	1010	0.899	0.138	0.735	1.000	0.948	1.000	110
	CHAF1A	rs243341	CT vs. TT	0.26[W]	1.25	1.04–1.50	0.0169	-	No	5	1010	0.975	0.330	0.944	1.000	0.980	1.000	110
	CHAF1A	rs105038	CT vs. CC	0.26[W]	1.25	1.04–1.50	0.0169	-	No	5	1010	0.975	0.330	0.944	1.000	0.980	1.000	110
	CHAF1A	rs2992	GG vs. AA	0.26[W]	1.47	1.05–2.04	0.023	-	No	5	1010	0.548	0.112	0.975	1.000	0.995	1.000	110
	DCLRE1B	rs3761936	CC vs. TT	0.19[W]	0.36	0.20–0.65	0.0007	-	No	5	1010	0.020	0.003	0.972	1.000	0.996	1.000	110
	DCLRE1B	rs12022378	TT vs. CC	0.19[W]	0.36	0.20–0.65	0.0007	-	No	5	1010	0.020	0.003	0.972	1.000	0.996	1.000	110
	ERCC1	rs3212986	GT vs. GG	0.27[W]	0.76	0.63–0.92	0.0045	-	No	5	1010	0.911	0.172	0.842	1.000	0.966	1.000	110
	ERCC1	rs3212955	AG vs. AA	0.26[W]	0.79	0.66–0.96	0.0137	-	No	5	1010	0.956	0.296	0.949	1.000	0.984	1.000	110
	IL4	rs2243248	TG vs. TT	0.05[W]	1.44	1.05–1.97	0.0231	-	No	2	654	0.601	0.127	0.974	1.000	0.994	1.000	111
	IL6	rs1800795	GG vs. CC	0.45[W]	0.70	0.51–0.96	0.0271	-	No	2	654	0.619	0.140	0.977	1.000	0.995	1.000	111
	NEIL3	rs12645561	CT vs. CC	0.13[W]	1.29	1.05–1.59	0.0161	-	No	5	1010	0.921	0.249	0.949	1.000	0.986	1.000	110
	MSH5	rs707938	CC vs. TT	0.36[W]	0.67	0.50–0.89	0.0065	-	No	5	1010	0.514	0.066	0.917	1.000	0.989	1.000	110
	POLD1	rs1673041	AA vs. CC	0.26[W]	0.53	0.35–0.79	0.0022	-	No	5	1010	0.130	0.013	0.933	1.000	0.993	1.000	110
	RPA3	rs4140805	GG vs. TT	0.40[W]	1.43	1.11–1.85	0.0061	-	No	5	1010	0.642	0.091	0.910	1.000	0.986	1.000	110
	RPA3	rs2160138	CC vs. TT	0.44[W]	1.46	1.14–1.88	0.003	-	No	5	1010	0.583	0.064	0.852	1.000	0.981	1.000	110
	RPA3	rs6947203	TT vs. CC	0.33[W]	1.47	1.11–1.94	0.0068	-	No	5	1010	0.557	0.076	0.921	1.000	0.988	1.000	110
	TP53	rs8079544	CT vs. CC	0.06[W]	1.34	1.04–1.72	0.0226	-	No	5	1010	0.812	0.193	0.964	1.000	0.991	1.000	110
Head/neck																		
	GSTM1	null	null vs. present	0.47–0.54[W]	1.16	1.01–1.33	0.0345	Yes	No	11	3754	1.0	0.686	0.971	1.000	0.980	1.000	112
	GSTT1	null	null vs. present	0.11–0.53[S], 0.14–0.52[W]	1.08	1.02–1.14	0.0067	No	No	23	3974	1.0	1.0	0.840	1.000	0.840	1.000	113
	MGMT	Leu84Phe	CT+ TT vs. CC	0.16[M]	0.74	0.55–1.00	0.0483	-	No	3	514	0.752	0.220	0.985	1.000	0.996	1.000	114
	MGMT	Ile143Val	AG + GG vs. AA	0.13[M]	0.73	0.53–1.00	0.0520	-	No	3	536	0.714	0.205	0.986	1.000	0.996	1.000	114
	XPC	PAT+/−	+ vs −	0.67[S],0.59[W]	1.29[4]	1.04–1.59	0.0187	No	No	2	720	0.921	0.249	0.949	1.000	0.986	1.000	102
Leukemia (acute)																		
	GSTM1	null	null vs. present	0.28–0.57[W]	1.20	1.14–1.25	8.6×10^{-15}	No	No	19	3532	1.0	0.841	<0.001	<0.001	<0.001	<0.001	22
	GSTP1	Ile105Val	GA + GG vs. AA	0.25–0.35[W]	1.09	1.01–1.16	0.0147	No	No	8	1571	1.0	0.999	0.869	1.000	0.869	1.000	22
	GSTT1	null	null vs. present	0.08–0.32[W]	1.19	1.14–1.29	3.5×10^{-8}	No	No	17	3484	1.0	0.581	0.023	0.960	0.039	0.976	22
	MTHFR	C677T	TT vs. CT+CC	0.27–0.43[W]	0.84	0.71–0.99	0.0398	No	No	13	2191	0.997	0.538	0.974	1.000	0.986	1.000	115
Lung[6]																		
	CYP1A1	MspI (T3801C)	MspI/MspI vs. not present	0.22[W]	2.36	1.16–4.81	0.0180	No	No	17	1759	0.106	0.031	0.994	1.000	0.998	1.000	116
	CYP1A1	exon7 poor	AG+ GG vs. AA	0.26[S]	1.61	1.24–2.08	0.0003	No	Yes	11	1176	0.294	0.012	0.477	0.999	0.956	1.000	117
	CYP2D6		poor vs. extensive	0.08[W]	0.69	0.52–0.90	0.0080	-	No	17	7504	0.600	0.082	0.912	1.000	0.987	1.000	118
	GSTT1	metabolizer[5]	null vs. present	0.54[S]	1.28	1.10–1.49	0.0014	No	No	8	1364	0.980	0.203	0.596	0.999	0.877	1.000	119
	MDM2	SNP309	GG vs. TT	0.37[W], 0.48[S]	1.27[4]	1.12–1.44	0.0002	-	Yes	7	4276	0.995	0.188	0.162	0.995	0.505	0.999	13
	mEH	His113Tyr	CC vs. TT	0.36[W], 0.43[S]	0.70	0.51–0.96	0.0271	No	Yes	8	986	0.619	0.140	0.977	1.000	0.995	1.000	120
	MPO	G463A	AA vs. GG	0.23[M]	0.71	0.57–0.88	0.0020	No	No	10	3688	0.717	0.072	0.711	1.000	0.961	1.000	121
	XPA	G23A	GA vs. AA	0.37[M]	0.73	0.61–0.89	0.0011	No	No	7	1913	0.815	0.095	0.694	1.000	0.951	1.000	14
	XPC	Lys939Gln	CC vs. CA+AA	0.38[W],0.36[S], 0.28[A]	1.30[4]	1.11–1.53	0.0014	No	No	6	2580	0.957	0.168	0.625	0.999	0.905	1.000	84
	XPD	Lys751Gln	CC vs. AA	0.30[M]	1.30	1.13–1.49	0.0002	No	No	15	5004	0.980	0.125	0.143	0.994	0.566	0.999	14
	XRCC1	Arg399Gln	AA vs. GG	0.27–0.46[S]	1.34	1.16–1.54	5.2×10^{-5}	No	No	6	1702	0.944	0.060	0.038	0.975	0.383	0.998	17
Non-melanoma skin																		
	XRCC3	Thr241Met	TT vs. CC +CT	0.30–0.41[W]	0.76	0.62–0.93	0.0080	No	No	4	1599	0.898	0.186	0.896	1.000	0.976	1.000	122
Meningioma																		
	BRIP1	rs4968451	AC vs. AA	0.15[W]	1.61	1.26–2.06	0.0001	-	No	5	631	0.287	0.010	0.347	0.998	0.940	1.000	123
Non-Hodgkin Lymphoma																		

Cancer Site	Gene	Variant	Comparison	MAF or Freq at Risk[1]	OR	95%CI	p-value	Evid for Pub Bias[2]	Evid for Het[2]	Studies N	Cases	Power[3] OR:1.5	Power[3] OR:1.2	FPRP values at Prior Probability OR:1.5 0.001	OR:1.5 0.000001	OR:1.2 0.001	OR:1.2 0.000001	Ref
	IL10	−3575T>A	TA+AA vs. TT	0.36[W]	1.11	1.01–1.23	0.0379	-	No	8	3030	1.0	0.932	0.979	1.000	0.980	1.000	124
	IL1RN	9589A>T	AT +TT vs. AA	0.27[W]	1.08	1.00–1.17	0.0547	-	No	8	3020	1.0	0.995	0.983	1.000	0.984	1.000	124
	MTHFR	677C>T	TT vs. CC	0.29–0.45[W]	1.17	1.02–1.34	0.0241	No	No	11	4121	1.0	0.643	0.959	1.000	0.973	1.000	125
	TNF	−308G>A	GA+AA vs. GG	0.14[W]	1.19	1.05–1.33	0.0039	-	No	8	2718	1.0	0.559	0.685	1.000	0.795	1.000	124
Ovarian																		
	CDK6	IVS2–4184C>T	CT vs. CC	0.21[W]	1.09	1.00–1.19	0.0521	-	No	11	3597	1.0	0.984	0.982	1.000	0.982	1.000	126
	CDKN1B	Val109Gly	GG vs. TT	0.25[W]	0.79	0.65–0.95	0.0149	-	Yes	11	3618	0.964	0.285	0.927	1.000	0.977	1.000	126
	CDKN2A/2B	4780C>T	CT vs. CC	0.27[W]	0.89	0.81–0.97	0.0113	-	Yes	11	3601	1.0	0.933	0.888	1.000	0.895	1.000	126
Prostate																		
	AR	CAG_{21}	$>CAG_{21}$ vs. $\leq CAG_{21}$	0.50[M]	1.19	1.07–1.31	0.0008	No	No	22	4274	1.0	0.568	0.279	0.997	0.405	0.999	127
	AR	GGN16	$\leq GGN_{16}$ vs. $>GGN_{16}$	0.50[W]	1.31	1.06–1.61	0.0113	No	No	8	1918	0.901	0.202	0.919	1.000	0.981	1.000	127
	CDH1	−160C>A	AA+CA vs. CC	0.14–0.61[M]	1.31	1.08–1.60	0.0071	No	Yes	8	2633	0.908	0.195	0.899	1.000	0.977	1.000	105
	CYP17	rs2486758	TC vs. TT	0.21[M]	1.07	1.00–1.14	0.043	-	No	7	7914	1.0	1.0	0.973	1.000	0.973	1.000	89
	CYP17	rs6892	AG vs. AA	0.18[M]	1.08	1.00–1.15	0.0309	-	No	7	8013	1.0	0.999	0.942	1.000	0.942	1.000	89
	RNASEL	Asp541Glu	GT +GG vs. TT	0.42–0.57[W]	1.27	1.13–1.44	0.0001	-	No	6	3038	0.995	0.188	0.162	0.995	0.505	0.999	15
Upper digestive tract																		
	XRCC1	Arg399Gln	AG+GG vs. AA	0.28–0.47[M]	0.85	0.75–0.98	0.0172	No	No	7	1672	1.0	0.607	0.962	1.000	0.976	1.000	128
Urothelial																		
	CDH1	−160C>A	AA vs. CC	0.23–0.43[W], 0.14–0.61[S]	2.57	1.55–4.24	0.0002	No	No	3	558	0.018	0.001	0.926	1.000	0.994	1.000	105

[1] Minor allelic frequency for [W]Whites, [S]Asians, [M]Mixedor [A]Africans or frequency at risk for variants that are not SNPs.

[2] Evidence for publication bias and heterogeneity represent whether quality assessment of studies was performed and the corresponding results from those tests as reported by each published meta- or pooled analysis. "–" Dash indicates unclear whether test was performed.

[3] Statistical power to detect an OR of 1.5 (0.67=1/1.5) or an OR of 1.2 (0.83=1/1.2)

[4] Fixed effect estimate

[5] Phenotype and genotype methods of detection.

[6] Although HRAS1 alleles were significantly associated with breast cancer this finding is the consequence of an error in genotyping - see text.

[*] Shading indicates noteworthiness of association at 0.2 level