DNA Damage and Repair and Cancer Risk: A Systematic Review and Meta-Analysis of 55 Case-Control Studies

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Abstract

DNA repair phenotype can be measured in blood and may be a potential biomarker of cancer risk. We conducted a systematic review and meta-analysis of epidemiological studies of DNA repair phenotype and cancer through March 2021. We used random-effects models to calculate pooled odds ratios (ORs) of cancer risk for those with the lowest DNA repair capacity compared with those with the highest capacity. We included 55 case-control studies that evaluated 12 different cancers using 10 different DNA repair assays. The pooled OR of cancer risk (all cancer types combined) was 2.92 (95% Confidence Interval (CI)= 2.49, 3.43) for the lowest DNA repair. Lower DNA repair was associated with all studied cancer types, and pooled ORs (95% CI) ranged from 2.02 (1.43, 2.85) for skin cancer to 7.60 (3.26, 17.72) for hepatocellular carcinoma. All assays, except the homologous recombination repair, showed statistically significant associations with cancers. The effect size ranged from 1.90 (1.00, 3.60) for ETOP-induced double strand break assay to 5.06 (3.67, 6.99) for γ-H2AX. The consistency and strength of the associations supports the use of these phenotypic biomarkers; however large-scale prospective studies will be important for understanding the use of this biomarker related to age and screening initiation.

Introduction

Cancer initiation is classically associated with the induction of mutations in key oncogenes or tumor suppressor genes, due to the presence of unrepaired/misrepaired DNA lesions produced by endogenous or exogenous genotoxic agents[1]. Many risk factors for cancer such as smoking, ionizing radiation, and diet can induce DNA damage[2]. Higher levels of DNA/protein adducts in blood from exogenous exposures are associated with increased cancer risk[3]. DNA repair plays a fundamental role in the maintenance of genomic integrity[4]. Individuals with deficiency in DNA repair capacity might be more susceptible to cancer risk.

DNA repair capacity can be assessed either with genomic/proteomic approaches or with phenotypic approaches[5]. A concern with genomic/proteomic approaches is that mammalian DNA damage repair mechanisms are extraordinarily complex. In humans it involves ~ 450 genes in 13 different pathways, with over half the proteins interacting with other proteins from different pathways[6]; it follows that any specific genomic or proteomic methodology is unlikely to reflect overall DNA repair capacity. If it were possible to characterize the genetic complexity, it would be extremely challenging to implement at a clinical level. By contrast, phenotypic approaches - e.g., inducing DNA damage and then measuring the rate of DNA repair or the amount of unrepaired DNA damage, or both - have the potential to be more reflective of overall DNA repair capacity[7]. DNA repair phenotyping assays use fresh or cryopreserved peripheral blood mononuclear cells (PBMC) or lymphoblastoid cell lines as a surrogate marker for target tissue of DNA repair[7]. A phenotypic assay, if it is high throughput, may be more feasible to implement in a clinical setting as phenotypic approaches can reflect the totality of multiple complex pathways.

The purpose of our systematic review and meta-analysis is to quantitatively and qualitatively summarize the literature regarding DNA repair phenotype across difference cancer types. We assessed the association of DNA repair phenotype biomarkers with the risk of cancer by conducting a meta-analysis from all epidemiological studies published through March 2021.

Materials And Methods

We used the following MeSH terms in our literature search: “cancer” AND “DNA repair phenotype” OR “DNA repair capacity” OR “comet assay” OR “Host-cell reactivation” OR “γ-H2AX assay” OR “Mutagen sensitivity assay” for studies published from 1980 to 20 March 2021 **(Supplemental Fig. 2)**. Our initial search of the PubMed database restricted to studies that were conducted in humans and published in the English language returned 2045 publications for further screening. We first reviewed the title and abstract of each study and excluded 1932 studies that 1) did not examine cancer as an outcome, 2) did not have a cellular based assay for DNA damage and repair, and 3) did not compare differences in DNA damage and repair between cancer cases and unaffected controls using either case-control or cohort study designs. We then reviewed the remaining 113 studies and restricted our analysis to studies (n = 55) that estimated effect size of DNA damage and repair between cancer cases and unaffected controls. We searched the reference lists of the included publications for additional eligible publications, but no additional studies were identified. The remaining 55 publications were included in our review[8,29,32–84]. We extracted data on study population, study design, sample size, DNA repair phenotyping assay, confounding assessment, and effect estimates for the group with the lowest DNA repair capacity compared with the group with the highest capacity, and the corresponding 95% confidence intervals (CIs) from the included publications. When a study reported results on different racial groups or different damage reagent, we treated each group as a separate comparison in our meta-analysis. Studies included in the current meta-analysis have to meet all of the following criteria: (1) use an epidemiological study design such as a case–control or cohort study design, and (2) present odds ratios or rate ratios.

Statistical Analysis

We conducted a meta-analysis to calculate pooled estimated odds ratio (ORs) across studies using random-effects models to account for between study heterogeneity. To assess the heterogeneity among studies, we used the Cochran Q test[85] and I squared (I^2) statistics[86]. To examine possible publication bias, we generated funnel plots and used the Egger’s test[87] to examine if there were small study effects. We also used an influence plot to evaluate if individual studies were impacting overall summary estimates. We performed subgroup analyses d stratified by the tumor site and assay type. We only report results from the random-effects models, and not fixed-effects models, as we found there was significant heterogeneity across the different studies. Analyses were performed using the software Stata 15.1 (College Station, TX). All P-values were two-sided.

Results

Overall summary of number and study design of studies: Detailed characteristics of the included studies are shown in **Supplemental Table 1**. Based on the inclusion eligibility, we identified 55 studies of 12 different cancer types: lung (n = 20), breast (n = 10), skin (n = 7), head and neck (n = 7),, bladder (n = 2), esophageal (n = 2), upper aerodigestive tract (n = 2), prostate (n = 1), gastric (n = 1), colorectal (n = 1), gliomas (n = 1) and liver (n = 1). All studies used a case-control study design and most used blood collected at the time of cancer diagnosis; only two studies were nested case-control studies using blood collected before cancer diagnosis.[8,9] The first nested-case control study was by Sigurdson et al. [8] and used three DNA repair assays: comet assay, host cell reactivation assay and mutagen sensitivity assay in blood collected between 0.3 and 6 years before lung cancer.[8] The authors reported an OR of 2.09 (95%CI = 1.00, 4.37) for lung cancer risk among individuals at the highest quartile of chromatid breaks/cell compared with individuals at the lowest quartile measured by the mutagen sensitivity assay. The ORs were 1.2 (95%CI = 0.54, 2.65) for the comet assay and 0.96 (0.45, 2.04) for the host cell reactivation assay. The second nested case-control design was by Shen et al[9] and used a modified host cell reactivation assay to measured homologous recombination repair capacity in bloods collected from 152 breast cancer patients and their matched controls and reported an OR of 1.42 (95%CI = 1.21, 2.52). A similar magnitude effect size was then found in the validation set of 50 cases-control pairs using blood collected before cancer diagnosis.[9]

The overall pooled OR (95%CI) for DNA repair deficiency and cancer risk was 2.92 (2.49, 3.43) (Fig. 1). We saw significant heterogeneity across different studies (I^2 = 84.2%; p-value from Cochran's Q < 0.0001), and the Funnel plot suggested possible publication bias (p-value from Egger's Test < 0.0001; see **Supplemental Fig. 1**). We further looked by cancer type and assay to better understand the sources of heterogeneity.

Cancer type

We found lower DNA repair phenotype was associated with all studied cancer types, and the pooled ORs ranged from 2.02 (1.43, 2.85) for skin cancer to 7.60 (3.26, 17.72) for hepatocellular carcinoma (Fig. 2). We observed heterogeneity across skin, lung, bladder, and breast cancer studies, while there was no evidence of heterogeneity across studies for esophageal, head and neck, or upper aerodigestive tract cancers.

Assay type

In our meta-analysis, there were 10 DNA repair phenotyping assays including the host-cell reactivation (n = 18), mutagen sensitivity assay (n = 16), comet assay (n = 6), radiolabeled synthetic assay (n = 5), γ-H2AX (n = 4), end-joining assay (n = 2), ETOP-induced double strand break assay (n = 1), nucleotide excision repair protein assay (n = 1), homologous recombination repair assay, (n = 1), and immunofluorescence (n = 1). The pooled ORs (95%CI) were 2.34 (1.75, 3.14) for the host-cell reactivation assay, 3.26 (1.75, 3.14) for the mutagen sensitivity assay, 3.21 (1.97, 5.21) for the comet assay, 5.06

(3.67, 6.99) for the γ-H2AX assay (Fig. 3). Studies using host-cell reactivation, mutagen sensitivity assay, comet assay, radiolabeled synthetic assay had evidence of heterogeneity across studies.

We further examined the association of DNA repair deficiency by assay type among lung and breast cancer studies- most number of studies and common cancers. We found the effect of lower DNA repair capacity for lung cancer risk were similar across different assay types (range of ORs = 2.14, 3.57) (Fig. 4A). Although there was heterogeneity across studies within assay groups, we did not see statistically significant heterogeneity in the ORs for lung cancer pooled across assay groups (p = 0.21). We did observe statistically significant heterogeneity across different assays in breast cancer studies (p = 0.01), where the host cell reactivation assay showed the largest effect size with a pooled OR of 7.75 (1.79, 33.49) (Fig. 4B).

Discussion

We found that deficient DNA repair capacity is associated with an increased risk of cancer using meta-analytic methods that summarized data from 55 studies. The magnitude of the associations between DNA repair phenotype and cancer risk is much stronger compared with the effect size measured by genetic variants of DNA repair genes (ORs range from 1 to 2)[10]. Accurately identifying high-risk individuals is essential for effective primary prevention (e.g., chemoprevention)[11], and for risk-based screening options[12] which emphasize risk rather than age for optimal screening outcomes. For example, many different risk models exist for breast cancer including the Breast Cancer Risk Assessment Tool (BCRAT, or Gail model)[13,14], IBIS[15], BOADICEA[16] and risk models exist for other common cancers including colorectal and prostate cancer. However, most cancer risk models currently have only modest discriminatory accuracy at the individual level (AUC ~ .6-.65).[17] Modest improvements have been achieved by incorporating genetic variants[18] and epigenetic markers[19] into cancer risk prediction models. Although these studies suggest that some gains can be made through incorporating non-invasive blood markers, no cancer risk model has yet considered incorporating non-invasive phenotypic markers that have substantially greater magnitude of association with breast cancer risk. DNA repair plays an essential role in preventing mutations and genomic instability that are critical for the effects of carcinogen exposure[1]. Our meta-analysis concluded that individuals with lower DNA repair capacity are at increased susceptibility to cancer development and the capacity to repair DNA damage is therefore an important factor to consider in risk assessment.

When DNA repair machinery is not working efficiently, the generation of DNA damage and mutations leads to carcinogenic transformation and, eventually, to cancer[1]. We found lower DNA repair phenotype was statistically significantly associated with all cancer types. This suggests that measuring DNA repair phenotype can potentially identify high-risk individuals for effective primary prevention, and for risk-based screening options. However, to potentially integrate DNA repair phenotyping data into risk assessment, more studies are needed to examine intra-individual variability in DNA repair phenotyping

over time, to assess whether a single measure at the time of first breast screening is useful or whether multiple measures over time are needed.

In our meta-analysis, we found there was significant heterogeneity across studies, which might be related to different cancer types and different DNA repair phenotyping assays. A potential explanation for why we observed heterogeneity across studies of different cancer types and assays might be related to the complex interplay of genetic and environmental factors in most cancer types. There are substantial differences in the mutational burden between cancer types[20]. Analysis of the mutation burden of 27 tumor types found that tumor types with higher somatic mutation burden such as melanoma and lung cancers are the result of environmental exposure[20]. In addition, there is substantial inter-individual variation in tumor mutational burden within individual tumor types[20]. These observations suggest that both genetic and environmental factors might be involved in most human cancers.

There are numerous methods for measuring DNA repair directly, and each has its strengths and weaknesses[21]. Most of the assays such as the host-cell reactivation and mutagen sensitivity assays measure nucleotide excision repair capacity[22]. Nucleotide excision repair eliminates a wide variety of different forms of DNA damage and especially deals with bulky DNA damage/adducts induced by chemical carcinogens and dimers induced by ultraviolet light[23]. In addition to nucleotide excision repair, other major DNA repair pathways including base excision repair, mismatch repair, homologous recombination and non-homologous end joining are active throughout the different stages of the cell cycle. In our analysis, we found the estimated effect sizes were consistent and of high magnitude across different assays and pathways.

Recently, several assays have been developed to measure multiple repair pathways[24]. Moreover, functional DNA repair assays are fundamentally more powerful than genotyping. But currently, there are few DNA repair assays available for epidemiologic studies because the assays are labor and time intensive. Thus studies to date are limited and there are no large-scale prospective studies or high-throughput phenotypic assays[25]. The resultant lack of population studies integrating these potentially informative measures with other factors limits our understanding of the fundamental cellular response to environmental exposures. However, recently our group developed a high-throughput γ-H2AX assay based on imaging flow cytometry (IFC) which is a faster and more efficient technique for assessing global double strand break repair capacity[26]. This IFC-based γ-H2AX protocol may provide a practical and high-throughput platform for measurements of individual global DNA double strand break repair capacity which can facilitate precision medicine by predicting individual radiosensitivity and risk of developing adverse effects related to radiotherapy treatment.

For over four decades, cancer incidence has been increasing the most in adults under 55 years in the U.S. In our recent report based on Surveillance Epidemiology and End Reports (SEER) data, we found overall cancer incidence increased by 1.15% per year in 25- to 39-year-old women and by 0.46% per year in 25- to 39-year-old men[27]. Moreover, we forecasted that overall cancer incidence will increase by an additional

11–12% by 2030 in 25- to 39-year-old women and men[27]. However, most cancer screening guidelines do not recommend screening begins until after age 40 (e.g., mammography is recommended to start at 45 years of age for breast cancer screening)[28].

Therefore, developing tools that can accurately predict risk of early onset cancer might be a key factor in addressing these trends. However most of the studies that have been conducted have not stratified by age. However, our previous study compared DNA double strand break repair capacity between breast cancer cases and their unaffected sister controls[29]. We found there was an association between lower DNA repair capacity and breast cancer risk, and that the largest differences in the mean value of repair between cases and controls were observed in women younger than 40 years[29]. Moreover, cases younger than 40 years had lower DNA repair capacity than older cases. Results from our sibling studies[23,24] suggest that phenotypic measures will be an important determinant of risk over and beyond family history. More studies are needed to better understand if deficiency in DNA repair capacity is an important risk factor for early onset cancer specifically.

Moreover, most studies use PBMC as surrogate tissues, assuming PBMC are a legitimate surrogate for DNA repair in other tissues. The correlation between DNA repair capacity between target and blood is limited to one study that found a good correlation between OGG activity in blood and lung tissues from the same individual[30]. Although assays using blood samples are more feasible to implement in a clinic setting, more studies needs to evaluate the correlation of DNA repair phenotype between blood and target tissues using different assays.

Cancer susceptibility is inherently complex, and polygenetic risk scores using genetic data have been established and show improvement in prediction accuracy for cancer[31]. Our meta-analysis supports a strong association between global repair capacity and cancer risk. Measuring DNA repair capacity is a potentially powerful marker to identify subgroups at high risk of cancer. Measuring overall DNA repair capacity markers in blood may be one way of understanding the role of DNA damage and repair in cancer risk and might provide intermediate outcome markers in prevention studies. Measuring DNA repair capacity may provide a potentially robust to identify individuals that can may benefit from individual-based health risk assessment and personalized risk reduction strategies. Established high-through measurement of DNA repair phenotyping may also be more feasible to implement in a clinic setting as opposed to complex genomic and proteomic approaches. Incorporating DNA repair phenotype into risk models may improve model discriminatory accuracy but will need large-scale prospective evidence to understand the role of timing and age at measurement and cancer screening initiation.

Abbreviations

BCC: basal cell carcinoma; CMM: cutaneous malignant melanoma; CI, Confidence interval; DSB, double strand break, ORs, odds rations; PBMC, peripheral blood mononuclear cells; SCC, squamous cell carcinoma;

Declarations

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Author contributions Study design: HC.W, and MB.T; organized and performed the analysis: HC.W and R.K; Data analysis: HC.W, R.K and MB.T; Paper writing: HC.W, R.S, MB.T, and R.K. HC.W and R.K. prepared figures and tables. All authors review the manuscript and approved the final version of the manuscript.

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Figures

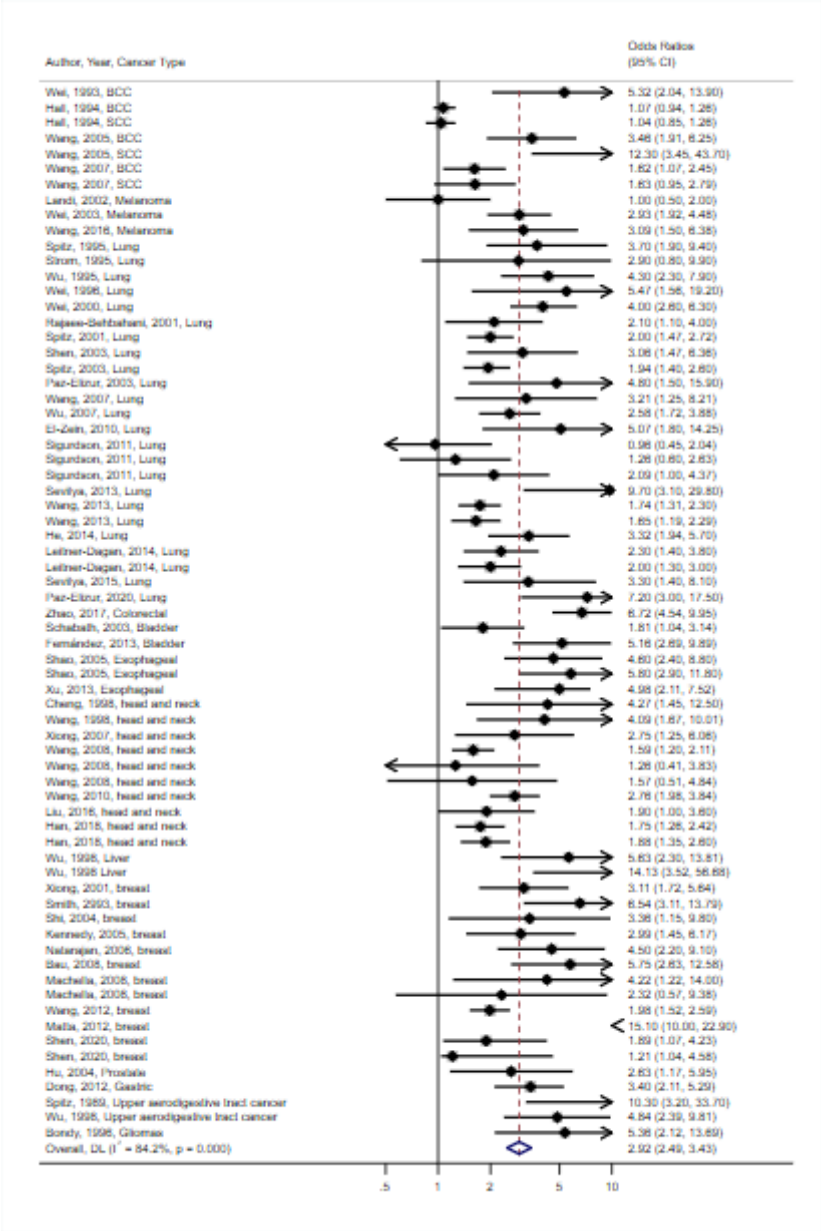

Figure 1

Forest plot of meta-analysis of lower DNA repair capacity and cancer risk in random effect model. Individual studies represented by OR and 95% confidence interval.

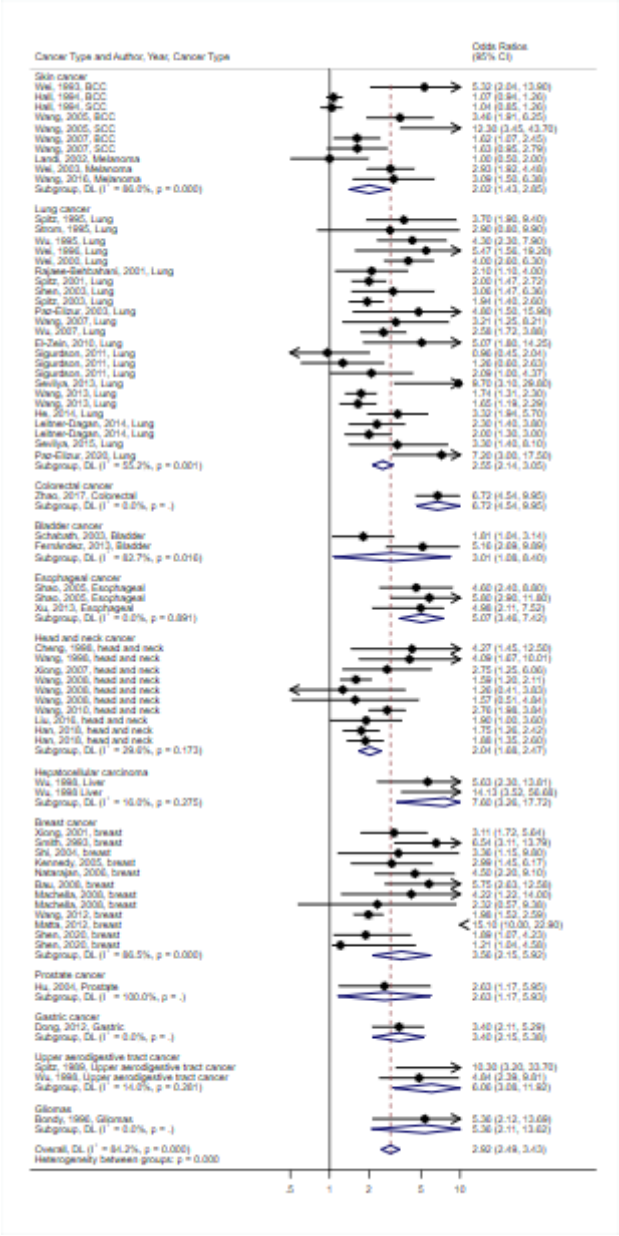

Figure 2

Forest plot of meta-analysis of lower DNA repair capacity and cancer risk by cancer type in random effect model. Individual studies represented by OR and 95% confidence interval.

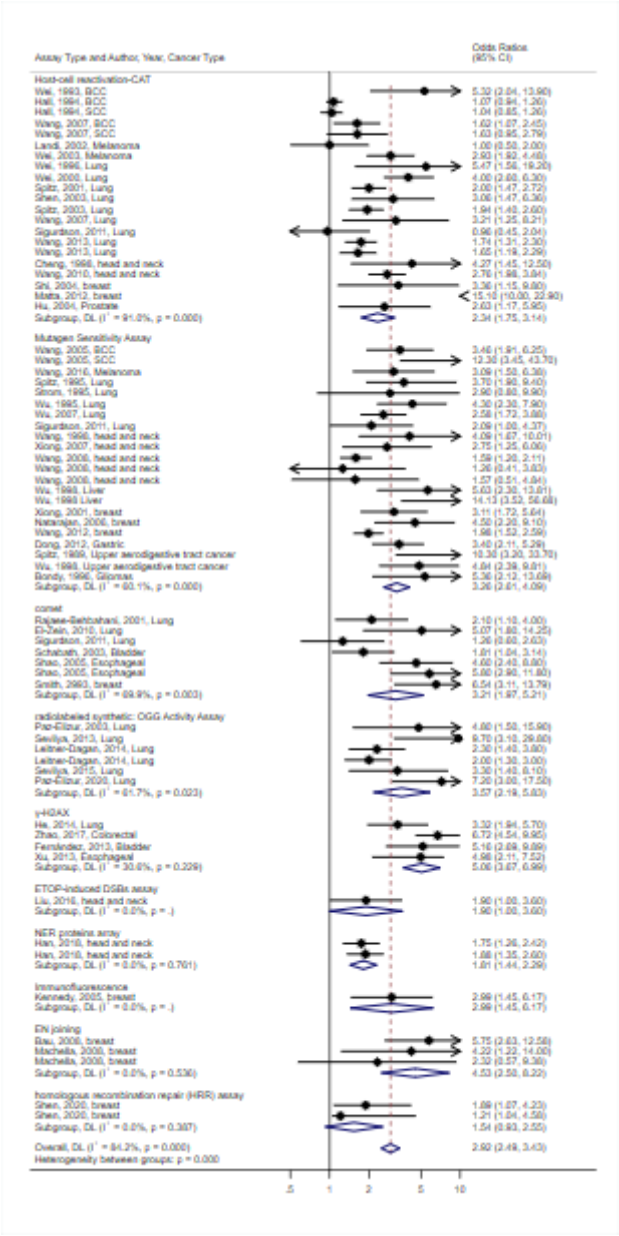

Figure 3

Forest plot of meta-analysis of lower DNA repair capacity and cancer risk by assay type in random effect model. Individual studies represented by OR and 95% confidence interval.

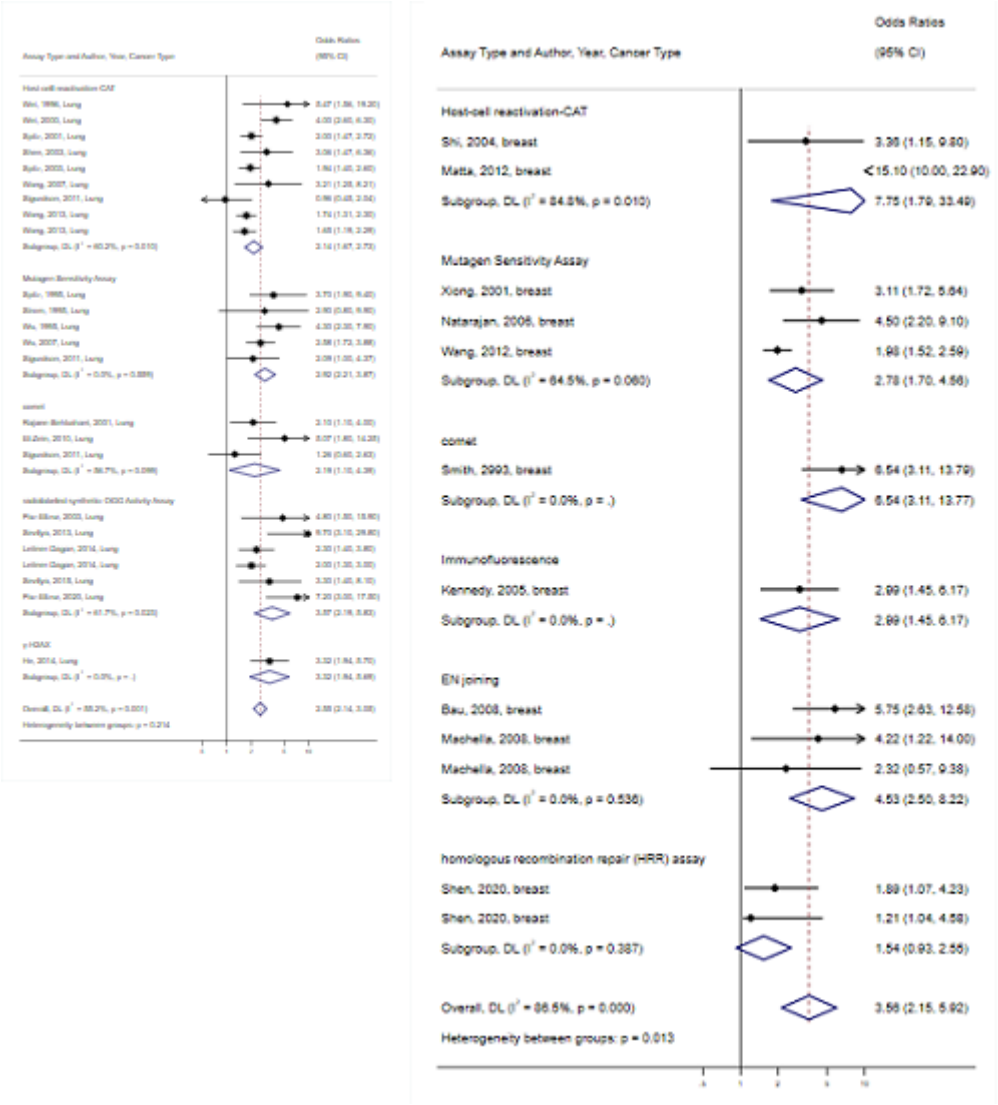

Figure 4

A. Forest plot of meta-analysis of lower DNA repair capacity and lung cancer risk by assay type in random effect model. Individual studies represented by OR and 95% confidence interval. B. Forest plot of meta-analysis of lower DNA repair capacity and breast cancer risk by assay type in random effect model. Individual studies represented by OR and 95% confidence interval.

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