Cari Kitahara Explores Medical Radiation Exposures and Thyroid Cancer Etiology

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Tenure-track investigator Cari Kitahara, Ph.D., has built a multidisciplinary research program in the Radiation Epidemiology Branch (REB) with a dual focus: to explore cancer risks from occupational and medical radiation exposures, and to investigate the etiology of radiosensitive tumors, including thyroid cancer.

Her work is helping to advance our understanding of the health consequences of low-dose radiation and may address important public health and clinical concerns about radiation exposure from medical sources. In addition, her research on thyroid cancer has provided some of the strongest and most compelling evidence to date to support a true increase in the incidence of the disease in the United States.

Occupational and Medical Radiation Exposure and Cancer

Exposure to ionizing radiation from both natural and man-made sources is ubiquitous in today’s world. Although recognized as a known carcinogen, there are important public health questions related to quantifying the health risks from the low levels of ionizing radiation received by most of us in the general population.

Dr. Kitahara is particularly interested in cancer risks associated with occupational exposure to low-dose radiation from emerging medical practices and procedures. “Occupational groups, such as radiologic technologists, are routinely monitored for radiation exposure as part of worker-safety measures,” she said. “This provides a unique setting for studying associations between radiation and cancer.”

Much of her current work focuses on nuclear medicine (procedures that use radioactive substances to diagnose and treat disease) and fluoroscopically-guided interventional (FGI) procedures, which use ionizing radiation to guide small instruments such as catheters through blood vessels or other pathways in the body. As these types of procedures have increased in number and complexity over time, concerns have grown about the possible risks associated with radiation exposure to the medical workers who perform and assist with them, as well as the patients who receive them.

“We hope that findings from these studies can inform current radiation protection practices for medical workers and, more broadly, improve our understanding of the impact of low-dose radiation exposure on the risk of cancer in the general population,” Dr. Kitahara said.

To better understand the exposures from these new procedures, Dr. Kitahara recruited postdoctoral dosimetry fellows Daphnée Villoing, Ph.D., and David Borrego, Ph.D. “We have dosimetrists and epidemiologists...
working side-by-side to incorporate state-of-the-art exposure assessment into our epidemiologic work,” she said. “Bridging these two fields helps to advance our studies.” Drs. Villoing and Borrego assist with organ and tissue dose calculations that will eventually become available for retrospective and prospective evaluations of radiation dose-response for risks of cancer and other serious health outcomes in medical radiation workers and patients.

**Risks from Nuclear Medicine, Occupational Exposure**

The NCI began studying cancer risks in medical workers exposed to ionizing radiation decades ago. The U.S. Radiologic Technologists (USRT) study was launched in the early 1980s and continues to yield important information on cancer and other disease risks among workers enrolled in the cohort. Dr. Kitahara has been working with USRT for several years: “One of my first projects looked at cancer and cardiovascular disease in a subset of technologists who performed nuclear medicine procedures.”

Together with her colleagues, Dr. Kitahara reported an increased risk of certain cancers and cardiovascular diseases in that group. “In contrast to professionals who work with standard radiologic procedures, those who work with nuclear medicine cannot avoid being in close contact with radioactive pharmaceuticals as they prepare or administer injections and during the imaging process.” To pursue these observations, she utilized more detailed nuclear medicine work histories collected in a follow-up of the USRT cohort to evaluate risks for a wide range of cancers and other serious diseases. Among her latest results was an increased risk of cataracts among technologists who reported performing diagnostic or therapeutic nuclear medicine procedures.

Despite the value of the USRT cohort, to fully characterize occupational radiation exposure and associated risks, Dr. Kitahara needed more contemporary data. So, she launched a new study among certified nuclear medicine technologists. “These are professionals who received training in more recent years,” she said. “We noticed that the annual exposure levels of certified nuclear medicine staff are higher relative to most other medical radiation workers, and may be increasing due to the growing number of higher-dose procedures performed in recent decades.”
Risks from Fluoroscopically-guided Interventional (FGI) Procedures, Occupational Exposure

FGI procedures are often an alternative to more invasive surgeries, because they require only a very small incision, substantially reduce the risk of infection, and allow for shorter recovery time compared to surgical procedures. These interventions are used by a rapidly expanding number of health care providers in a wide range of medical specialties. However, many of these specialists have little training in radiation science or safety measures.

Clinical reports of higher-than-expected frequency of left-sided brain tumors in physicians who do these procedures have raised concerns about occupational exposure to ionizing radiation; higher doses to the left side of the clinician’s body result from their typical positioning to the right of the patient’s bed.

In a recent study, Martha Linet, M.D., M.P.H., REB Chief Amy Berrington de González, D.Phil., Dr. Kitahara, and colleagues found no overall increased risk of death among U.S. physicians who performed FGI procedures, compared to a group of physicians who did not. Importantly, they noted no elevated risk for brain cancer mortality.

Though reassuring, Dr. Kitahara notes that no dose information was available to assess whether these risks increased with greater exposure. She is exploring the possibility of linking this population to dosimetry data from the largest U.S. commercial dosimeter badge provider to obtain more precise measures. Additionally, follow-up of the cohort has been limited to mortality based on death certificate data, which does not provide information on the specifics of a cancer diagnosis (hemisphere of the brain, leukemia subtype, etc.). “I hope to link our cohort to state cancer registries to obtain more detailed diagnostic information,” she said.

Under Dr. Kitahara’s supervision, Raquel Velazquez-Kronen, M.S., a doctoral student in epidemiology, is evaluating the long-term risk of cataracts in radiologic technologists who assisted with FGI procedures. Physicians conducting these procedures have an increased risk of cataracts, but there has been limited information about the risk to other radiation-exposed staff.

Estimating Risks to the Patients

Radiation is a valuable tool for diagnosing and treating many life-threatening conditions. As with any medical intervention, there are risks and benefits to the patient. The investigations by Dr. Kitahara and others provide information for clinicians and patients as they make decisions about which techniques are most appropriate.

Dr. Kitahara is leading the largest and most comprehensive study to date on the long-term health effects of internal radiation exposure for patients who have been treated with radioactive iodine for hyperthyroidism, an over-active thyroid condition. This approach has generally been considered safe and effective, compared to alternatives like surgery or anti-thyroid medications, but there is limited information about the long-term risks for leukemia and other cancers among patients. Dr. Kitahara is applying newly estimated doses to organs and tissues in dose-response analyses of site-specific cancer mortality. The results of her study may have direct implications for clinical treatment guidelines.

Dr. Kitahara plans to continue expanding her research on radiation-related disease risks among patients who have undergone other nuclear medicine and FGI procedures.
Etiology of Thyroid Cancer

When Dr. Kitahara arrived at DCEG in 2008 as a predoctoral fellow, the known risk factors for thyroid cancer included ionizing radiation exposure, history of thyroid nodules, and rare familial and genetic syndromes. However, these factors account for just a portion of thyroid cancer cases and were unlikely to explain the rapidly increasing incidence of the disease in the United States and many other developed countries over the past few decades. Dr. Kitahara recognized the need for large prospective studies to evaluate potential risk factors for this relatively uncommon malignancy.

“This is a challenging area of research due, in part, to the rarity of the disease and the need to distinguish indolent versus clinically-relevant cancers,” Dr. Kitahara said. “Until recently, most studies of thyroid cancer were case-control in design and relied on retrospectively-collected exposure information, which makes it difficult to rule out certain biases, or they included too few cases from which to draw meaningful conclusions. And then there’s the problem of detection bias: our ability to detect thyroid cancers has improved dramatically with the use of ultrasound technology. Very few studies have attempted to control for the shift in detection rates.”

Utilizing the NCI Cohort Consortium, Dr. Kitahara was initially interested in exploring the possible effects of obesity and other lifestyle-related factors. In a pooled analysis of five prospective studies, she observed that the risk of thyroid cancer was greater with increasing body mass index. She also reported an inverse association between cigarette smoking and alcohol consumption with thyroid cancer risk, a finding consistent with earlier studies. She estimates that the increasing prevalence of obesity and decreasing smoking rates could explain about 40 percent of new thyroid cancer cases in the United States each year.

“The NCI Cohort Consortium data helped to establish obesity as a risk factor for thyroid cancer, identifying elevated risk for more aggressive types as well as death from the disease,” she said.

Compared to most other malignancies, thyroid cancer is diagnosed more frequently in women and at earlier ages—however, there are few compelling hypotheses to explain these patterns. “I’ve been interested in evaluating whether hormonal influences in early life, especially the timing of puberty and pregnancy, may play a role in thyroid carcinogenesis,” Dr. Kitahara said.

Dr. Kitahara has sought to identify additional datasets and populations with which to evaluate this novel hypothesis. In collaboration with investigators in Denmark, she demonstrated for the first time a positive association between childhood and adolescent measures of height and weight and risk of thyroid cancer in adulthood. More recently, she launched investigations of perinatal characteristics and birth outcomes in relation to maternal and offspring thyroid cancer risk using data from a Nordic registry-based linkage study and two large cohort studies in Israel and the United Kingdom (see related Summer 2016 Linkage article on early-life registries). “I’m looking at various pregnancy characteristics and birth outcomes to determine whether they are related to risk of developing thyroid cancer later in life for the mother or her offspring,” said Dr. Kitahara. She is also launching a new study to assess sex steroid hormones and thyroid function markers during pregnancy in relation to maternal thyroid cancer risk.
Understanding what factors might play a role in the etiology of thyroid cancer, particularly in view of the notable increase in incidence, has been a priority for Dr. Kitahara. In addition, she has collected descriptive data at the population level to study thyroid cancer incidence and mortality trends over time.

Dr. Kitahara recently led a landmark effort to evaluate long-term U.S. thyroid cancer incidence and mortality trends using data from the Surveillance Epidemiology and End Results program. She and her colleagues observed substantial increases in thyroid cancer incidence and more modest, but statistically significant, increases in thyroid cancer mortality. The increases in thyroid cancer mortality were almost exclusively among patients diagnosed with advanced-stage papillary thyroid cancer, which has also increased in incidence.

“These findings are consistent with a true increase in the occurrence of the disease, which challenges the prevailing notion that rising thyroid cancer rates are solely related to over-diagnosis with newer screening techniques,” Dr. Kitahara said. “This is important, because it suggests there may be modifiable risk factors that are contributing to the increase.”

Her recent studies of thyroid cancer in high-risk patient populations, including organ transplant recipients, individuals with a history of benign thyroid conditions, and cancer survivors, have specifically evaluated risks for advanced-stage thyroid cancers, as these are less likely to be influenced by detection bias. This approach has led to some interesting new findings, including a possible etiologic contribution from chronic kidney and liver disease.

“There are still many hypotheses that have yet to be tested. The goal of this work is to identify individuals who might benefit from prevention or early detection efforts.”

“The field has come a long way over the past decade,” Dr. Kitahara said. “Obesity and smoking appear to be important risk factors operating in opposite directions. They explain a large proportion of the increasing incidence. Other possibilities have emerged, including growth factors in early life and certain medical conditions, such as hyperthyroidism and chronic kidney disease; these need to be evaluated in greater detail. There are still many hypotheses that have yet to be tested. The goal of this work is to identify individuals who might benefit from prevention or early detection efforts.”
References


