Radiation therapy remains a cornerstone of breast cancer treatment, and although advances in technology have helped to limit radiation exposure to unaffected tissues, radiation exposure to the heart may increase a patient’s risk of ischemic heart disease (IHD).

A multinational, population-based, case-control study was performed to evaluate the effect of cardiac radiation exposure on IHD risk. All women who received radiotherapy and were registered in the Swedish National Cancer Register (diagnosed between 1958 and 2001; younger than seventy years of age) or the Danish Breast Cancer Cooperative Group (diagnosed between 1977 and 2000; younger than seventy-five years of age) were reviewed for inclusion in the study. Women diagnosed with unilateral non-metastatic breast cancer, with no previous exposure to radiotherapy or history of major coronary events, were included in the study (n=2168). Women who had documented major coronary events (myocardial infarction, coronary revascularization, or death from IHD) were classified as cases (n=963). Controls (n=1205) were matched by country of residence (one per case in Sweden; two per case in Denmark), receipt of radiotherapy, and age of both at cancer diagnosis and year of diagnosis within 5 years.

The primary endpoint was the risk of major coronary events in relation to the average dose of radiation delivered to the heart. Secondary endpoints included the risk associated with the average dose of radiation delivered to the left anterior descending artery (LAD), preexisting cardiac risk factors, and time from treatment. The risk of major coronary events increased by 7.4% for every 1 gray increase in mean radiation dose delivered to the heart (95% CI, 2.9 to 14.5%; p<0.001). Increased risk was also associated with irradiation of cancer of the left breast (p=0.002) and the first 10 years after treatment (p<0.001).

The authors concluded that incidental heart exposure to radiotherapy increased the rate of major coronary events by 7.4% per gray. This rate was similar among patients regardless of pre-existing cardiac risk factors, which further affirmed an absolute increase in risk associated with radiation exposure. Limitations include the unavailability of CT-based radiotherapy information due to the time frame, the use of estimations to calculate radiotherapy dose based on an average anatomy, and the inclusion of few women under the age of forty.

**CONCLUSION:** Exposure of the heart to radiation increased coronary events in women receiving radiation therapy to treat breast cancer. However, further studies are needed to evaluate the risk to women younger than 40 years of age and the effects of chemotherapy, especially anthracycline-based chemotherapy.


By Mark Raschkow, Pharm.D. Candidate
Several studies have shown cardiovascular benefit from an α-linolenic acid-rich Mediterranean diet which emphasizes bread, fruits, nuts, vegetables, fish, and olive oil. This diet discourages dairy products, saturated fats, and red meats. Older studies have shown secondary reduction of cardiovascular disease with a Mediterranean diet. A recent large European study found primary prevention of cardiovascular events as well.

A randomized, single-blind, controlled study from 1988-1992 compared the effect of an α-linoleic acid-rich Mediterranean diet on post-myocardial infarction (MI) cardiac morbidity and mortality compared with a prudent diet recommended by hospital physicians and dieticians. Patients were less than 70 years old and had survived an MI in the previous 6 months. Those with heart failure, angina, or dysrhythmia were excluded. A total of 584 patients were randomized to either the control group or the Mediterranean diet group. The control group received advice on a prudent Western diet. The Mediterranean diet group had an hour-long meeting with a cardiologist and dietician, who recommended a diet rich in olive and canola oil, margarine, vegetables, fruits, bread, and fish, with limited red meat. Each group met with their physicians and dieticians 8 weeks after the initial visit, then once a year. The average follow-up duration was about 4 years. Primary endpoints consisted of the incidence of non-fatal MI and death from cardiovascular disease. Secondary endpoints were the incidence of non-cardiovascular mortality and the development of non-MI cardiovascular diseases.

The Mediterranean diet group had lower rates of the cardiovascular-related endpoints. Mediterranean diet patients had fewer primary endpoints than control patients (24/100 patients per year compared to 4.07/100 patients per year; relative risk reduction [RRR] 0.72, 95% CI 0.47-0.85; p=0.0001). All-cause mortality was also reduced in the Mediterranean diet group (RRR 0.56, 95% CI 0.06-0.79; p=0.03). The authors concluded that MI survivors on a Mediterranean diet group (RRR 0.56, 95% CI 0.06-0.47) had a significantly lower risk of MI recurrence compared with the control group (HR=0.7, 95% CI 0.55-0.89, p=0.003). There was a significant reduction in stroke among the combined Mediterranean diet groups compared with control (HR=0.61, 95% CI 0.44-0.86, p=0.005). The other secondary endpoints were not statistically significant. Dropouts were significantly higher in the control group compared to the olive oil and nuts groups (11.3%, compared to 3.6% and 6.3%, respectively). The authors concluded that a Mediterranean diet supplemented with extra-virgin olive oil or nuts reduced cardiovascular events in patients without cardiovascular disease. Limitations include differences in dietary counseling between treatment and control groups and the higher dropout rate in the control group.

There is evidence that an α-linolenic acid-rich diet provides both primary and secondary prevention of cardiovascular disease. More studies are warranted for evaluating prevention in patients who are not at an increased cardiovascular risk. Healthcare professionals should feel comfortable encouraging patients who are at an increased risk for cardiovascular disease to adopt aspects of the Mediterranean diet.

By Edward Coulston, PharmD Candidate

(References on page 4)
New Recommendations for Pertussis Vaccine in Pregnant Women

As of October 2012, The Advisory Committee on Immunization Practices (ACIP) recommends that women receive a dose of Tdap (tetanus diphtheria and pertussis) vaccine during every pregnancy, optimally between 27 and 36 weeks gestation, regardless of vaccination status or previous pregnancy. Vaccination of the mother during this time period protects newborn infants from pertussis infection in two ways—by preventing viral transmission from the mother to the infant and by providing extra protection against the virus by passing maternal antibodies on to the infant.

Whooping cough (pertussis) infections are severe in infants and can result in death. Over the past three decades, there has been a gradual increase in pertussis cases reported in the United States despite the availability of vaccines. In 2010, 3350 cases were reported in infants younger than six months, 25 of which resulted in the infant’s death. Mothers were the source of infection in 30-40% of infant cases.

Current recommendations suggest that all family members and caregivers receive Tdap vaccination at least two weeks prior to contact with the infant, as peak antibody effect takes place approximately two weeks post-injection. Compliance with this recommendation has been a barrier to protecting infants from pertussis exposure. Postpartum vaccination of mothers is also believed to be less effective in preventing transmission than administration during pregnancy due to the time it takes for the vaccine to reach peak effect.

Currently no pertussis vaccination is recommended or approved for infants at the time of birth. Routine pertussis vaccination of infants currently takes place at two months. Maternal antibodies received from vaccination during pregnancy should help prevent pertussis infection if exposure were to occur. Levels of these antibodies decline rapidly after birth, but theoretically provide the infant with protection until routine vaccination at 2 months. Breast feeding is not contraindicated in patients receiving Tdap and is in fact promoted as breast feeding can also help facilitate the transfer of maternal antibodies to the infant. It remains unclear if circulating maternal antibodies would blunt the effect of the routine vaccination due to a reduced infant immune response. Studies are currently underway to evaluate this effect.

A multicenter, prospective study of 24 women in Belgium evaluated the effect of a pertussis booster when given to women between pregnancies. Eligible women had not received pertussis vaccine in their adult life. Antibody levels were taken from blood samples obtained from the mother, the infant and the umbilical cord at the time of the birth of the first child and from the child at 1 month. Mothers were offered a Tdap booster after the cessation of breast feeding. Antibody levels were drawn from mothers at 1 month post-vaccination and then again at the birth of the second child along with levels taken from the second infant, the umbilical cord, and the infant at 1 month. Statistically significant increases in antibody levels were seen in the mothers, umbilical cords, and infants after vaccination booster when compared to the first pregnancy before vaccination. Limitations include small sample size and lack of blinding.

The ACIP has determined that there is no increase in adverse effects from pertussis vaccination in pregnant women. In addition, tetanus and diphtheria vaccines have been used in pregnant women since the 1960s and have not shown harm to either the mother or fetus. Vaccination of pregnant women between 27 and 36 weeks gestation is theoretically safe and effective in preventing pertussis transmission to newborn infants. More data is needed to evaluate the effects that Tdap administration during pregnancy will have on the efficacy of subsequent pediatric vaccination.

By Mark Raschkow, PharmD Candidate

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Melatonin has gained popularity for its role in sleep regulation, but it has also been linked to improved metabolic function. Several small cross-sectional studies have found an association between low levels of melatonin and diabetes, but large prospective studies are lacking. The implications for a relationship between melatonin and diabetes could be clinically significant, creating a potential new target for diabetes prevention and treatment.

A retrospective, case-control study nested in the Nurses’ Health Study evaluated the association between melatonin secretion and the incidence of type 2 diabetes. Three hundred seventy eligible women with a diagnosis of type 2 diabetes between the years 2000-2012 were matched with 370 female controls without type 2 diabetes. Melatonin is converted to 6-sulfatoxymelatonin and excreted in the urine, and the ratio of 6-sulfatoxymelatonin to creatinine is correlated with night-time melatonin secretion. Creatinine levels were similar among groups and a higher 6-sulfatoxymelatonin/creatinine ratio was associated with greater melatonin secretion. First morning-void urine samples were collected to determine nighttime melatonin secretion.

The case group had higher body mass indices (BMIs), less physical activity, and consumed more fat and less fiber than the control group. Cases had a higher incidence of hypertension and a family history of hypertension and diabetes. Cases also slept fewer hours per night and snored more than controls. Melatonin secretion was separated into low, medium, and high secretion groups. There were more people without diabetes in the high melatonin secretion group and more people with diabetes in the low melatonin secretion group. Melatonin secretion was closely correlated with insulin sensitivity but was not correlated with BMI, duration of sleep, or frequency of snoring. The risk of developing diabetes was higher in people who secreted low amounts of melatonin compared to people who secreted higher amounts of melatonin (odds ratio 2.17, 95% CI 1.18-3.98) after adjusting for predicted confounders, including BMI, lifestyle factors, menopausal status, hypertension, and inflammatory markers. As with any observational study, there is always a risk of confounding variables and conclusions cannot be made about causality. This study was conducted in mostly white female nurses, and the results may not be extrapolated to other populations. The correlation could be a reverse causality, and insulin resistance could cause decreased melatonin secretion.

CONCLUSION: Melatonin secretion is independently associated with a decreased incidence of type 2 diabetes.

Data from the study support the need for large, randomized, controlled trials to determine whether melatonin supplementation decreases the risk of developing type 2 diabetes.


By Betsy DeMarois, Pharm.D. Candidate

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Literature Highlight:
Artificial Pancreas and Glucose Control

Studies have established that stringent glucose control in patients with type 1 diabetes results in fewer long-term adverse health outcomes. Automatic artificial pancreases have been shown to provide this glucose control in inpatient settings, but outpatient application has yet to be established.

A randomized, crossover, controlled study compared the safety and efficacy of an artificial pancreas with an interstitial sensor-augmented insulin pump in the management of nocturnal blood glucose levels for pediatric patients with type 1 diabetes. Inclusion criteria consisted of patients 10-18 years old participating in a diabetes camp, at least a 1-year history of diabetes, at least a 3-month history of using an insulin pump, and HgA1C of 7-10%. Patients were excluded if their body mass index (BMI) was above the 97th percentile for their age, they had concurrent disease states, or they experienced ketoacidosis or severe hypoglycemia in the previous month. Fifty-six patients were randomized to receive either overnight insulin control via sensor-augmented pump the first night and an artificial pancreas the second night, or the same treatments in reverse order. The artificial pancreas automatically dosed insulin according to the patient’s interstitial glucose levels.

The medical staff administered boluses throughout the night with the sensor-augmented pump. Capillary glucose tests were performed every 3 hours. Primary endpoints included total occurrences of glucose levels below 63 mg/dL (hypoglycemia), time spent below 60 mg/dL, and average glucose levels. Secondary endpoints included various measures of glucose fluctuation.

The pancreas group had fewer hypoglycemic events with 7 occurrences compared with 22 in the control group (p=0.003). No patients experienced glucose below 60 mg/dL in the pancreas group. In the control group, the inter-quartile range of time spent below 60 mg/dL was 0 to 27.5 minutes. Patients in the pancreas group spent more time between 80-120 mg/dL than those in the control group (median=3.9 hours and 2.2 hours, respectively; p<0.05). Capillary glucose levels at wakeup were lower in the pancreas group compared with the control group (median=132 mg/dL and 168.5 mg/dL, respectively; p<0.05). In the pancreas group, tighter glucose control was seen as glucose was between 70 and 180 mg/dL for 61% of the night versus 22% of the night in the control group. Adverse effects were similar between groups and included headache, dizziness, and an “ill” feeling. Dropouts included one patient who left after the first night and another patient who experienced equipment failure. Limitations include the necessity for equipment calibration, which may limit generalizability and ease of use, as well as the single-night design, which limits generalizability for long-term glucose control.

CONCLUSION: The artificial pancreas provided fewer nocturnal hypoglycemic events and less nocturnal glucose variation than the sensor-augmented pump. Further studies in older patients and patients with poorly controlled diabetes are warranted.


By Edward Coulston, Pharm.D. Candidate