Commentary

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Gall stones, colorectal and other cancers

Johansen and colleagues present the results of a cohort study with a substantial size and a non-differential follow up with regard to different cancer outcomes. However, this paper is, in essence, two different studies. One part constitutes an in depth study of the potential association between gall bladder disease and colorectal cancer and the other part constitutes a 'fishing expedition' with regards to other cancer sites without any a priori hypothesis. In this latter study, the authors found an association between gall bladder disease and cancer of the pancreas and small intestine as well as for breast cancer in women.

The association between colorectal cancer and gall bladder disease has been the subject of a veritable abundance of studies, which, three years ago, were summed up in a meta-analysis[1] followed by a commentary by Dr Robert Sandler in which he stated that there are probably 'more fruitful fields for the understanding of colorectal cancer' and 'future researchers should provide the underlying reason why an additional study on this subject is needed'.[2] However, this study includes at least two unique features. Firstly, in the analysis the authors were able to adjust for clinically defined obesity. Secondly, besides confirming previous results of, at most, a modest increased risk of cancer of the colon, the authors were also able to differentiate between patients with gall bladder disease subjected to cholecystectomy and those left with an intact gall bladder. The results show that the operation as such does not change the risk but, as the authors point out, the weak association is probably due to shared risk factors for the two diseases.

There was also an increased risk for cancer of the small bowel confined to carcinoid tumours most prominent during the first five years of follow up. Because of the insidious symptoms of carcinoid tumors such a finding is not surprising as the symptoms from the tumour could be the underlying reason for the diagnosis of gall stones and a subsequent cholecystectomy. As the duration between symptoms and the final diagnosis of carcinoid can exceed five years,[3] this could also explain the longterm increased risk evident in the results. A similar explanation for the first five years of follow up could also explain the findings of an increased risk for pancreatic cancer in the cohort. A recent Swedish cohort study showed similar results[4] and findings from follow up studies from patients with diabetes mellitus have also indicated that the latency time between the first symptoms of the pancreatic cancer and clinically manifest disease could be longer than previously thought.[5] The slightly increased risk five years or more after start of follow up could, of course, be due to chance as proposed by the authors or could be due to the existence of a common feature for both diseases, a hypothesis strengthened by the similarity of the risk estimates in this study and the Swedish study mentioned above.[4] However, this common exposure remains unidentified as smoking, the most established risk factor for pancreatic cancer,[6] can probably be ruled out as a potential confounder as the incidence of lung cancer in the present cohort did not differ from that expected.

Finally, with regard to breast cancer, previous studies have shown contradictory results and this study is therefore of great interest – especially because of its size. Moreover, the results are similar to those presented in the only previous cohort study with substantial size.[7] The point estimate below unity the first two years after start of follow up is probably, as the authors point out, the result of the exclusion of early asymptomatic breast cancers diagnosed during the investigation for gall bladder disease. However, after two years or more different confounders could be operating. Although surveillance bias is probably not the sole underlying reason for the positive findings it is possible that women entering a health care system because of gall bladder disease are more likely to have better access to this system. For instance, they could be subjected to hormonal replacement therapy due to natural menopause or secondary to a hysterectomy more frequently than the general population. Hormonal replacement therapy is associated with a modest increased risk for breast cancer and could therefore act as a confounder.[8] The existence of better access can also be inferred from the decreased risk for cervical cancer in the cohort, which could be interpreted as a higher frequency of hysterectomies or better access to screening for cervical cancer, or both, and thus probably a better compliance to mammographic screening programmes. One should therefore be extremely cautious before inferring that common metabolic or hormonal determinants will act as risk factors for both gall stones and breast cancer.

In conclusion, this paper confirms previous findings of, at the most, a modest association between cancer of the colon and gall bladder disease but because of possible confounders and the potential for a surveillance bias, additional data are needed before definite inference of an association between gall bladder disease and breast cancer can be made.

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