A Strong Case for Personalized, Targeted Cancer Prevention

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Abstract

The study reported by Lee and colleagues in this issue of the journal (beginning on page 185) incorporated global genetic variation within a new assessment of the outcome of a previously reported phase-III trial of low-dose 13-cis-retinoic acid (13-cRA) for preventing second primary tumors (SPT) or the recurrence of head-and-neck cancer. This analysis identified genotypes of common single-nucleotide polymorphisms (SNP) and cumulative effect and potential gene–gene interactions that were highly associated with increased placebo-arm risk (prognostic) and/or with reduced treatment-arm risk and longer event-free survival (predictive). For example, the wild-type rs3118570 SNP of the retinoid X receptor alpha gene (carried by 71% of the 13-cRA trial population) marked a 3.33-fold increased SPT/recurrence risk in the placebo arm and a 38% reduced risk in the treatment arm. Adding two other informative genotypes strengthened the treatment-arm risk reduction to 76%, although the genotype trio reflected only 13% of the trial population. This report extends the concept of personalized therapy to cancer prevention.


The retinoid 13-cis-retinoic acid (13-cRA, or isotretinoin) once was among the most promising agents for cancer chemoprevention in the modern day. Outcomes of phase-III cancer prevention trials of 13-cRA in the lung and head and neck, however, were disappointing (1–3). Now in this issue of the journal (4), Lee and colleagues report an additional assessment of one of these phase-III trials, which evaluated 13-cRA for head-and-neck cancer prevention, that brings new hope for successful cancer prevention with retinoids in certain at-risk populations and suggests that outcome analyses incorporating genotypic data can detect positive aspects of otherwise negative cancer prevention trials. This new study also provides a proof of principle of the potential of pharmacogenetics to personalize cancer prevention.

13-cRA is currently used for the systemic treatment of severe cystic acne and other cutaneous conditions such as severe acne rosea, harlequin ichthyosis, and xeroderma pigmentosum keratoses. This RA isomer is considered to be transcriptionally inactive and functions instead as a prodrug that is transformed in vivo to all-trans-retinoic acid (ATRA, or tretinoin) and its 9-cis isomer (9-cRA, or alitretinoin). Both ATRA and 9-cRA have roles in regulating cell proliferation and inducing cell differentiation through their interaction with nuclear retinoid X receptors (RXR) and RA receptors that function as transcription factors. In the presence of light or a mercaptan such as reduced glutathione, RAs undergo double-bond isomerizations to produce mixtures containing about 80% ATRA and 8% to 10% 9-cRA (5–7). Therefore, dosing with 13-cRA was anticipated to minimize the adverse effects caused by administering high levels of the transcriptionally active RA isomers (8). However, even at the low dose levels used in cancer prevention trials, subjects taking oral 13-cRA have experienced significant dose-related toxic effects (9–11).

The major cause of head-and-neck squamous cell carcinoma (SCC) is the use of tobacco and the subsequent exposure to its carcinogens and irritants. Indeed, 85% of head-and-neck cancers have been linked to tobacco use (smoking and chewing; ref. 12). Although human papillomavirus (HPV) is a rapidly increasing cause of head-and-neck cancer (predominantly through effects in the oropharynx; ref. 13), this cause did not play a major role in the population of the phase-III 13-cRA trial examined by Lee and colleagues (4). In 2010, the U.S. yearly incidence of head-and-neck SCC, which includes the upper aerodigestive tract sites of the oral cavity, pharynx, and larynx, was estimated to be more than 49,000 cases (3% of all new cancers) by the American Cancer Society; the annual number of deaths from this disease was estimated to be approximately 11,500 (14). With an annual incidence estimated at more than 0.5 million cases, head-and-neck cancer is the fifth most common cancer worldwide. Stage I–II disease is usually curatively treated by surgical resection and/or radiation; long-term survival, however, has continued to be problematic because of frequent recurrence and the development of second primary tumors (SPT). Head-and-neck cancer development is a multistep process that involves the accumulation of genetic and epigenetic alterations in chromosomes including 3p, 9p, 13q, and 17p and gene
mutations leading to constitutive activation of oncogenes and loss of function of tumor suppressor genes, many of which have been shown to be associated with SPT appearance or cancer recurrence (15). Khuri and colleagues (1, 16) reported that about 15% to 25% of early-stage head-and-neck SCC patients developed SPTs and 10% had local recurrences within 5 years of surgery and/or radiation.

The original analysis of the phase-III trial of 13-cRA to prevent SPTs and recurrence of head-and-neck cancer (recruitment from 1991–1999) did not support continued investigation of 13-cRA as a cancer preventive agent (1). The trial randomly assigned 1,190 stage-I and stage-II head-and-neck cancer patients to low-dose 13-cRA or placebo. These patients had previously undergone surgical resection and/or radiation therapy and were disease-free at 16 weeks or more after treatment. SPTs were defined as tumors that appeared at least 3 years after the primary tumor and had a different histology than or were 2 cm or more away from it; recurrence was defined as new cancer with a similar histology to the primary tumor and occurring within 2 cm or within 3 years of primary tumor diagnosis. Combining SPTs and recurrence in this trial reflects the problem of distinguishing these two treatment failures in the head and neck and lung. Patients who developed symptoms of grade-2 or higher toxicity (29.5% on 13-cRA and 9.2% on placebo) were withdrawn from treatment until symptoms of toxicity resolved, and then they were allowed to resume therapy until toxicity recurred, when their drug dosage was reduced. No statistically significant reduction in the rates of SPT (HR = 1.06; 95% CI, 0.83–1.35) or recurrence (HR = 0.79; 95% CI, 0.55–1.14) and no increased survival time (HR = 1.03; 95% CI, 0.81–1.71) occurred in the 13-cRA treatment arm compared with the placebo arm.

The influence of a patient’s genetic background on the risk and prognosis of cancer is increasingly recognized (17). A previous analysis of this phase-III 13-cRA trial involved the first comprehensive global genotyping approach to analyzing clinical trial results in this setting (18). That analysis assessed associations between certain single-nucleotide polymorphisms (SNP) and an increased risk of SPT/recurrence among 150 patients with and 300 matched controls without SPT/recurrence from the original trial population.

Genotyping in these patients involved 9,645 candidate SNPs derived from 998 cancer-related genes having roles in 12 cellular signaling pathways. Seven chromosomal SNPs were significantly associated with the risk of SPT/recurrence after adjusting for multiple comparison, and genes associated with these SNPs have roles in cellular processes such as proliferation, DNA repair, stem-cell differentiation, carcinogen metabolism, growth-factor signaling, and apoptosis.

Six mitochondrial DNA SNPs also were associated with an increased risk of SPT/recurrence after multiple comparison adjustment. The authors concluded that the most significant mitochondrial SNP was that located in the NADH dehydrogenase subunit 4 (ND4) gene, which previously had been found to be associated with head-and-neck cancer (19). The protein encoded by ND4 is a subunit 4 of the NADH dehydrogenase, which resides in the mitochondrial respiratory chain that generates ATP complex I, and has a role in carcinogen metabolism. Two other mitochondrial SNPs associated with altered risk were SNPs of the mitochondrial cytochrome B gene (mtCYB), which encodes the P450 enzyme mtCYB, another component of the respiratory chain and also found to be associated with head-and-neck cancer. A deletional mutation leading to overexpression of mtCYB is reported to increase reactive oxygen species (ROS; ref. 20) and to enhance bladder cancer cell proliferation (21). Tobacco carcinogens also increase ROS leading to DNA damage, thereby suggesting an additive relationship between tobacco use and mtCYB activity.

Wu and colleagues constructed prediction models, as illustrated by receiver operating characteristic curves in their Figure 2 (18), by adding these genetic variables to the clinical (tumor stage, site, and treatment) and smoking (pack-years) variables. They showed that the area-under-the-curve increased dramatically from 0.64 (clinical and smoking variables) to 0.84 (clinical, smoking, and genetic variables), indicating a significant improvement in prediction efficiency with the addition of genetic variables. The authors pointed out that a blood draw is a far less-invasive and less-expensive method of obtaining samples for genotyping than is biopsy via bronchoscopy.

This global genotyping study of the phase-III 13-cRA trial analyzed the prognostic value of SNPs in a combined group of patients from the placebo and treatment arms. Lee and colleagues (4) have gone a step (13-cRA or placebo) further by stratifying the same genotyping data by treatment in the same patient population used by Wu and colleagues (18). This new study first identified prognostic loci for increased SPT/recurrence risk in the placebo group, focusing on the previously genotyped chromosomal SNPs (not the much lower number of mitochondrial SNPs), and then examined whether these loci also identified individuals who received benefit from 13-cRA treatment. Furthermore, by focusing on wild-type genotypes (or common genotypes present in the majority of the population) associated with an increased placebo-arm SPT/recurrence risk and a reduced 13-cRA-arm risk, this study aimed to identify genotypes that could mark a substantial proportion of the patients who might benefit from 13-cRA prevention. The wild-type genotypes of 45
SNPs were associated with an increased risk of SPT/recurrence in the placebo group. Of these 45 loci, 17 were associated with a decreased risk of SPT/recurrence in the 13-cRA group (compared with placebo), and 13 were statistically significantly ($P < 0.05$). Placebo patients with wild-type genotypes for SNPs in the genes for RXR-alpha (RXRA), Janus kinase 2 (JAK2), metalloproteinase 3 (MMP3), RAD54-like (RAD54L), and cell division cycle 25 homologue C (CDC25C) had a 1.85- to 3.57-fold higher risk of SPT/recurrence. Of note, placebo patients with the wild-type genotype RXRA rs3118570 (present in 71% of the trial population) exhibited a 3.33-fold increased risk of SPT/recurrence and a 1.5-year longer event-free survival than the placebo patients with the same genotype. Furthermore, patients in the treatment arm with the wild-type JAK2 and CDC25C genotypes plus the RXRA wild-type genotype (representing 13% of the trial population) had an increased benefit from 13-cRA of a 76% reduced risk for SPT/recurrence and a more than 5 years event-free survival advantage (versus placebo-arm patients with the same 3 genotypes). Subgroup analyses of SPT or recurrence only in the head and neck or lung revealed the same pattern of prognostic and predictive effects for 2 (RXRA and JAK2) of the 3 SNPs. Although RXRA, JAK2, and CDC25C were most significant, several genetic loci within TSC1 (which regulates PI3K/AKT/mTOR signaling, a critical pathway in head-and-neck carcinogenesis) were among the top hits (e.g., Table 2 of ref. 4), which supports future, more-depthful genotyping analysis of this pathway that may further improve the prediction models in this setting.

The analysis of Lee and colleagues (4) highlights the importance of stratifying global genotyping analyses by treatment and the limited ability of unstratified (by treatment) analyses to detect markers with predictive effects in treated individuals and prognostic effects in untreated individuals that are opposite to each other. For example, the RXRA SNP was not observed to be significantly associated with SPT/recurrence risk in the unstratified analysis of Wu and colleagues (18). Its effect was essentially "washed-out" by the difference in the placebo and 13-cRA arms. This wash-out likely also occurred in 3 other unstratified/combined-arm studies focusing on SPT/recurrence prognostic factors by the same group of investigators in the phase-III 13-cRA trial (22–24). In the past, investigators have tended to combine arms for genotyping studies of negative/neutral trials. These previous unstratified, combined-arm analyses produced significant prognostic factors. The present stratified-by-treatment analysis suggests prognostic and predictive markers. No overlaps in the top hits occurred between the unstratified and stratified analyses of the same panel of chromosomal SNPs in the same patients, which is not surprising. Further research remains to be done to discern how each of the risk-reducing genotypes and their related proteins exert protective effects in combination with 13-cRA.

It is hoped that such predictive analyses can be extended to other large cohorts, including cohorts of people at risk of primary head-and-neck cancer, head-and-neck cancer patients, and long-term randomized trials of retinoids that had original statistical analyses of outcomes leading to conclusions that their treatments had failed to prevent SPT development or recurrence (17). Such trials include the phase-III U.S. National Cancer Institute Lung Inter-group Trial of 13-cRA to prevent recurrence and/or SPTs in the setting of non-small-cell lung cancer (2, 3) and a phase-III trial of N-(4-hydroxyphenyl) all-trans-retinamide (fenretinide) to prevent recurrence and/or SPTs in the setting of breast cancer (25).

In conclusion, the important genotyping work reported by Lee and colleagues in this issue of the journal (4) in the setting of recurrence and SPTs in head-and-neck cancer patients indicates the potential of genotyping for helping to personalize cancer prevention. Although perhaps less advanced than this global approach in a phase-III clinical trial, genotyping work in other sites, including the colorectum (aspirin, celecoxib, statins), prostate (selenium), and bladder (BCG), is beginning to make headway toward personalized cancer prevention as well (26–29). Similar personalized genotyping approaches are being applied in research in tobacco dependence (30) and cancer therapy (31). Although Lee and colleagues did internal validation of their results using a bootstrap resampling analysis, it will be important to test their findings in an external validation cohort. It also will be important to extend global genotyping analyses to cohorts of patients with HPV-associated head-and-neck cancer since HPV-related cases are increasing dramatically, have distinct risk factors and clinical features (13, 32), and likely will not have the same prognostic and predictive profiles that classic smoking-related cases have. The combined results of all such analyses may culminate in a strong case for personalized, targeted cancer prevention.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References


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