**Contributions to Science, Amanda I. Phipps**

* 1. Much of my early work as a cancer epidemiologist was focused on characterizing *risk factors for molecular subtypes of breast cancer*, particularly triple-negative breast cancer. Characterized by the absence of estrogen receptor, progesterone receptor, and HER2/neu expression, triple-negative breast cancer accounts for only 10-25% of all breast cancers; however, this disease subtype has emerged as being of particular clinical and public health significance due to its typically poor prognosis and the fact that no targeted cancer therapies exist for the treatment of this disease. At the time I began research into risk factors for triple-negative breast cancer, exceptionally little was known about the epidemiology of this aggressive disease. Through my work, I demonstrated that nulliparity and late age at first birth – both established risk factors for estrogen receptor-positive breast cancer – are, if anything, inversely associated with risk of triple-negative breast cancer, whereas other traditional breast cancer risk factors, such as lack of breastfeeding and postmenopausal obesity, are more consistently associated with disease risk across molecular subtypes. These studies highlight the **distinct etiologies of molecularly distinct cancer subgroups**. My work in this area utilized several existing data resources, including the Women’s Health Initiative and the Breast Cancer Surveillance Consortium.

1. **Phipps AI**, Chlebowski RT, Prentice R, McTiernan A, Wactawski-Wende J, Kuller LH, Adams-Campbell LL, Lane D, Stefanick ML, Vitolins M, Kabat G, Rohan TE, Li CI. Reproductive history and oral contraceptive use in relation to risk of triple-negative breast cancer. *J Natl Cancer Inst* 2011;103:470-7. (PMCID: PMC3057984)
2. **Phipps AI**, Chlebowski RT, Prentice R, McTiernan A, Stefanick ML, Wactawski-Wende J, Kuller LH, Adams-Campbell LL, Lane D, Vitolins M, Kabat G, Rohan TE, Li CI. Body size, physical activity, and risk of triple-negative and estrogen receptor-positive breast cancer. *Cancer Epidemiol Biomarkers Prev* 2011;20:454-63. (PMCID: PMC3064558)
3. **Phipps AI**, Buist DSM, Malone KE, Barlow WE, Porter PL, Kerlikowske K, Li CI. Reproductive history and risk of three breast cancer subtypes defined by three biomarkers. *Cancer Causes Control* 2011;22:399-405. (PMCID: PMC3042513)
4. **Phipps AI**, Malone KE, Porter PL, Daling JR, Li CI. Body size and risk of luminal, HER2-overexpressing, and triple-negative breast cancer in postmenopausal women. *Cancer Epidemiol Biomarkers Prev* 2008;17:2078-86. (PMCID: PMC2561180)
   1. In recent years, I have shifted the focus of my research from the impact of molecular heterogeneity on cancer risk factors to the impact of such heterogeneity on *cancer outcomes*. In this regard, I have conducted multiple secondary data analyses leveraging data from the Colon Cancer Family Registry characterizing the relationship of somatic mutations and tumor attributes with colorectal cancer outcomes. Unlike with breast cancer, the **implications of molecular heterogeneity in colorectal cancer** have been poorly studied, and molecular subtypes of colorectal cancer remain poorly understood. Through my work, I have contributed to this gap in knowledge – conducting and publishing several studies into the relationship between individual tumor characteristics and colorectal survival, and one of the first studies characterizing differences in survival across molecular subtypes of colorectal cancer defined by tumor marker combinations reflecting distinct etiologic pathways (*Gastroenterology* 2015;148:77-87.e2 – see *Personal Statement*). With respect to this latter publication, we found that colorectal cancers with molecular attributes believed to reflect an origin in sessile serrated polyps exhibit a significantly poorer prognosis than those likely derived from the traditional adenoma-carcinoma pathway. I was responsible for the conception, design, implementation, and interpretation of secondary data analyses I conducted in this area.
   2. Dienstmann R, Mason MJ, Sinicrope FA, **Phipps AI**, Tejpar S, Nesbakken A, Danielsen SA, Sveen A, Buchanan DD, Clendenning M, Rosty C, Bot B, Alberts SR, Milburn Jessup J, Lothe RA, Delorenzi M, Newcomb PA, Sargent D, Guinney J. Prediction of overall survival in stage II and III colon cancer beyond TNM system: a retrospective pooled biomarker study. *Ann Oncol* 2017;28:1023-31. (PMCID: PMC5406760)
   3. **Phipps AI**, Limburg PJ, Baron JA, Burnett-Hartman AN, Weisenberger DJ, Laird PW, Sinicrope FA, Rosty C, Buchanan DD, Potter JD, Newcomb PA. Association between molecular subtypes of colorectal cancer and patient survival. *Gastroenterology* 2015;148:77-87.e2*.* (PMCID: PMC4274235)
   4. **Phipps AI**, Buchanan DD, Makar KW, Win AK, Baron JA, Lindor NM, Potter JD, Newcomb PA. *KRAS*-mutation status in relation to colorectal cancer survival: The joint impact of correlated tumor markers. *British J Cancer* 2013;108:1757-64*.* (PMCID: PMC3668469)
   5. **Phipps AI**, Lindor NM, Jenkins MA, Baron J, Win AK, Gallinger S, Gryfe R, Newcomb PA. Colon and rectal cancer survival by tumor location and microsatellite instability: The Colon Cancer Family Registry. *Dis Col Rect* 2013;56:937-44*.* (PMCID: PMC3708260)
5. Building on my research into the relationship between colorectal tumor biology and disease outcomes, and my research into the heterogeneity in risk factor associations across tumor subtypes, I have also conducted multiple studies exploring the *relationship of modifiable lifestyle factors with colorectal cancer survival according to tumor attributes*. Although much is known about the relationship of lifestyle factors and colorectal cancer risk, relatively few studies have considered the possible impact of such factors on colorectal cancer outcomes. I am presently addressing this gap in knowledge through my K07 career development award, and have conducted multiple secondary data analyses articulating the impact of pre-diagnostic smoking, alcohol consumption, physical activity, and NSAID use on post-diagnostic colorectal cancer outcomes. In particular, my work has suggested a favorable association between wine consumption and CRC survival. My work has also demonstrated that cigarette smokers experience significantly poorer disease-specific survival after colorectal cancer than do their non-smoking counterparts, particularly among individuals with tumors that exhibit microsatellite instability or a somatic *KRAS* mutation – illustrating the **importance of considering downstream tumor attributes** **when evaluating the relationship of patient attributes and cancer outcomes**. These findings, and additional research in this area, may ultimately provide clinicians with targeted messages for empowering colorectal cancer patients with ways to improve their prognosis.
   1. **Phipps AI**, Shi Q, Limburg PJ, Nelson GD, Sargent DJ, Sinicrope FA, Gill S, Goldberg RM, Kahlenberg M, Nair S, Shields AF, Newcomb PA, Alberts SR. Alcohol consumption and colon cancer prognosis among participants in North Central Cancer Treatment Group phase III trial N0147. *Int J Cancer* 2016;139:986-95*.* (PMCID: PMC4911257)
   2. **Phipps AI**, Shi Q, Newcomb PA, Nelson GD, Sargent DJ, Alberts SR, Limburg PJ. Associations between cigarette smoking and colon cancer prognosis among participants in a North Central Cancer Treatment Group Phase III Trial N0147 (Alliance). *J Clinical Oncol* 2013;108:1757-64*.* (PMCID: PMC3661936)
   3. **Phipps AI**, Baron J, Newcomb PA. Prediagnostic smoking history, alcohol consumption, and colorectal cancer survival: the Seattle Colon Cancer Family Registry. *Cancer* 2011;117:4948-57. (PMCID: PMC3138819)
   4. Hardikar S, Newcomb PA, Campbell PT, Win AK, Lindor NM, Buchanan DD, Makar KW, Potter JD, **Phipps AI**. Prediagnostic physical activity and colorectal cancer survival: Overall and stratified by tumor characteristics. *Cancer Epidemiol Biomarkers Prev* 2015;24:1130-7*.* (PMCID: PMC4491038)

4. As a co-Investigator with the Genetics and EpidemioIogy of Colorectal Cancer Consortium (GECCO), I have also applied my expertise in characterizing factors associated with colorectal cancer survival to the study of *common genetic variation* – leveraging **high-dimensional data** to enhance our understanding of CRC survival. Genome-wide association studies (GWAS), as well as candidate gene and family studies, have underscored the key role of germline genetics in influencing colorectal cancer susceptibility. Until recently, however, very few studies had considered the role of genetic variation in colorectal cancer survival – and those that had have typically been focused on familial syndromes of colorectal cancer and candidate genes involved in pathways of action for cancer therapeutics. In addressing this important gap, I have contributed to studies of candidate pathways, candidate genes, and candidate polymorphisms in relation to colorectal cancer survival, and led the first-ever GWAS for colorectal cancer survival(*Carcinogenesis* 2016;37:87-95 – see *Personal Statement*). This agnostic GWAS approach to polymorphism discovery led to the identification of novel loci in *ELOVL5* that were strongly associated with survival outcomes among individuals diagnosed with stage IV colorectal cancer. Other candidate studies have yielded less consistent findings, highlighting the need for replication and collaboration across studies, and the fact that those polymorphisms that are important to colorectal cancer risk are distinct from those that influence colorectal cancer susceptibility.

1. **Phipps AI**, Passarelli MN, Chan AT, Harrison TA, Jeon J, Hutter CM, Berndt SI, Brenner H, Caan BJ, Campbell PT, Chang-Claude J, Chanock SJ, Cheadle JP, Curtis KR, Duggan D, Fisher D, Fuchs CS, Gala M, Giovannucci EL, Hayes RB, Hoffmeister M, Hsu L, Jacobs EJ, Jansen L, Kaplan R, Kap EJ, Maughan TS, Potter JD, Schoen RE, Seminara D, Slattery ML, West H, White E, Peters U, Newcomb PA. Common genetic variation and survival after colorectal cancer diagnosis: A genome-wide analysis. *Carcinogenesis* 2016;37:87-95*.* (PMCID: PMC4715234)
2. Smith CG, Fisher D, Harris R, Maughan TS, **Phipps AI**, Richman S, Seymour M, Tomlinson I, Rosmarin D, Kerr D, Chan AT, Peters U, Newcomb PA, Idziaszczyk S, West H, Meade A, Kaplan R, Cheadle JP. Analyses of 7,635 patients with colorectal cancer using independent training and validation cohorts show that rs9929218 in CDH1 is a prognostic marker of survival. *Clinical Cancer Res* 2015;21:3453-61*.* (PMCID: PMC4526710)
3. Passarelli MN, **Phipps AI**, Potter JD, Makar KW, Coghill AE, Wernli K, White E, Hutter CM, Peters U, Newcomb PA. Common single nucleotide polymorphisms in the 5’ promoter region of estrogen receptor β are associated with colorectal cancer survival in postmenopausal women. *Cancer Res* 2013;73:767-75. (PMCID: PMC3588850)
4. **Phipps AI**, Newcomb PA, Garcia-Albeniz X, Hutter CM, White E, Fuchs CS, Hazra A, Ogino S, Nan H, Ma J, Campbell PT, Figueiredo J, Peters U, Chan AT. Association between colorectal cancer susceptibility loci and survival time after diagnosis. *Gastroenterol* 2012;143:51-4.e4. (PMCID: PMC3579620)