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Genetic Predisposition to Radiation-related Cancer and Potential Implications for Risk Assessment

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Abstract

Several lines of evidence suggest that risk estimates for cancer associated with radiation exposure incorporate individuals who are more and less inherently susceptible to radiation's carcinogenic effects, and the technology to further evaluate this issue is now available. For example genome-wide association scan studies could be undertaken to at least partly address the direction of causality in the observations of differential sensitivity to radiomimetic agents in cancer cases versus normal individuals; thereby building on previous observations that sensitivity to these agents is higher in apparently normal individuals carrying gene mutations in *NBS* and *ATM*. Direct studies of risk of second cancers in relation to radiation are underway and some results have been reported, e.g. for the *PRDM1* gene as related to sensitivity to radiation-related cancers after treatment for Hodgkin lymphoma. The risk synergies between variants affecting associations with various cancers defining susceptibility in unexposed populations and the excess risk in populations therapeutically or occupationally exposed to radiation will be important to understand for the purpose of risk protection, especially as additional baseline risk variants are discovered in increasingly large-scale analyses. While there are studies that are beginning to address these questions, at the present time there are no compelling new discoveries that would indicate that predisposition information should now be included in risk assessment. The conclusions in ICRP Publication 79 and 103 appear relevant today.

Keywords

Genetic susceptibility; radiosensitivity; cancer; risk factors; interaction; synergy

1. INTRODUCTION

There has been a veritable explosion in information from genome-wide association scan (GWAS) studies that hold the promise in predicting risk of complex diseases (Hindorff et al, 2011; www.genome.gov/GWASStudies) and potentially radiation-associated cancers (Takahashi M et al, 2010; Best et al, 2011). The question of whether and when such information might be judged useful for incorporation into risk assessment for radiation-associated cancer risk remains, but at the present time is considered premature. In International Commission on Radiological Protection (ICRP) publications 79 (1998) and 103 (2007) the same judgement was made. Despite considerable recent advances on several significant fronts, there is insufficient compelling evidence to change it.

Specifically, ICRP 103 (2007) states on page 143 that “Genetic susceptibility to radiation-induced cancer involving strongly expressed genes is judged to be too rare to appreciably distort estimates of population risk; the potential impact of common but weakly expressing genes remains uncertain” and on page 192 “the Commission believes that strongly expressing, high penetrance, cancer genes are too rare to cause significant distortion of the population-based estimates of low-dose radiation cancer risk made in this Section of the report. However, as noted in Publication 79, there are likely to be implications for individual cancer risks, particularly for second cancers in gene carriers receiving radiotherapy for a first neoplasm. Although the Commission recognises that weakly expressing variant cancer genes may, in principle, be sufficiently common to impact upon population-based estimates of radiation cancer risk, the information available is not sufficient to provide a meaningful quantitative judgement on this issue.”

With the advent of new knowledge, such judgements must be re-considered and examined. This report is an update on selected pertinent information with respect to genetic susceptibility to radiation exposure and cancer that might have bearing on progress in identifying those who may be at heightened risk.

2. RADIATION-SENSITIVE SUB-POPULATIONS

Several lines of evidence suggest that risk estimates for cancer associated with radiation exposure are composed of individuals who are more and less inherently susceptible to radiation's carcinogenic effects. Measures of radiosensitivity include several different types of cellular materials and endpoints, and is complicated by the reality that radiosensitivity, increased genetic instability and cancer susceptibility are intertwined (Streffler, 2010). DNA repair capacity or fidelity of repair is one means by which radiosensitivity could manifest as variation among human populations. The early pioneering assays measured chromatid breaks and gaps after administering bleomycin (a radiomimetic agent) or gamma-radiation in the G2 phase of the cell cycle to assess repair efficiency (Hsu 1983; Hsu et al, 1989; Parshad et al, 1983; Parshad et al, 1985). These tests have become known collectively as the mutagen sensitivity or G2-phase chromosomal radiosensitivity assays, and over the past 3 decades, have employed various mutagen challenges to assess DNA damage responses in a range of cell types, including peripheral blood lymphocytes, lymphoblastoid cell lines, skin fibroblast lines, white blood cells and buccal cells (Berwick and Vineis, 2000; Wu et al, 2007; Li et al, 2009; Kato et al, 2009). With newer tools, such as the detection of DNA double-strand breaks by quantifying the levels of gamma-H2AX foci or measuring cellular sensitivity to low-dose-rate ionizing radiation, investigators have observed a variability of around 1.5-fold in strand break repair efficiency among ataxia telangiectasia heterozygotes, retinoblastoma family members, and apparently normal individuals (Wilson et al 2010, Kato et al, 2006; Kato et al, 2007). Further evidence for a disparity in DNA repair or a DNA damage phenotype emerges in family and twin studies, where heritability of radiation sensitivity associates with family members who are radiation sensitive or in families with breast cancer-affected relatives (see reviews in Wu et al 2007 and Kato et al 2009; Roberts et al, 1999). The prevalence of mildly radiosensitive individuals can't be known, but estimates of about 30% have been proposed (Kato et al, 2009). In considering the prevalence of sensitive individuals, it is also likely some proportion may be mildly resistant, who would hypothetically influence risk estimates in the opposite direction.

Mutation-sensitive phenotypes or measures of DNA damage and association with cancer risk have been reported extensively (see reviews in Berwick and Vineis, 2000; Wu et al, 2007; Li et al 2009). Limitations of these primarily case-control approaches have been discussed in detail (Berwick and Vineis, 2000; Collins and Harrington, 2002; Caporaso, 2003) with the chief concern that the assays are unable to discriminate between the host's

response to cancer and the presumed underlying genetic susceptibility. Prospective studies have been small (Chao et al, 2006) or the effect estimates were strongly reduced (Sigurdson et al, 2011) suggesting the assays would need to improve considerably for use as predictive tests to detect susceptible sub-populations.

3. DISCRIMINATING SPORADIC FROM RADIATION-RELATED TUMOURS

A so-called radiation “signature” within a tumour has long been sought. The ability to discriminate tumours caused by radiation exposure apart from their sporadic counterparts would be an enormous step forward. Especially critical is the identification of cancers associated with ever lower doses of radiation such that these tumours might be detected despite their spontaneous background rates, where epidemiologic methods are known to be uninformative (Streffer, 2009). Prospects to identify radiation-induced tumours using gene expression methods are improving, at least after high-dose radiotherapy, for thyroid tumours (Ory et al, 2011) and sarcomas (Hadj-Manou et al, 2011). As laboratory and analytic methods are refined (Ugolin et al, 2011) it may be possible to attribute a portion of tumours to specific carcinogens similar to those between aflatoxin and hepatocellular carcinoma.

4. GENOME-WIDE ASSOCIATION STUDIES

Genes and pathways involved in radiosensitivity or normal tissue toxicity include sensing DNA damage, cell cycle checkpoints, intermediate protein recruitment, repair pathways (base excision, homologous recombination, nonhomologous end-joining), apoptosis, inflammatory cytokines, fibrotic proteins, extracellular matrix, antioxidant enzymes, cytokines, and growth factors (Barnett et al, 2009) suggesting radiation susceptibility to increased cancer risk is polygenic. The inheritance of several low penetrance risk alleles would have the greatest impact on risk assessment but the predictive power is unknown or low, and while not without progress, remains insufficient to affect previous judgements (ICRP 79, 102).

Two GWAS studies among cases and controls with high attributable risks for radiation-related cancers have uncovered variants in the *FOXO1* gene in thyroid cancer and the *PRDM1* gene for multiple cancers sites after Hodgkin lymphoma. The thyroid cancer study was conducted among those exposed in the Chernobyl accident (Takahashi et al, 2010) and confirmed an earlier report with respect to *FOXO1* in sporadic thyroid cancer (Gudmundsson et al, 2009) suggesting the loci’s importance with or without previous radiation exposure. Nevertheless, with familial thyroid cancer risk on the order of 4- 6-fold (Dong and Hemminki, 2001; Frich et al, 2001; Goldgar et al, 1994; Hemminki and Li, 2003; Hrafinkelsson et al, 2001) compared to breast cancer at 2- 3-fold, the use of denser genotyping platforms in the future, and incorporation of radiation dose in the risk calculations are likely to enhance discovery of many more risk variants with some specifically associated with radiation-related thyroid cancer. Radiation-related second cancers after a first diagnosis of Hodgkin lymphoma in the Childhood Cancer Survivor Study (CCSS) cohort revealed a role of the *PRDM1* gene, for which replication sets gave some support in childhood but not adult settings and functional studies showed the protective genotype was related to *MYC* suppression (Best et al; 2011).

If a radiosensitivity assay emerges with high predictive value for radiation-associated cancers, then GWAS studies could be applied in a similar way as that used to recently identify the *PMAIP1/Noxa* gene’s association with sensitivity to the radiomimetic agent bleomycin (Gu et al, 2011). While this approach is encouraging, the reality remains that a genetics-based test for a radiosensitivity phenotype is a prospect for the future.

5. POLYMORPHISM ASSOCIATIONS WITH RADIATION-RELATED CANCER RISK

Cancer-associated genetic variants identified through GWAS studies are distributed across the genome with a few exceptions such as clustering in the 8q24 region, *TERT* and *TP53* (Hindorff et al, 2011) and suggests pleiotropy would also be unlikely for genes involved in radiation-related cancers. This means that several different sets or “constellations” of genes would probably be involved in different radiation-related cancers. For example, the organs of breast and lung are known to be radiation-related sites. Based on candidate gene and GWAS studies, the gene sets for breast and lung cancer involve completely different genes and very different numbers of genes with varying allele frequencies (see Figs 2 and 5 in Hindorff et al, 2011). Adding to gene heterogeneity is phenotype heterogeneity since breast and lung cancer are comprised of different histologies and molecular sub-types. So, despite the initial association with *PRDM1* and several radiation-associated cancer outcomes, it is not promising that interrogating a small set of variants would appreciably capture radiation-related cancer risk.

Assessing polymorphic variation within pathways (such as homologous recombination or non-homologous end-joining DNA repair) or specific up- or downstream interacting genes and proteins with genes of interest (eg. *ATM*, (Brooks et al, 2011) has been applied with variable success with respect to radiation-associated contralateral breast cancer in the Women’s Environmental Cancer and Radiation Epidemiology (WECARE) study and other studies. A strategy of counting potentially functionally deleterious polymorphisms (Johnson et al, 2007) or using GWAS study findings in aggregate to overcome low predictive power by combining variants with individually weak effects (Jostins and Barrett, 2011) may prove useful as more studies are done with denser gene coverage or sequencing. For example, after sequencing the *BRCA1* and *BRCA2* genes, hierarchical methods were used to estimate risk when the variants found were of uncertain or unknown significance (Capanu et al, 2011). Again, while promising, these efforts represent applications still in relative infancy and without robust predictive ability that would be required to affect estimates of risk for individuals or populations.

6. THEORETIC IMPLICATIONS

To date one somewhat surprising overall result of cancer GWAS studies is that few “interactions” have been observed between the risk alleles that have been uncovered. Interaction is a tricky concept since the scale that an effect is measured on underlies its definition. What is often observed in case control studies analyzed using logistic regression is that few departures from the additive logistic model (which is close to a multiplicative model for most diseases) have been seen when pair-wise or higher order interaction terms are considered (i.e. few such terms are significant). As described above it appears that for most cancers the risk associated with each allele is modest and that as GWAS studies and meta-analyses of GWAS studies become larger, more and more alleles with modest effect will be discovered (Fletcher & Houlston 2010); thus GWAS study findings to date tend to support a simple polygene model in which genetic risk acts nearly multiplicatively, as $\exp(w)$, where w is a weighted composite summation over many modestly risk-associated variants, with weights reflecting the individual contributions of each risk variant.

Under this lognormal model, and assuming Mendelian inheritance of each of the individual contributions to w , one can relate the variance of w to the familial relative risk (FRR) between relatives (ignoring any other causes of familial similarity). For example if the FRR is 2 between two siblings (meaning that disease in one sibling doubles the risk in the other sibling, a value not unreasonable for many cancers) then the variance of w is $2\log(2)$. The

general formula is $\text{Var}(w) = \log(\text{FRR})/r$ where r is the coefficient of relationship between the two relatives considered, i.e. 1/2 for siblings or parent-offspring, 1/8 for cousins, etc. Under these assumptions consider the situation (perhaps far in the future) when all contributions to w are known. If the variance of w is $2\log(2)$ then we would expect that the highest quintile of the population would have average risk approximately 6.8 times the rest of the population; looking at this another way the upper 20 percent of the risk distribution would contribute approximately 63 percent of cases. With such a powerful risk factor available it seems extremely important to understand how radiation modifies the risk not just of individual genetic elements that compose w but also (and perhaps more importantly at least for prediction) of the effect of w overall. Suppose that radiation exposure also acts multiplicatively on risk irrespective of w , i.e. that there is no sub- or super-multiplicative interaction between w and radiation. An interesting consequence of this supposition is that the distribution of genetic risk among the cases will not depend upon radiation exposure. For the above example population the same 63 percent of the excess cases (those that would have not been seen had there not been radiation exposure) would be expected to come from the upper quintile of the distribution of genetic risk no matter how heavily exposed. This could raise issues for radiation protection in the future, centered on whether the genetically susceptible would either desire to be or should be forced to be subject to greater protections, e.g. in occupational, diagnostic, or therapeutic settings, than are those with different (protective) pattern of alleles. Super-multiplicative interactions between risk score and radiation exposure would mean that the genetically susceptible would comprise even greater proportions of any excess cases expected in the population.

An important current question has to do with the reasonableness of the assumptions that go into calculations like these, for example at this point today only a small fraction of the "heritability" of most common diseases is explained by either the high risk variants discovered by linkage studies or the far more modestly associated common risk alleles discovered by GWAS studies. Some however (Yang et al, 2010; Yang et al, 2011; Lee et al, 2011; Purcell et al, 2009), perceive suggestive patterns that lend credence to the notion that a high degree of genetic variation may be better explained by common SNPs, when (and if) much larger sample sizes are available in the future than are today. More specifically: the reasonableness of a simple polygene effect (as opposed to much more complex genetic interactions) can be investigated by comparing "long range" heritability to "short range" heritability, since the heritability of the effects of complex (nonmultiplicative) interactions drops off quickly as the relationships among individuals become more distant. Indeed the methods of Lee et al (2011) applied to several common diseases appear to provide evidence of strong polygenic effects over a very long range (i.e. extending to the background relatedness of "randomly sampled" persons). The consideration of how such a polygene synergizes with radiation exposure will be an important problem as further risk alleles are discovered; studies such as WECARE and the CCSS offer the chance to directly test whether risk allele counts or weighted risk scores involving known risk alleles from other GWAS studies synergize either sub- or super-multiplicatively with second cancer risk after treatment for breast or Hodgkin lymphoma, respectively.

7. CONCLUSIONS

Despite promising recent advances in phenotypic assays of human radiosensitivity, molecular radiation signatures in tumors, genetics of common and radiation-related diseases, and the statistical theory and computing power that would assist in quantifying variation in radiation susceptibility, there is insufficient compelling evidence to change current ICRP recommendations with respect to risk assessment and radiation protection. The progress and efforts described herein still represent applications at relatively early stages and without robust predictive ability that would be required to affect estimates of risk for individuals or

populations. On the other hand, as more and more baseline risk variants are discovered in ever larger analyses, it will be important to understand susceptibility with respect to risk synergies between variants and host characteristics. Whether risk allele counts, weighted risk scores involving known variants, or other new theoretical approaches are used remain prospects for the future. Also required is a more complete understanding of the intertwined biologic processes underlying radiosensitivity, genomic instability, and cancer susceptibility.

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