Letter to the Editor

Response: Risk of prostate, breast and colorectal cancer after skin cancer diagnosis

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Dear Sir,

Recently, Levi *et al.*[1] reported the risks of developing a prostate, breast or colorectal cancer after an initial skin cancer diagnosis. The hypothesis was that skin cancer patients would have higher vitamin D levels through higher sun exposure and would, therefore, be at reduced risk of these types of cancer. Contrary to their expectations, overall, a 15–20% higher risk of breast, prostate and colorectal cancer was observed in the cohort as compared with the general population.

This is not the first paper to be written about this topic, some of which are summarized in other articles by de Vries *et al.*[2,3] and Nugent *et al.*[4] Most other studies obtained similar results to the findings of Levi *et al.* This might be because skin cancer patients do not have higher vitamin D levels or because vitamin D does not protect against the development of second tumors. However, any decreased or an increased risk might also be obscured by some methodological issues, that are illustrated later.

Surveillance bias

As mentioned by Levi *et al.*,[1] higher frequency of prostate-specific antigen (PSA) utilization or mammography, especially among cancer survivors, may lift the relative risk estimates of second cancer. Levi *et al.* reported 680 prostate cancers among 31,377 skin cancer patients. Although they did not state the number of male skin cancer patients, nor their number of accumulated person-years at risk, let us assume that they are about half: 15,000 patients. In the report from the Dutch group, only 317 prostate cancers were observed among the 13,541 male skin cancer patients.[2] It is known that PSA testing is much more common in Switzerland than in The Netherlands, which might be a reason for the differences between these 2 regions.

Even if the real incidence of second prostate or breast cancer was decreased, such surveillance bias could lead standardized incidence ratio (SIR) estimates of second cancer to be close to unity or slightly increased. Studies often stratified risk of second cancer by time since diagnosis to assess for surveillance bias.[1–3,5] A reduction of second cancer risk in the early years after diagnosis of the skin cancer[2,3] may exclude this bias. In addition, a reduced risk[2,5] that disappeared with time can also further support the Vitamin D hypothesis. After a skin cancer diagnosis, most patients would reduce their exposure to the sun, causing a gradual decrease of Vitamin D level[6] thus diminishing protective effect against cancer.

Stratifications

Stratification by sub-group of first skin cancer:
Histology, location, age and gender

Epidemiological studies have suggested different sun exposure pattern to be related with different subgroups and location of skin cancer, and age as well as gender.[7,8] Squamous cell carcinomas (SCC), skin cancers in the head and neck region, older age and male gender are usually associated to chronic sun exposure. Therefore, patients with these characteristics are expected to have a higher Vitamin D status and possibly a lower risk of certain second cancers.[2–5,9] Indeed, similar to previous studies,[2–4,10] Levi *et al.* found lower SIR point estimates for SCC and basal cell carcinoma (BCC) than for melanoma, although no decreased risks were observed. After stratification by location and subtype of skin cancer, neither Levi *et al.*[1] nor Milan *et al.*[11] found a relationship, though others found the contrary.[2,3] Finally, though Levi *et al.* did not stratify by gender they stratified by age, but no systematic differences were observed between the young (<60) and elderly (≥60) patients.

Stratification by stage

Vitamin D has been shown to inhibit invasiveness, angiogenesis and metastatic potential, hence delaying cancer progression and improving prognosis.[12,13] For example, analytical studies showed protective effects of sun exposure against fatal prostate cancer.[2,14] Unfortunately, Levi *et al.* did not report on stage at diagnosis, which would not only have shed light on this aspect, but would also give some insight into the degree to which PSA screening has 'artificially' contributed to the high numbers of prostate cancer cases.

Conclusions

The question as to whether or not skin cancer patients are at decreased risk of developing some types of second cancers remains unanswered, as is the question whether or not vitamin D would be responsible for this. It would be useful to determine vitamin D levels among the different subgroups of skin cancer patients at several time-points since diagnosis. As for studies within cancer registries, international collaborations[10] may increase number of cases making stratification possible with sufficient statistical power.

Yours sincerely,
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