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Perspectives on a Global Change in Testicular Cancer Incidence

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Testicular cancer is the most common malignancy among young men and although the cure rate is excellent, the condition is a major health concern both because of potential loss of life and the side effects of treatments [1]. Furthermore, testicular cancer is associated with a range of other health concerns, including developmental defects of the male reproductive tract and reduced semen quality [2]. In this issue of *European Urology*, Gurney and co-workers [3] present updated data on the incidence of testicular cancer over a period of 35 yr using registry data from 41 countries. The results are comprehensive and represent an important resource when considering testicular cancer epidemiology. They confirm an overall increase in incidence over time, with well-known differences in age-standardized incidence between certain countries and regions, ranging from a high of 11.5 cases/100 000 person years in Norway to a low of 0.3/100 000 person years in Uganda for 2008–2012.

The most interesting finding highlighted by the authors is that the increase in testicular cancer incidence seems to be stabilizing in high-incidence countries, while it is increasing in some former low-incidence countries. These findings are consistent with previous results, which is unsurprising as the same databases were used, primarily the *Cancer Incidence in Five Continents* (CI5) volumes [4,5]. However, examination of the results reveals that this is not a systematic trend but applies only to specific comparisons, mainly within Europe. For example, the average annual percentage increase is still higher in Norway at 2.4% than in many low-incidence countries, and the confidence intervals for most individual comparisons between countries overlap. The results therefore suggest that the gap between countries has stopped widening, but it seems premature to state that it is closing on the basis of the

current findings. Nevertheless, it is worth noting that changes in testicular cancer incidence seem to be accelerating, especially in some Eastern and Southern European countries, with Croatia as the unfortunate frontrunner, showing a 6% average annual increase.

The authors offer a variety of possible explanations for their finding that the incidence gap in some regions seems to be closing. The most obvious, but also the least colorful, is that the detection of testicular cancer and the qualities of cancer registries in the former low-incidence countries may simply have been improved and are now picking up more cases of cancer. The authors are quick to dismiss this possibility, but in our opinion it cannot be completely discounted. Health care access and quality have generally improved over recent decades in the countries with the most rapidly rising incidence of testicular cancer, and the website for CI5 quality documents that the registry data used by Gurney and co-authors is of varying quality. An important example is that the proportion of microscopically verified cases of testicular cancer has been as low as 65.9% in Croatia in CI5 volume IX, while it has been stable at 97–99% in Switzerland and Denmark, where the increase in incidence is most notably leveling out [6]. This means that there is a risk of bias for some of the testicular cancer incidence rates reported and the data need to be interpreted with this limitation in mind. Meanwhile, we agree with the authors that competing morbidity and migration are unlikely to explain the changes.

The final explanation is that the findings may be due to an actual increase in the prevalence of etiological risk factors for testicular cancer in some populations. This is by far the most interesting possibility as it points to environmental rather than genetic causes of testicular cancer. Furthermore, it suggests that the data can aid in

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identifying these causes and it is in concordance with previous research showing a positive correlation between the gross domestic product and testicular cancer in Europe [7]. Unfortunately, it is not an easy task to formulate viable hypotheses for future testing based on epidemiological data. It is currently believed that testicular cancer may in part be caused by maternal exposure to exogenous toxins broadly termed *endocrine disruptors* during pregnancy [2]. This means that any associations are obscured by a long time span between exposure and disease, and that potentially important information may be unavailable at diagnosis. In addition, endocrine disruptors are a highly heterogeneous group of different chemical substances that when investigated individually tend to give contradictory results [8]. The task will therefore be to consider suspected endocrine disruptors and identify time-specific changes in the environment in the countries that have seen the highest increase in testicular cancer. Such changes should then be compared to the situation in countries where the risk is leveling off. The issue is complicated by the fact that many pollutants remain in the environment for many years after they have been introduced, and genetic influences may mean that the same pollutants have different effects across various populations [9]. Furthermore, endocrine disruptors are only part of a multifactorial etiology with many unknown factors, and their role can never be clearly identified, as randomized exposure studies among pregnant women are impossible to carry out. The paper by Gurney and co-workers certainly highlights a difficult but important problem and time will tell if the data can help to improve our understanding of the environmental causes of this important disease.

Conflicts of interest: The authors have nothing to disclose.

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