Breaking it Down

How the Chemistry of Digestion is Uncovering Sex-Specific Causes of Colon Cancer

Sometimes the tiniest clues can solve the biggest mysteries.

A new technology called metabolomics allows researchers to explore the small chemicals formed and used during digestion as a window into the formation of diseases such as colon cancer, seeking early warning signs and potent tactics for prevention.

“Women have a lower rate of colon cancer than men but a higher prevalence of right-sided colon cancer, which is associated with a 20 percent increased risk of death compared with cancer of the left side,” said Dr. Caroline Johnson, a leading expert in metabolomics research. “And we don’t know why.”

With a Women’s Health Research at Yale Pilot Project grant, Dr. Johnson is answering the question: Can digestive chemistry uncover sex-specific causes of colon cancer? The answer promises crucial clues about the biological underpinnings of this disease leading toward effective therapies for women who develop this more lethal type.

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A Type of Colon Cancer More Deadly in Women

Colon cancer is the second most common cancer diagnosed among women worldwide. In the United States, colon and rectal cancer are together the number three cause of cancer death for women and the number two cause for men. This year, more than 50,000 people are expected to die of the disease.

With WHRY’s grant, Johnson is investigating “downstream” products of what we consume, what our hormones produce, and what bacteria reside in the colon. With this information, she is learning what may lie behind this sex difference in colon cancer risk and what can be done to prevent the worse outcomes for women.

“This is the first study of its kind,” said Dr. Carolyn M. Mazure, Director of WHRY. “It is unique because of the innovation and the power of metabolomics and because of Dr. Johnson’s expert training in this new biologic technique. We are so pleased to have her at Yale, where she was recruited specifically to develop this new technology and examine the causes of colon cancer.”

Trained at Imperial College London as an analytical chemist and then at The Scripps Research Institute and The National Institutes of Health, Johnson has, through her WHRY-funded study, already begun to uncover markers of colon cancer in women and men that can aid in early diagnosis and treatment and guide strategies for prevention.

“Our early results are revealing multiple pathways that show a significant difference — not due to chance — between how colon cancer develops in women and men,” Johnson said, noting how the work will benefit all women but particularly black women, who are at higher risk for colon cancer compared with other races or ethnic groups. “And we have many promising leads to follow up.”

A Unique Study Producing Significant Results

As part of this study, Dr. Johnson and her colleague Dr. Sajid Khan from Yale School of Medicine have acquired a colorectal tumor tissue biobank with help from colleagues at Memorial Sloan Kettering Cancer Center (MSKCC) in New York. They have obtained 3,000 tissue samples from MSKCC’s unique biobank of colorectal tumors, which

WHAT IS METABOLOMICS?

Metabolism is the process by which the body converts, or digests, what we eat and drink into energy. Metabolites are small chemicals which are transformed and used during this process. There are about 3,000 internally derived metabolites and an unknown number of metabolites externally derived from environmental chemicals that we ingest, absorb, or breathe into our body, including those found in medications, cosmetics, dietary supplements, consumer products, and tobacco products. Evidence of external metabolite exposure can help strengthen our understanding of their associations with particular disease outcomes.

Bacteria in the colon produce metabolites that help the body digest food and in the process absorb substances such as cholesterol and fat-soluble vitamins. But in high concentrations, some of these metabolites can promote a toxic imbalance that leads to cancer.

The metabolome is a term used to describe the collection of all the metabolites within a sample. It is heavily influenced by a person’s genes, what we consume, and the external stressors to which we are exposed, giving rise to an individual metabolic “fingerprint.” Such fingerprints can provide snapshots of what is happening to our bodies.

Both changes in metabolite concentrations and how metabolites relate to each other can serve as biomarkers — reliable clues signaling the presence of a disease — and provide insights into how a disease can develop.

EXAMINING COLON CANCER

Using mass spectrometry imaging, Dr. Johnson can locate higher densities of bile acids within colon tumor tissues (in yellow) and reveal the diverse distribution of metabolites within a tumor (in red).
were individually collected during surgery and immediately flash frozen into liquid nitrogen — one of the very few large biobanks available for metabolomics analysis.

After studying the samples, Dr. Johnson identified 207 that met the study’s criteria. For example, her team excluded samples from patients who underwent chemotherapy before surgery, which can affect metabolite levels in colon tissue.

Her laboratory has successfully optimized the experimental procedure, extracting each sample to purify the metabolome, performing liquid chromatography to separate the thousands of metabolites within each sample, and conducting mass spectrometry to measure masses within a sample using a new, sensitive machine that requires only a small amount of each sample to determine the weight and abundance of each metabolite.

Johnson continues to analyze the data and run tests. But initial results show great promise.

The tests have demonstrated that when comparing tumor tissues from women with stage 3 right-sided colon cancer (RCC) to tissues from men with stage 3 RCC, there is a difference in the production of saturated and polyunsaturated fatty acids (PUFAs). This is quite informative because fatty acids are important small molecules that can come from the diet or can be made from the cells themselves when supply is low. They play crucial roles in maintaining cellular structures and function, and changes in dietary intake or PUFA metabolism contribute to cancer risk and progression.

In addition, Johnson has found that Vitamin E metabolism is decreased in women with RCC. This is important information because Vitamin E serves to protect fatty acids from oxidative damage that can cause cancer growth.

**About the Investigator**

Dr. Caroline Helen Johnson earned her Ph.D. at Imperial College London, her M.S. at University College London, and her B.S. at Keele University. She is currently an Assistant Professor of Epidemiology at Yale School of Public Health.

Dr. Johnson’s research uses mass spectrometry-based metabolomics to understand the role of metabolites in human health. Her primary research interest is to investigate the relationship between genetic and environmental influences (diet, microbiome) in colon cancer. WHRY funded this work through our Naratil Pioneer Award and in collaboration with the Maximilian E. and Marion O. Hoffman Foundation and the Yale Cancer Center.

**Much More to Learn**

Dr. Johnson and her team are just getting started.

The study will next examine how the stage of cancer affects fatty acid levels and whether fatty acid metabolism genes are altered in women with RCC, thus confirming whether cellular replication is different between men and women with RCC. The study will also carry out experiments to determine how fatty acids are regulated by sex hormones and determine if these metabolites can be used as biomarkers for the aggressiveness of RCC.

Dr. Johnson has leveraged her early findings to earn an external two-year grant to advance this work, allowing for additional mass spectrometry analysis to correlate metabolites with patient outcomes. And she is gathering additional clinical data on the sample subjects in search of any significant connections that might offer clues about the sources of their particular metabolites.

“The more we learn about a patient’s race, diet, hormone levels, pregnancy history, and cancer treatment, the more we can determine how all of these factors and their metabolome interact during the progression of cancer,” Johnson said. “And then we can better predict — and possibly prevent — the worst types of cancer.”

She has also successfully shared her work with influential colleagues, including a planned presentation at the Johns Hopkins School of Medicine Microbiome Forum. Dr. Johnson is a member of the advisory committee for a postdoctoral fellow at the school who recently received a large federal grant to study the effect on colon cancer of densely packed bacteria called biofilms. The scholar plans a visit to Dr. Johnson’s lab in the new year to learn more about metabolomics.

Next steps beyond the current study will involve comparing the colon cancer samples with healthy controls collected during a colonoscopy. Ultimately, targeted investigations to discover and then disrupt a pathway that leads to right-sided colon cancer in women could lay the groundwork for developing new therapeutics and interventions.

Possible treatments include antibiotics that eliminate an identified type of disease-causing bacteria or enhanced prevention methods through diet and lifestyle.

“We have learned so much already,” Johnson said. “I’m excited and optimistic for where this work will lead.”
What Your Support Produces

When people ask me about supporting Women's Health Research at Yale, they quickly understand the urgent practical importance of a donation.

After all, it wasn’t until the 1990s that women were required to be included in clinical studies seeking grants from the National Institutes of Health — the single largest provider of biomedical research funding.

For 20 years, WHRY has led efforts to fill an enormous gap in knowledge about women’s health and to understand critical differences between women and men and among populations of women and men.

Thanks to the ripple effects of WHRY’s research studies, the influential careers of the students and junior faculty members the center has trained, and its effective communications to medical professionals, policymakers, and the public, we are changing the landscape of medical research and practice.

This isn’t just about catching up and declaring victory. This is a mission with no end. The fact is that there will always be a need to study women and to understand how sex and gender influence the development of and treatments for diseases and other medical conditions.

A few recent examples:

- Dr. Erica Spatz developed an improved classification system to describe and group heart attacks that accounts for the different ways they can develop and present in women. While previous systems can actually obscure heart disease and its risk, this new system ensures more informed medical decisions and better outcomes for women.

- Dr. Pamela Ventola (pictured) tested, for the first time, a socio-behavioral treatment, Pivotal Response Therapy, for autism spectrum disorder on girls. She showed how the treatment not only works for girls but shows better results in girls than boys. Now applied clinically, her findings allow researchers and therapists to explore the specific and diverse needs of girls and boys with autism.

- Dr. Peter Glazer discovered that one product of the body’s immune system associated with the disease lupus can penetrate cancer cells, which can then become sensitive to radiation and chemotherapy. Dr. Glazer continues to advance this method for treating cancer with a focus on types of cancer that develop from inherited mutations to the tumor-suppressing BRCA2 gene.

- Dr. Martin Kriegel showed that bacteria in the small intestines can travel to other organs and confuse immune cells into attacking the body. He also found that targeting the bacteria can suppress this autoimmune response. Such findings provide new ways for treating autoimmune conditions, such as lupus, which occur at far greater rates in women.

In addition, WHRY’s work is directing attention to cancers more common and more deadly in women, reducing viral infections during pregnancy, using real-time brain scans to examine for the first time how smoking cannabis affects women and men differently, and improving the lives of women experiencing chronic urinary tract infections, domestic violence, depression, and much more.

There are so many good reasons to donate to WHRY. As a self-supporting center, we need your help to continue this work. Without you, it won’t get done.

With thanks for your generous contributions,

Barbara M. Riley
Philanthropy Chair
Happy Anniversary, Women’s Health Research at Yale

Reflecting on 20 Years of Progress and Promise

Twenty years ago, Dr. Carolyn M. Mazure was awarded a generous grant by The Patrick and Catherine Weldon Donaghue Medical Research Foundation with which she founded Women’s Health Research at Yale. This self-sustaining interdisciplinary research center within Yale School of Medicine rapidly became a national model for initiating and supporting research on women and the influence of sex and gender on human health.

In recognition of this anniversary, the center’s many supporters, scientists, students, and mentees offered their thoughts and feelings about the last two decades and the changes WHRY has made in leading us toward a healthier and happier future.

“Thanks to WHRY’s Addictive Disorders Core, we have discovered gender differences in problem gambling and substance use disorders that tell us how best to design treatments that really help. By bringing together researchers of different disciplines, we have created a unique opportunity to uncover the many ways in which men and women and boys and girls differ in regard to specific addictions.”

— Marc Potenza, Ph.D., M.D., Professor of Psychiatry at Yale School of Medicine in the Child Study Center and of Neuroscience, and Director of WHRY’s Women and Addictive Disorders Core

“It is spectacular to see how Women’s Health Research at Yale has grown in stature and impact over its first 20 years. Its role is essential: If we want everyone to live healthier lives, we must have medical research that studies women and explores sex and gender differences. It has been an honor to be a cheerleader for WHRY since its inception and to witness the extraordinary work it has undertaken under the leadership of an exceptional director and council of advisors.”

— Linda Koch Lorimer
WHRY Special Advisor and former Yale Vice President

“Women’s Health Research at Yale is the best of what the university represents. I’m proud to support this center’s innovative and practical work while also supporting my alma mater and staying informed about the latest developments in women’s health. I encourage others — both inside and outside our Yale community — to learn more about WHRY’s vital mission.”

— Elisa Spungen Bildner,
Yale Class of ’75 and member of the Advisory Council for Women’s Health Research at Yale
“WHRY’s mentorship and collaboration on a recent high-impact publication drew a meaningful response from the Food and Drug Administration regarding the importance of attention to sex differences in the approval process for medical devices. As a research fellow, this provided a real opportunity to learn more about and address continuing gaps in knowledge in women’s health, particularly in my field of cardiovascular disease, where women remain understudied.”

— Sanket Dhruva, M.D., M.H.S.
Clinical Instructor in Cardiology at Yale School of Medicine

“I am extremely grateful to WHRY for providing me with the guidance and direction to launch my career and connect with other investigators — both at Yale and nationally — who are focused on advancing women’s health and exploring sex and gender differences. Your leadership and this growing network have allowed me to advance a community care center that conducts and applies research to improve the lives of socially and economically disadvantaged pregnant and parenting women.”

— Megan Smith, Ph.D.
Associate Professor of Psychiatry in the Yale Child Study Center, Associate Professor of Social and Behavioral Sciences in the Yale School of Public Health, and Founder and Director of Mental health Outreach for MotherS (MOMS) Partnership

We’ve been sharing messages from our friends, partners, and supporters all year long.

To catch up on any you might have missed, visit our website, yalewhr.org, and look for our 20th Anniversary banner on the home page.

To contribute your own message, join us on Twitter @WHRYale or contact Rick.Harrison@yale.edu.
Why and How We Do Research

At a community event to celebrate 20 years of Women's Health Research at Yale, three of the center’s successful faculty partners discussed why and how they conduct sex- and gender-based research.

Dr. Ryan Jensen, a leading researcher on the genetic origins of cancer, explained his acclaimed progress toward fully understanding how DNA repairs go awry in the tumor-suppressing BRCA2 gene, leading to mutations that result in breast and ovarian cancer.

“Most cancer is caused by a multitude of different mutations in different genes — very complex and very difficult to approach from a scientific standpoint,” Jensen said. “In part, I’m using BRCA2 as a model to understand how cancer cells initiate and how we can treat cancer. My feeling is that DNA repair really lies at the root of the whole problem in cancer.”

WHRY has provided funding for Dr. Jensen’s work twice, as he nears a practical test that can quickly and accurately determine whether an individual’s particular genetic mutation is harmful. With his most recent grant, funded with a WHRY Naratil Pioneer Award, Jensen has expanded his work from breast cancer to include ovarian cancer. In this work, he is focusing on how cells from fallopian tubes and ovaries react with and without a working BRCA2 protein able to repair routine DNA errors. He also hopes to eventually understand why a new therapy called PARP inhibitors, which block an enzyme that help cancer cells repair damage to their own DNA, can effectively target BRCA2-deficient tumors before some patients become resistant and relapse.

“We’re learning how this therapy works and how to overcome that resistance,” Jensen said.

Dr. Megan Smith, the founder and Director of a nationally acclaimed community-academic partnership to help women in need, explained how meticulous mental health research can lead to the creation of effective, data-driven social programs that improve the daily lives of women.

“I always talk about my work as harnessing the link between mental health and wealth,” Smith said. “The promotion of women’s mental health can really send women on a positive trajectory for economic and social mobility.”

She discussed how she has built on the training she received through WHRY to form a community-academic partnership with nationwide programs to improve maternal mental health and economic stability among low-income women through a community-driven approach.

In creating Mental health Outreach for MotherS (MOMS) Partnership, Dr. Smith has successfully aligned with federal and state government agencies to integrate mental health for women within existing social services.

“We’ve shown that when something is cost-effective, when you are able to show that there are quantifiable benefits for both women and especially
their children, then you can garner the attention of policymakers,” Smith said.

For example, Smith described how MOMS is working with state workforce programs to first provide mental health treatment for women with depression or post-traumatic stress disorder so these women can then move on to an employment training program.

“It may not sound novel, but it is in practice quite novel,” Smith said. “This is one of the first times we are actually embedding mental health care into a social services delivery system.”

The third panelist, active cardiologist and educator Njeri Thande, M.D., discussed how her research with WHRY assesses the integration of sex and gender-based findings into the traditional medical school curriculum.

“When I was in medical school, we learned that the reference model for patients was a 150-pound man,” Thande said. “It was not implicitly stated, but it was assumed that women were small men or a deviation from the norm.”

Dr. Thande said she would have hoped that much has changed since then, but only 35 percent of medical students responding to a 2016 survey said they felt comfortable addressing sex and gender differences in health care.

To address this issue, Dr. Thande and WHRY launched a study encompassing 548 sessions of the pre-clinical curriculum at Yale School of Medicine and are using the data to propose changes that would offer a more expansive, integrated coverage of sex and gender.

“We found that in a lot of cases, instructors would talk about the relative prevalence of certain disease states in women versus men, and that was the end of the conversation,” Thande said. “Nothing about why there is a difference or its physiological basis. And no discussion of the different ways men and women might present symptoms or suggest different prognoses and treatments.”

Thande said that working with students, including WHRY undergraduate fellows, helped drive the administration toward taking action.

“A lot of the students had a background in gender studies,” Thande said. “They were really calling for a change in what and how they were being taught.”

Thande is currently a member of a national collaborative of educators from different institutions writing papers and working to change medical school examinations to reflect sex and gender content.

“Because if it’s on the exams, you have to teach it,” she said.

Dr. Mazure sees this and the other panelists’ contributions as important models for exporting and influencing health research, education, and practice around the country and the world.

“The good news is that we have more and more people who are committed to this kind of work.”

Linda Calarco understands that the sources of a long, healthy life – both mental and physical – start at the very beginning.

“I’ve always been interested in health and human behavior,” Calarco said. “I realized the beginning for much of who we become starts literally in the cradle. Early development is a critical factor for how we develop into adults.”

She gained increased appreciation for this perspective from her years as a guidance counselor and middle school teacher in New York and then in her current post as a member of the Board of Directors for The Gessell Institute of Child Development in New Haven, on which she served as President for three years.

As the newest addition to Women's Health Research at Yale’s Advisory Council, Calarco will now focus her efforts on highlighting the critical role that sex and gender play in health and well-being.

“My goal is to foster broader interest in the mission of WHRY,” Calarco said. “I’m very interested in learning more about the center’s science and helping more people understand what this work means for their health.”

A Woodbridge, Conn., resident for the last 40 years, Calarco served Continued on next page...
WHRY Makes the Case for Women’s Health to the Country — and the World

Women’s Health Research at Yale is dedicated to ensuring that our community’s health needs are represented in the national conversation on health research and policy. Led by Director Carolyn M. Mazure, Ph.D., WHRY provides outreach on women’s health research to local, regional, national, and global communities and policymakers.

For example, Dr. Mazure was invited to speak at the United Nations for the Annual Ideagen Empowering Women & Girls 2030 Summit in September. Addressing industry leaders across sectors gathered to discuss solutions to meet the UN’s sustainable development goals, Dr. Mazure underscored the importance of ensuring that plans for improving the health of women are tied to economic security and advancement.

Dr. Mazure also spoke at an invitation-only meeting in October at the United Hospital Fund in New York, founded in 1879. This nonprofit organization forges private-government partnerships to improve community health. The meeting focused on helping state and city policymakers understand how the opioid crisis is affecting women and families.

Later that month, Dr. Mazure spoke at The Leaders in Women’s Health Summit at The Laura W. Bush Institute for Women’s Health in Dallas, Texas.

Another prominent way in which WHRY leads national efforts in women’s health is through Dr. Mazure’s elected membership on the National Institutes of Health Office for Research on Women’s Health (ORWH) Advisory Committee. In this role, Dr. Mazure has a direct line into the national discourse on the status of contemporary research in this field and into the data stream on women’s health provided to communities across the nation.

This winter, Dr. Mazure will serve as a subject matter expert at the invitation of ORWH Director Janine Austin Clayton, M.D., to develop a new online training course for researchers and clinicians on consideration of sex as a biological variable.

And next year, Dr. Mazure will speak on the state of women’s health research before influential audiences at The University of Bordeaux and Sorbonne University in France, where two of her mentees, Drs. Mathilde Husky and Joel Swendsen, respectively, now work as full professors.
One of Women’s Health Research at Yale’s core initiatives is communicating new health information.

But before we can “start communicating,” it’s important to know with whom we are exchanging information and ideas. Because WHRY has various, often overlapping audiences with differing needs and interests.

For example, for our faculty colleagues at Yale School of Medicine, WHRY communicates how we represent a unique, rare, and necessary source of funding for their research.

As Yale faculty continue to confront increases in programmatic costs and federally determined decreases in funding for research and health education, WHRY steps in to spark vital work that would otherwise sit stalled on the launch pad.

And so we explain the types of studies we fund and share our success stories of research discoveries. In doing so, we continue to inspire the school’s most innovative minds to focus on exploring women’s health and sex and gender differences.

As a result, our researchers see WHRY as a life preserver in the choppy seas of science funding and a helping hand, offering professional support and opportunities for collaborations that address real-world health problems requiring different fields of expertise.

We communicate our research successes for another important audience as well. As a self-supporting center, we are committed to our generous donors and prospective donors. We want to convey how their thoughtful generosity is transformed into action that advances our common goals and overcomes decades in which women were hardly studied at all.

We are also here for the general public. We want our scientific conclusions and data-driven messages put to practical use, and so we share our findings in order for people to make informed decisions about their health. In addition, the center provides guidance to local, state, and national decision-makers so that health policy reflects the unique health needs of women and men.

We talk to medical professionals and educators, too. For example, we are working to infuse the empirical findings of health studies on sex and gender into Yale School of Medicine’s curriculum. We are here for our future scientists, doctors, nurses, and technicians — at Yale and other institutions. And so we stress the importance of treating sex and gender as a core variable to examine in every study and in every patient.

This audience overlaps with our undergraduate, graduate, post-doctorate, and junior faculty trainees, who receive career guidance and gain knowledge and insight about women’s health and sex differences in health through our hands-on mentorship programs.

Messages conveyed to this audience attract new trainees and reverberate beyond their time with WHRY, as our students and junior faculty members go on to influence their colleagues and ensure that our work endures and spreads.

WHRY also amplifies our messages through the news media. This requires the center to regularly call attention to the most recent and impressive accomplishments in our 20-year-long-and-growing list of practical medical advances. In today’s cluttered and fragmented media environment, we are here so that people can rely on WHRY as a clear, authoritative voice.

And there you have it. Women’s Health Research at Yale has something important to share with you. No matter who you might be.
Women’s Health Research at Yale

Women’s Health Research at Yale is changing the landscape of medical research and practice by ensuring the study of women and examining health differences between women and men to improve the lives of everyone.

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