A 26-Year Study Highlights Invasive Breast Cancer Recurrence After DCIS

BY AMY GALLAGHER

It is widely accepted that most cases of ductal carcinoma in situ (DCIS) are now diagnosed through breast cancer screening programs and 20 percent of all breast carcinomas are in situ lesions, according to a March 2020 report from the National Center for Biotechnology Information. It is also commonly understood that effective delivery of population-based breast cancer screening can maximize benefits and minimize harms.

To understand the epidemiology of DCIS in the context of a population-based mammographic screening program, researchers at the University of Oxford and Public Health England evaluated the long-term risks of invasive breast cancer (IBC) and of death from breast cancer after DCIS through breast cancer screening (BMJ 2020; doi: https://doi.org/10.1136/bmj.m1570).

The population-based cohort study compared the rates of IBC and breast cancer mortality with the corresponding national United Kingdom (UK) rates for women of the same age in the same calendar year, according to lead author Gurdeep S. Mannu, DPhil, Academic Clinical Lecturer in General Surgery and Clinical Research Fellow in Cancer Surgery in the Nuffield Department of Population Health at the University of Oxford, Medical Sciences Division.

The peer-reviewed, observational study assessed the accumulated data of 35,024 women in England diagnosed with DCIS during mammogram screenings conducted by the UK’s National Health Service Breast Screening Program from 1988 to March 2014.

“Several findings regarding the impact of different treatments on the long-term outcome of women with DCIS were quite interesting,” he said.

The risks were more than double those of the general population, even for women diagnosed with low or intermediate grade DCIS, said Mannu. “In particular, the women with DCIS who were detected by screening had twice the rates of IBC than that of the general population.”

Yet another notable finding from the study showed that, for both IBC and death from breast cancer, the increased risk continued through at least 20 years after the diagnosis. “This finding has not previously been shown,” he noted.

The Underlying Cause

There are two types of ductal carcinoma: invasive ductal carcinoma (IDC), also known as infiltrating ductal carcinoma; and DCIS, also called intraductal carcinoma. IDC is the most common form of breast cancer, representing 80 percent of all breast diagnoses.

The results of the study concluded that by December 2014, 2,076 women had developed IBC, which is an incidence rate of 8.82 per 1,000 per year and more than double the number expected from national rates.

“[A total of] 310 women who died had breast cancer as the underlying cause of death on their death certificates,” said Mannu. Additionally, the death rate increased during the years 5-9 after being diagnosed with DCIS, but the primary reason for the increase in death rate requires further study.

“DCIS isn’t invasive cancer nor is it immediately life-threatening,” said Mannu. “Although it usually has a good prognosis, DCIS can increase the risk of developing an IBC in the future.” Although women can develop DCIS at any age, it is more common over age 50, according to the NIH. “Based on the study, the age range of women who died from breast cancer was wide and ranged between 53 and 94 years,” Mannu noted.

Factors Influencing IBC After DCIS

“The risk of developing IBC following DCIS is influenced by several factors,” said Mannu, including final margin distance, type of surgery received, whether mastectomy or breast-conserving surgery [BCS], and if BCS was elected, and whether or not radiotherapy was received.

“Another factor to consider for those with estrogen-receptor positive DCIS lesions, who were eligible, was whether or not endocrine therapy was used,” he stated. All of these factors play a role, to varying degrees. “It is not a case of one single principle cause for IBC occurrence after DCIS.”

Factors Influencing Surgery

Although the cumulative rate of IBC for women who had BCS increased, with or without radiotherapy, compared to those who had a mastectomy, the conclusion does not point to mastectomy as the solution, said Mannu.

“I certainly don’t think mastectomy is the answer for many women with DCIS, particularly as many cases of DCIS involve small and prognostically favorable lesions,” he commented. “However, I equally feel mastectomy certainly can be the most appropriate option for some women. The decision on whether to opt for mastectomy or BCS [with or without radiotherapy] is based on a number of factors.”

Mannu said the factors that currently influence the choice of surgery in the treatment of DCIS are patient preference (some women may ask for a mastectomy), the health of the patient (age, frailty, and other medical problems), tumor characteristics (grade, tumor size in relation to breast size, hormonal status), and clinician recommendations based on experience and research.

Identifying ‘Favorable Characteristics’

Although results suggest that treatment generally reduces the risk of IBC for women with DCIS, some groups of women with favorable characteristics may exist for whom surgery may not be necessary, said Mannu.

“In the context of ‘favorable characteristics,’ we should consider the factors underpinning the eligibility criteria of the ongoing trials of non-operative treatment of DCIS, such as the LORD, LORIS, and COMET trials,” he said.
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While the criteria for each of these trials differ from each other in small ways, generally speaking, favorable characteristics often refer to women aged in their mid-forties or older, diagnosed with DCIS detected through screening (rather than symptomatically), and diagnosed by the use of vacuum-assisted biopsy rather than core biopsy, as well as cases showing a diagnosis of low-grade disease under the microscope rather than high-grade DCIS, Mannu noted.

Understanding the Confounding Factors

“As a researcher primarily focused on epidemiological analyses of population-level data, this type of research can be challenging as confounding factors can sometimes make interpretation difficult,” said Mannu. For example, he noted the role of non-operative treatment in the management of low-risk DCIS can only be reliably evaluated in the setting of randomized trials.

“Our findings have, however, shown the risk of IBC continues for at least 2 decades following DCIS diagnosis, and as a result, such randomized trials should aim to follow women up for at least 10 years, if not longer.”

Further Studies to Identify DCIS Type

The study’s conclusion identified the need for more intensive treatment and larger final surgical margins associated with lower risks of IBC, he said.

“Further studies are needed to build on these findings, specifically to identify which cases of DCIS are most closely linked to the development of IBC,” said Mannu. “This may have implications for follow-up and the frequency of surveillance imaging.”

The overall benefits and risks of treatment can be reliably evaluated only in the setting of randomized trials with long-term follow-up, he noted. “In the meantime, I hope that the findings presented in this research help to further inform the discussion between patients and clinicians in relation to this,” Mannu concluded.

Amy Gallagher is a contributing writer.

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Patients should contact their health care provider if they experience any of the following: Signs of infection (fever, chills, cough, painful urination, headaches), bleeding, and uncontrollable GI toxicity.

What else should I know about azacitidine?

- Due to pharmacokinetic differences, the dose and schedule of oral azacitidine is different than the intravenous and subcutaneous azacitidine. They should not be substituted or used interchangeably.
- Patients should receive supportive care, including growth factor support during periods of neutropenia.
- Interruption of azacitidine treatment occurred in 35 percent of patients for neutropenia (20%), thrombocytopenia (8%), and nausea (6%). Permanent discontinuation due to AE occurred in 8 percent of patients mostly for nausea, diarrhea, or vomiting.
- Embryo-fetal harm may occur. Effective contraception should be utilized during treatment and for 6 months after last dose for females and at least 3 months for males.

What useful links are available regarding azacitidine?

- Prescribing Information: https://www.onuregpro.com/

Any ongoing clinical trials related to azacitidine?

Clinical trials with azacitidine are being conducted to investigate its place in therapy or effectiveness for AML, MDS, CMML, diffuse large B-cell lymphoma, and various solid tumor malignancies. It is currently being studied in combination with other agents such as venetoclax, rituximab, cyclophosphamide, doxorubicin, fulvestrant, and pembrolizumab, and in the maintenance setting post-HSCT. More information is available about the clinical trials at https://clinicaltrials.gov.