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Comment on 'The incidence of leukaemia in women with *BRCA1* and *BRCA2* mutations: an International Prospective Cohort Study'

A V Paradiso*[,1], M Digennaro[1] and D Sambiasi[1]

[1]*Centro Studi Tumori Eredo-Familiari, Oncologia Medica Sperimentale, Department Medical Oncology, Istituto Tumori G Paolo II, IRCCS, Via O Flacco, 65, 70124 Bari, Italy*

Sir,

The increased risk of leukaemia in women with a BRCA2 mutation who receive chemotherapy for breast cancer reported in the prospective study by Iqbal *et al* (2016) is of particular interest because it further confirms the idea of the delicate role that DNA repair genes-cytotoxic drug interaction can have in haemato-cancerogenesis. The author reached this conclusion by comparing the risk of developing leukaemia for the first time in a prospective cohort of breast cancer patients, BRCA1/2 mutation carriers and receiving chemotherapy with respect to Standardized Incidence Ratio of general population.

Several different lines of investigation strongly call for a role of BRCA1 and BRCA2 deficiencies in haematologic cancers. Friedenson (2007) already reported BRCA1 deficiency as strongly associated with chemotherapy-related acute myeloid leukaemia; however, if that risk is independent from DNA-damaging drugs utilisation in BRCA carriers, it still remains to be definitely ascertained. How to answer properly this question by considering subgroups of subjects with similar environmental/voluptuary/genetic characteristics?

In our original approach (Figure 1), we collected data on leukaemia incidence in subjects belonging to hereditary (Subjects $n=1156$) and not-hereditary (Subjects $n=1062$) branches of the BRCA probands (Families $n=132$). We did not find any difference in terms of leukaemia incidence in subjects from previous I–II generations in Hereditary and not-Hereditary branches (Leukaemia in Hereditary vs not-Hereditary branches: 11 *vs* 12 cases; odds ratio = 0.98; 95% confidence interval 0.80–1.45) thus suggesting that BRCA alteration is not a 'per se' factor exposing to higher risk for haematological malignancies.

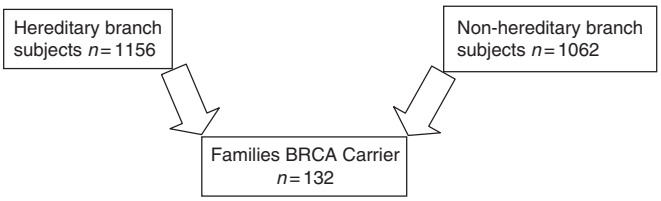

Figure 1. Study design.

Putting together our results as well as the results by Iqbal *et al*, it seems we can conclude that leukaemia does not seem directly related to breast hereditary syndrome, and then to BRCA mutation as risk factor, but rather to lack of DNA repairer function of BRCA gene needed just in case of DNA-damaging drug exposure.

It remains to be verified, like in other clinical scenarios (Cibula and Balmaña, 2015), the possibility to utilise this gene function as a predictive marker of drug response also in leukaemia patients

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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*Correspondence: Dr AV Paradiso; E-mail: a.paradiso@oncologico.bari.it

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