general population (SIR = 3.69, 95% CI: 1.39, 9.64; Table 1); however, because of the low number of cases (2 PV, 1 ET, and 1 myelofibrosis) such an association remains to be validated. The analyses stratified by sex (361 males/372 females), *JAK2*V617F mutational status (340 *JAK2*V617F mutated/137 wild-type), and cytotoxic therapy with hydroxyurea (59.6% of 659 evaluated) did not show any specific risk pattern (not shown in detail).

Our study is based on a smaller population compared with Frederiksen et al[1] and has the advantages of a slightly longer follow-up and of being conducted in a narrower area with an active local registry. Our carefully controlled patient series reduces the risk of possible misclassification at baseline, potentially present in a very large series obtained in a country-wide study, as mentioned by the authors.[1] In any case, we believe that the low SIR value (1.2 to 1.4) found in the Danish study,[1] together with our negative results, should call for much caution before accepting d'emblée the idea that the incidence of nonhematologic cancers is specifically increased in MPNs and, even more, before discussing such topic with the patients.

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Response

Cancer risk in chronic myeloproliferative neoplasms

We thank Susini and colleagues for their comments[1] to our article on the risk of a new cancer in patients with chronic myeloproliferative neoplasms (CMPNs).[2] We have read the results from their CMPN cohort from Tuscany with interest. We agree that any novel finding must be confirmed before generally accepted and shared with patients. However, other studies have found results in line with ours. Fallah et al reported an increased risk of kidney cancer, melanoma and nonmelanoma skin cancer, as well as endocrine cancers among patients diagnosed with polycythemia vera (PV).[3] Nielsen et al reported an increased risk of any cancer among *JAK2* V617F mutation-positive persons from the general population.[4] In their study most new malignancies were CMPNs but also solid tumors were reported.[4] Although we cannot rule out an effect of diagnostic misclassification of CMPNs in our study it is reassuring that we found similar risk of a new cancer among patients with chronic myeloid leukemia (CML) among whom diagnostic misclassification seems unlikely. We also found the expected increased risks of new hematologic malignancies. Furthermore, our results were robust across stratification according to a previous or current diagnosis of chronic obstructive pulmonary disease. The excess risk of nonhematologic cancers in our study is modest, ranging from 1.2 to 1.6, and might only be detectable in larger studies.

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To the editor:

Regulation of human dendritic cells by B cells depends on the signals they receive

B cells are classically known for producing antibodies. However, several reports also indicate that B cells are potent regulators of immune responses including those mediated by dendritic cells (DCs), although direct effect of B cells on DC was relatively unexplored.[1-4] Recently, Morva et al demonstrated that CD40 + TLR9 (CpG)–stimulated human B cells restrain the differentiation of monocyte-derived DCs and their maturation.[5] They further found that stimulation of B cells is necessary to trigger potent regulatory activities on DCs.

Under physiological conditions, there is a constant cross-talk between DCs and B cells. Although suppression of DCs may play a role in preventing the autoimmunity, normal functioning of DCs without suppression is also critical for immune homeostasis and immune response to tumor cells and foreign antigens. These views indicate that B cells are not continually inhibitory on DCs. As B cells can receive activation signals via diverse receptors including B-cell receptor (BCR), CD40 and TLR, we surmised that the effect of stimulated B cells on DCs depends on the type of signals they receive. In view of the importance of BCR signaling in B-cell activation and in generation of regulatory B cells,[1,2] we explored the role of BCR-stimulated B cells either alone or in combination with TLR9 stimulation on the differentiation and maturation of DC.

We found that when monocytes were differentiated into DCs in the presence of cytokines GM-CSF and IL-4 and B cells that were activated by combination of BCR + TLR9 (CpG) stimuli, there was a significant reduction in the expression of DC markers such as DC-SIGN, CD83, HLA-DR, CD40, CD80, CD86, and CD58 (Figure 1A). Thus, in accordance with Morva et al,[5] our results revealed a regulatory role of BCR + CpG-stimulated B cells on differentiation of DCs. However, B cells that received signals only via BCR were not inhibitory (Figure 1A), indicating that in the absence of TLR stimuli, activated B cells do not block differentiation of DCs. In addition, we report a novel mechanism of modulation of DCs by regulatory B cells. We found that BCR + CpG-stimulated B cells induce a high percentage of apoptosis in differentiating DCs (Figure 1B). Thus, regulatory B cells can modulate DC-mediated immune responses by controlling the number of DCs. Of note, Fas-FasL–mediated apoptosis of target cells is proposed to be one of the mechanisms of immune regulation by regulatory B cells.[1]

Furthermore, compared with profound inhibition of LPS-mediated maturation of DCs by CD40 + CpG-activated B cells,[5] we found that B cells that received BCR signaling alone were only partially inhibitory on DCs (Figure 1C). Together, our results indicate that regulation of DC differentiation and maturation by B cells depends on the type of stimuli they receive. B cells receiving BCR stimulation alone are not inhibitory on DCs while under inflammatory conditions as in TLR9 stimulation; these TLR-9–stimulated B cells can act as inflammation-limiting factors in part via inhibition of DC activation. These functional differences of B-cell stimuli were also reflected in their ability to induce the expression of key molecules CD62L and CD80/CD86 on B cells (Figure 1D) that are proposed to be important in the regulation of DC and T-cell functions, respectively, by regulatory B cells.[5,6]

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