Sir,

It is important to identify breast cancer patients at undue risk for leukaemia associated with breast cancer chemotherapy to measure risks vs benefits of chemotherapy. Iqbal et al (2016) conclude that although leukaemia in BRCA2 carriers is primarily caused by breast cancer chemotherapy, it is so rare that BRCA mutation carriers can be treated according to standard protocols. However there are multiple confounders in determining risks; and leukaemia in breast cancer patients can be caused by biological factors that go beyond chemotherapy.

All patients with leukaemia had breast cancer in the study (Iqbal et al, 2016) but they had different BRCA1 or BRCA2 mutations. Three breast cancer patients with leukaemia had deletions that cause major disruption in the activity of the BRCA1 or BRCA2 gene. Two of the three died. Complete inactivation of the BRCA2 gene occurs by germline mutations in some children. Of seven children with biallelic BRCA2 (FANC D1) mutations, at least five were diagnosed with childhood leukaemia before age 6 (Wagner et al, 2004). All six children with a mutation in FV5 of the BRCA2 gene were diagnosed with leukaemia before age 3 (Alter, 2014). In a larger study of 36 patients, 17 patients developed leukaemia, mostly acute myeloid leukaemias (AML) (Alter, 2014).

A total of 18 Fanconi anaemia proteins participate in pathways containing BRCA1 and BRCA2, and hereditary defects in some of the Fanconi proteins associate with very high risks for leukaemia (e.g. 20% by age 40) (Alter, 2014). Meta-analyses found the combined relative risks (confidence intervals) that a Fanconi anaemia patient will develop: AML as 703 (364–1355); leukaemia before age 15 as 170.3 (96.5–300.5); and the precancerous condition myelodysplastic syndrome as over 17,000 (Friedenson, 2007). These results show that breast cancer or leukaemia.

Elevated leukaemia risks were not found for BRCA1 mutation carriers (Iqbal et al, 2016), but chemotherapy is known to interfere with BRCA expression by inactivating the gene promoter (Scardocci et al, 2006). Most primary AML cell lines have low BRCA1 expression (Faraoni et al, 2016). Among 47 survivors of breast cancer who developed leukaemia caused by the known leukaemia/lymphoma virus HTLV-1 (Katoaka et al, 2015) were compared with a reference set of breast cancers (Banejri et al, 2012), and showed that 35% (104 out of 301) of exome genes mutated in leukaemias are also mutated in breast cancers. Genes mutated in the same breast cancer genomes (Banejri et al, 2012) were also compared with genes recurrently mutated in eight genomes from primary AML. In AML, 28 different genes are recurrently mutated and presumably linked to AML pathogenesis (Ding et al, 2012). Nine (32%) of the 28 genes are also mutated in the reference breast cancers but the similarities extended further, suggesting an even stronger relationship. For example, WAC and DCL1 were recurrently mutated genes associated with AML relapse (Ding et al, 2012) and were also mutated in some breast cancer genomes. Genes with functions similar to at least another 7 out of 28 (25%) additional recurrently mutated AML genes were also mutated in the breast cancers. Most breast cancer mutations occurred in genes with some connection to infection and immunity (Friedenson, 2015). At least 58 mutated genes were cancersally related to leukaemia/lymphoma (Banerji et al, 2015). BRCA2-associated breast cancer involve immune responses or other protective functions (Friedenson, 2013; Friedenson, 2014; Friedenson, 2015).

Convincing evidence associates human papilloma virus (HPV) (Glenn et al, 2012; Simoes et al, 2012) with some breast cancers. Genes that encode for pathways mediated by BRCA1, BRCA2 and Fanconi anaemia gene products are essential for immunity to clear HPV infection and to prevent replication of this dangerous pathogen (Hoskins et al, 2012). High percentages of genes damaged by mutation in BRCA1- and BRCA2-associated breast cancer involve immune responses or other protective functions (Friedenson, 2013; Friedenson, 2014; Friedenson, 2015). Human papilloma viruses interfere with multiple immune-associated responses (Lee et al, 2006; Deligeoroglou et al, 2013; Iijima et al, 2013; Sanchez-Reyes et al, 2014; Tummers and Burg, 2015) and cause major chromosome aberrations in human peripheral blood lymphocytes (Paz-y-Mino et al, 1992; Alvarez-Rosero et al, 2008). Human papilloma viruses are the established cause of cervical cancer. Chemotherapy given for cervical cancer in the presence of HPV infection increases leukaemia risk close to the level reported in BRCA2-associated breast cancers: SIR = 7.29 (2.67–15.86) (Morton et al, 2013).

Macrophages then lymphocytes have been implicated as essential first and second intermediates, respectively, in breast infection by some viruses that have been associated with breast cancers. Immune cells become reservoirs that deliver such cancer-associated infections to the breast (Domech et al, 2000; Zur Hausen, 2009; Holland and Pogo, 2012). Breast duct structures reveal integrated resident cells from the immune system (Degnim et al, 2014; Gulbahce et al, 2014) and breast cancers contain infiltrates with large numbers of macrophages and lymphocytes. Cancer or tumour virus infection of proliferating resident or infiltrated cells from the immune system can quickly spread to the breast and vice versa. There are clinical examples consistent with this explanation, for example, (Etkind et al, 2000; Salagovic et al, 2012).

Although a connection between BRCA mutations and leukaemia/lymphoma may cause concern in women who carry BRCA mutations, their cancers are often invisible (Lewin, 2008) and this connection may at last help us begin to understand and address the root causes of breast cancer.
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