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Introduction

Many of the known and suspected risk factors for prostate cancer are associated with elevated levels of ROS (advancing age, inflammation, androgen, high-fat diet), or decreased antioxidant capabilities (fruit and vegetable consumption, specific dietary antioxidants, such as selenium, vitamin E and carotenoids). Oxidative stress, which results from an imbalance between ROS and antioxidant capacities, can cause a wide range of direct or indirect DNA damage. There are extensive DNA repair systems that can correct DNA damage caused by ROS before cell replication and mutation fixation. For instance, ROS-caused base damages and single strand breaks are mainly repaired by BER and NER; DNA adducts caused by ROS-induced lipid peroxidation are repaired by NER; and ROS caused-DNA double strand breaks are repaired by HRR and NHEJ. However, DRC is substantially variable among individuals in the population, and suboptimal DRC of oxidative DNA damage might increase genomic instability and hence, increase risk of cancer. Although oxidative stress appears to be important in the etiology of prostate cancer, so far there is no study to comprehensively investigate the association between DRC of oxidative DNA damage as a phenotype and prostate cancer risk.

Body

Study subject recruitment: At the end of May of 2010, we have recruited 287 men diagnosed with prostate cancer as cases and 276 healthy men as controls. Both cases and controls were recruited through DataBank BioRepository (BDDR) of Roswell Park Cancer Institute (RPCI). On average, we have around 15 cases and 15 controls per month. We expect to complete the recruitment of 300 cases and 300 controls in tow months. Because we have extra time left, we will increase our sample size to recruit 50 more cases and 50 more controls.

Specific aim 1: we will measure levels of 8-OH-dG after exposure to H_2O_2 in PBLs in 300 men with prostate cancer and 300 healthy controls, using ELISA based mutagen sensitivity assay. Our hypothesis is that cases will exhibit higher levels of 8-OH-dG after exposure to H_2O_2 (reflecting lower BER activity) compared with healthy controls. So far, the proposed 8-OH-dG analysis has been carried out in 145 prostate cancer cases and 134 healthy controls. The mean levels of 8-OH-dG were significantly higher in cases than in controls (4.63 vs. 3.07, $P < 0.01$). In further stratified analysis, using median levels of 8-OH-dG in controls as the cutoff point, we found higher levels of 8-OH-dG was associated with 1.62-fold increased prostate cancer risk (OR= 1.62, 95% CI: 1.09 to 2.45). The association is consistent with what we found in previous annual report.

Specific aim 2: we will assess levels of DRC of DNA adducts induced by 4-HNE in PBLs in 300 prostate cancer cases and 300 healthy controls, using plasmid based modified HCR assay. 4-HNE is a major product of endogenous lipid peroxidation. 4-HNE caused DNA adducts is mainly repaired by NER. Our hypothesis is that cases will exhibit lower levels of NER of 4-HNE caused DNA adducts compared with healthy controls. So far, the proposed 4-HNE based host cell reactivation (HCR) assay has been

carried out in 145 prostate cancer cases and 134 healthy controls. The mean levels of 4-HNE based HCR were marginally lower in cases than in controls (6.3% vs. 8.5%, $P=0.067$). In further stratified analysis, using median levels of 4-HNE based in controls as the cutoff point, we found lower levels of 4-HNE based was not associated with the prostate cancer risk ($OR= 1.19$, 95% CI: 0.70 to 1.82). The association is consistent with what we found in previous annual report.

Specific aim 3: we will assess levels of HHR and NHEJ of double strand breaks in PBLs in 300 men with prostate cancer and 300 healthy controls, using plasmid based modified HCR assays. Our hypothesis is that cases will exhibit lower levels of HR and NHEJ compared with healthy controls. For HR assay, the assay has been carried out in 145 prostate cancer cases and 134 healthy controls. The mean levels of HR activity were lower in cases than in controls (10.1% vs. 11.6%, $P=0.51$), but the difference didn't reach statistically significant. For NHEJ assay, the assay has been carried out in 145 prostate cancer cases and 134 healthy controls. The mean levels of HR activity were lower in cases than in controls (8.0% vs. 8.8%, $P=0.56$), but the difference didn't reach statistically significant. The association is consistent with what we found in previous annual report.

Overall, we expect to complete the proposed analyses on time. Moreover, we expect to recruit 50 more cases and 50 more controls.

Key Research Accomplishments

1. At the end of May of 2010, we have recruited 287 men diagnosed with prostate cancer as cases and 276 healthy men as controls. We don't expect any delay in the study subject recruitment.
2. The proposed molecular analyses in specific aims 1-3 have run well. We expect to complete the proposed analyses on time.
3. We have obtained questionnaire data from 252 patients and 246 controls.
4. In training, Dr. Zhao has involved in Dr. Mohler's SPORE grant application.

Reportable outcomes

Because the study is still ongoing, at this point, we don't have any manuscript in preparation. But, we expect to begin to prepare two manuscripts pretty soon.

Conclusion

The study has run smoothly so far. We don't expect any delay.