The Link between Height and Cardiovascular Disease: To Be Deciphered

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Dear Editor,

More than 70% of all deaths worldwide are attributed to non-communicable diseases, such as cardiovascular disease (CVD) and cancer. Inarguably, identifying vulnerable populations is a critical step for developing preventive strategies to lower the rate of “premature death” from these diseases. Due to their simplicity and non-invasiveness, anthropometric measures are very appealing indices for estimating a person’s vulnerability to disease. An elevated body mass index (BMI), a proxy of excess adiposity, is a well-documented contributor to the etiology of both CVD and cancer.

Height has recently been linked to risks of both CVD and cancer, but its direction is the opposite: shorter people are at greater risk for CVD but lower risk of cancer [1, 2]. The associations are substantially linear and are robust across different ethnicities, for both sexes, and for subentities of each disease (i.e., various cancer sites and stroke subtypes). Although cancer investigators are finding answer at the increase in cell number and cell divisions marked by taller stature [3], a reasonable explanation for a high CVD risk in shorter people remains warranted [4–6]. Beyond simple epidemiological association, recent genetic studies

demonstrated a causal relationship, explaining this sophisticated biological mechanism via links with a third variable (i.e., lung function and metabolic profiles) [2, 7].

Both genetic and environmental determinants contribute to height. The main determinant of height across different populations is economic development and nutrition rather than genetics. For researchers investigating whether shorter populations are at higher risk for CVD, it may be impossible to reflect all forces driving socioeconomic, cultural, and behavioral changes. However, what about secular trends within a *single* population? With nutritional improvement, the average height of Korean people increased by approximately 2 cm per decade in the latter half of the 20th century. Did this increase in height contribute to the decline in CVD incidence? In cases of cancers, the trends in height may explain the rise in cancer incidence [1].

Two recent Korean studies [1, 8] used a similar database of nearly the same population; they only differed by follow-up duration and outcomes. These studies found approximately 500,000 CVD cases developed during a 9-year follow-up period and

approximately 750,000 cancer cases developed during a 5-year period. Under the same circumstances, cancer develops more frequently and earlier than CVD. If many tall people died from cancer and were then excluded, as a result, tall stature may be associated with a low mortality from CVD [9]. Likewise, if many tall people adopted healthy habits following the diagnosis of cancer or precancerous lesions, ultimately, tall stature may be related to a low risk of CVD [2].

Albeit commonly considered as separate entities, CVD and cancer have substantial similarities and possible interactions, including a number of risk factors (e.g., obesity, diabetes mellitus, and some health-related habits). Therapeutic advances have also increased the overlap [10], with survivors from one disease at risk of developing the other disease [11]. To unveil the complex interaction, we suggest that future studies should analyze both diseases simultaneously as outcomes rather than separately. To our knowledge, only one study has been performed with such an intention [12]; however, it reported no association in the risk of both diseases.

In addition, studies on height should pay close attention to the distribution of BMI. Tall women have a low BMI, whereas men show a highly positive correlation. Adjustment for BMI can affect outcomes – diluted in men and amplified in women [13]. Multicollinearity should not be a problem with these types of issues, as it is a matter of interpretation. This is also true for a smoking history. In developed countries where most studies have been performed on this issue, tall women – possibly young women – are more likely to currently smoke; however, in men, this association is weak. On the other hand, a

Mendelian randomization study reported an inverse association at the genetic level between height and smoking [14]. Thus, studies should not overlook these variables.

Obviously, height is an attractive indicator representing the interaction of one's genetic endowment and early life environments. If current evidence on the relationship between height and CVD risk is correct, short people could be targeted with more stringent strategies for CVD prevention. We would like to see more evidence-based rigorous investigations studying the effect of height on CVD.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

Not reported.

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