

EDITORIAL

Is breast cancer a part of Lynch syndrome?

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See related research by Lotsari *et al.*, <http://breast-cancer-research.com/content/14/3/R90>

Abstract

A long-standing question is whether breast cancer is an integral part of Lynch syndrome, also known as hereditary non-polyposis colorectal cancer. A recent study by Lotsari and colleagues analyzes molecular features of breast cancers from families with Lynch syndrome, including germline mutation carriers and their non-mutation carrier siblings, and controls with sporadic breast cancer. The study finds microsatellite instability and loss of mismatch DNA repair protein expression in one third and two thirds of Lynch syndrome samples, respectively, but in none of the non-mutation carriers or controls. Overall, the age of diagnosis of breast cancer in Lynch syndrome mutation carriers is no different than that in non-carriers, but diagnosis age was lower in those carriers whose breast tumors exhibited defects in mismatch repair. These results have important implications for genetic counseling and genetic testing of families with breast cancer and other tumors associated with Lynch syndrome, such as colorectal and endometrial cancers.

In a comprehensive analysis of all available breast cancers from among 200 Lynch syndrome (LS) families in a nationwide registry in Finland, Lotsari and colleagues [1] address the question of whether breast cancer is an integral part of LS. The results, published in the previous issue of *Breast Cancer Research*, are compelling and could inform the way we conduct genetic testing in the diagnosis of LS and set guidelines for breast cancer surveillance in LS mutation carriers.

A central tenet in cancer biology is that most human tumors are associated with, and often are caused by, abnormally elevated levels of genomic instability due to inherited or sporadically acquired defects in DNA repair mechanisms [2]. Although the comprehensiveness of this

hypothesis is vigorously argued in the literature, LS (also known as hereditary non-polyposis colorectal cancer) is considered a paradigm for the mutator phenotype [3,4]. An autosomal dominant Mendelian disorder caused by heterozygous germline mutations in one of four DNA mismatch repair (MMR) genes [5], tumors arising in LS mutation carriers usually undergo loss-of-heterozygosity in the corresponding normal MMR gene, typically resulting in loss of protein expression as assessed by immunohistochemistry (IHC), and exhibit an MMR functional deficiency as defined by the presence of microsatellite instability (MSI) [6]. Therefore, a set of readily available phenotypic assays (MSI and IHC for MMR proteins) can help identify underlying genomic instability and guide germline genetic testing to the appropriate causative allele, thereby greatly facilitating screening [7]. In addition to the two most common cancers that define LS (colorectal and endometrial cancer), a spectrum of malignancies – ovarian, stomach, small bowel, hepatobiliary, ureteral tract, pancreas, skin, brain, and others – has been associated with LS on the basis of their increased incidence in MMR gene mutation carriers and more recently on the basis of documented molecular phenotyping and genotyping of the tumors themselves.

Whether breast cancer is a component of LS has been debated since the latter was first suggested by Henry Lynch [8]. Beyond just an academic question, this issue is of importance for guiding genetic counseling and diagnostic testing of families with a history of breast cancer in addition to other LS-associated tumors, for screening surveillance and clinical management of breast cancer risk in LS, and potentially by providing prognostic or predictive information (or both). Both the revised Amsterdam criteria for diagnosis of LS [9] and the revised Bethesda criteria for identification of individuals for MSI testing [10] take into account extracolonic tumors but not breast cancer. Several studies have suggested an elevated risk for breast cancer in LS, but the issue remains controversial. Most studies are limited by being small, retrospective, and lacking in statistical power. More recently, molecular studies have been added to the epidemiologic approach. MSI is very rare (0% to 3% of cases) in sporadic breast cancer [11] but is observed in more than half of breast cancer cases diagnosed in LS

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mutation carriers [12,13]. Most recently, a prospective study of cancer risk in 446 MMR gene mutation carriers compared with 1,029 non-carrier relatives ascertained from the Colon Cancer Family Registry found a fourfold increased risk for breast cancer [14], although whether the age of diagnosis was younger in these seven cases could not be determined.

In this context comes the study by Latsari and colleagues [1]. In hopes of advancing the understanding of breast cancer as a possible tumor in the LS spectrum and the role of MSI in breast cancer tumorigenesis, the authors identify and study all cases of LS-associated breast cancer in the Finish Hereditary Colorectal Cancer Registry. In this well-designed and controlled study, MSI and IHC for the MMR proteins MLH1, MSH2, and MSH6 were performed on 23 breast cancers from 19 LS patients with known germline mutations, 18 breast cancers from 18 known non-mutation carriers from LS families, and 49 sporadic breast cancers from non-LS families and were presented together with detailed information on the tumor pathology and patient age at diagnosis. The results are quite interesting. MMR pathway defects were clearly associated with breast cancers from LS patients but were more frequently associated with other accepted extracolonic LS-associated tumors studied; approximately two thirds of the 23 breast cancers with germline LS mutations exhibited loss of MMR protein expression and only half of these exhibited MSI, but no LS non-mutation carriers or sporadic controls exhibited MMR defects. A closer look at the heterogeneity in MMR activity in LS-associated breast cancer is provocative. For example, none of the seven *MSH6* mutation carriers who developed breast cancer exhibited MSI in their tumors, whereas about half of the *MSH2* and *MLH1* mutation carriers did. In an overall analysis, no difference was seen in the age of mutation carriers and non-carriers or controls when diagnosed with breast cancer, but patients with breast cancers showing MSI or loss of MMR by IHC were statistically significantly younger.

So does LS lead to an increased incidence of breast cancer or younger age at diagnosis, or not? The numbers of participants remain too small to provide a definitive answer, but this retrospective study certainly suggests that, for the breast cancers that show MSI, their DNA repair defects contribute to their progression. However, there is no evidence in this cohort that MSI affects other aspects of the cancer phenotype, such as molecular pathology, stage, or outcome. Perhaps germline *MSH6* mutations, relatively over-represented here in breast cancer cases compared with other LS-associated tumors, lead to breast cancer risks in the absence of high-level MSI through non-canonical mechanisms. To address such fascinating mechanistic questions, as well as more

practical implications regarding the role of LS in breast cancer incidence and age at diagnosis, will require much larger studies. However, this study, together with others in the literature, does support a biologic role for LS-associated MSI in breast cancer progression. Since most patients with LS develop breast cancer after the age of 50, population-based breast cancer screening programs, including mammography, appear adequate for LS mutation carriers. A clear practical implication given the high specificity but modest sensitivity for MSI/IHC testing of breast cancer tumor tissue is that molecular phenotyping may be useful in the management and genetic testing of certain families when colorectal cancer or endometrial cancer tissue samples are unavailable. Finally, as 'universal' testing of all colorectal and endometrial cancers for MSI, independent of family history, becomes more standard [15], a similar approach in breast cancer will be a developing question. Ultimately, to determine whether breast cancer is a component of LS and, more importantly, whether MSI has prognostic or predictive value in breast cancer management, will require larger, population-based prospective studies.

Abbreviations

IHC, immunohistochemistry; LS, Lynch syndrome; MSI, microsatellite instability; MMR, mismatch repair.

Competing interests

The author declares that he has no competing interests.

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