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Commentary

# Telomere length: A possible link between phthalate exposure and cancer development?

Qiuyin Cai *

*Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center and Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN 37232, USA*

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Phthalates or phthalic acid esters are a class of synthetic chemicals used as plasticizers to soften polyvinyl chloride (PVC) in a wide range of consumer and personal care products. Phthalates are released into the environment and taken up by the general population mainly through ingestion, inhalation, and dermal contact. Phthalates are lipid soluble, have relatively short (less than 24 h) biological half-lives, and are quickly excreted in urine and feces. The measurement of phthalate metabolites in urine is currently the most accepted method in epidemiology studies for assessing phthalate exposure (Johns et al., 2015).

Phthalates have been classified as endocrine disrupting chemicals and linked to adverse health effects (Singh and Li, 2012; Roy et al., 2015; Caldwell, 2012). The International Agency for Research on Cancer classified di-2-ethylhexyl phthalate (DEHP) as "possibly carcinogenic to humans" (Group 2B). Cumulative evidence from *in vitro*, animal, and epidemiology studies indicate that phthalates cause DNA damage (Caldwell, 2012), affect DNA methylation (Singh and Li, 2012), alter expression of certain genes (Roy et al., 2015; Caldwell, 2012), and increase cell proliferation (Caldwell, 2012). In this issue of *EBioMedicine*, Scinicariello et al. (2016) evaluated the association of phthalate exposure with blood leukocyte telomere length (LTL). Telomeres, tandem hexametric nucleotide repeats (TTAGGG)n located at the end of chromosomes, are specialized chromatin structures essential for the maintenance of chromosomal integrity and stability. Telomeres are essential for the complete replication of DNA, and for protecting chromosomes from nuclease degradation, end-to-end fusion, and cellular senescence, thus playing a key role in promoting chromosome integrity and stability. Retrospective case–control studies have shown that shorter LTL is associated with increased cancer risk, while studies from prospective studies have found that both shorter and LTL are associated with increased risk for cancers (Seow et al., 2014; Qu et al., 2013).

The Scinicariello et al. study (Scinicariello et al., 2016) was conducted in 2472 adult participants of the National Health and Nutrition Examination Survey (NHANES, 1999–2002). Four major urinary phthalate metabolites, including mono-ethyl phthalate (MEP), mono-butyl phthalate (MBP), mono-(2-ethyl)-hexyl phthalate (MEHP), and mono-benzyl phthalate (MBzP) were measured in spot urine samples and the associations of these urinary metabolites with LTL were evaluated. Urinary MEHP, a metabolite of DEHP, was associated with longer LTL after adjusting for potential confounders. Participants in the 3rd and 4th quartiles of urinary MEHP had statistically significantly longer LTLs (5.34% and 7.14% longer, respectively), compared to the lowest quartile, with evidence of a dose–response relationship. Interestingly, the association was observed in all adult age groups (20–39 years, 40–59 years, and ≥60 years), in both men and women, and in both smokers and non-smokers. The study also found that two other phthalate metabolites (MBP and MBzP) in urine were associated with longer LTL, but only in participants who were at least 60 years old. Thus, both the timing of exposure and the type of phthalates to which an individual has been exposed need to be taken into consideration when evaluating the adverse effect of phthalate exposure. It would be interesting to see whether phthalate exposure is associated with LTL in children and adolescents, who are more sensitive to endocrine-disrupting chemical exposures.

The Scinicariello et al. study (Scinicariello et al., 2016) has several limitations and its results should be interpreted with caution. Because phthalates are metabolized and excreted rapidly, a single-spot urine exposure measure may not reflect an individual's long-term exposure level and outcomes of interest may be influenced by the timing and duration of exposure. It has been shown that ICCs are relatively higher (generally 0.3 to 0.6, greater temporal stability) for metabolites of the shorter-chained (DEP, DBP, DiBP and BBzP) phthalates and relatively lower (generally 0.1 to 0.3, lower temporal stability) for metabolites of the longer-chained (DEHP, DiNP, DiDP) phthalates (Johns et al., 2015). To control for variation in dilution in spot urine samples used for the study, the Scinicariello study used urinary creatinine level as an independent variable in the data analysis. However, an individual's urinary creatinine level is affected by muscle mass, BMI, and physical activity. It should also be noted that the study population may have been exposed to many other environmental toxicants which could also affect LTL. For example, it has been reported from studies conducted among

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* Vanderbilt Epidemiology Center and Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, 1161 21st Avenue South, Nashville, TN 37232, USA.
*E-mail address:* qiuyin.cai@vanderbilt.edu.

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NHANES participants that persistent organic pollutants were associated with longer LTL (Scinicariello and Buser, 2015; Mitro et al., 2015) while cadmium exposure was associated with a shorter LTL (Zota et al., 2015). Thus, the finding from the current cross-sectional study cannot rule out the effect of other environmental toxicants. Finally, the majority of the study population is non-Hispanic white. Further studies conducted in other racial/ethnic populations are warranted.

Notwithstanding these limitations, the Scinicariello et al. study (Scinicariello et al., 2016) provides first evidence of phthalates and telomere association. The mechanism underlying the association of phthalates with longer telomere length is not fully understood. One possible mechanism is that phthalate exposure may induce *c-myc* expression that activates telomerase reverse transcriptase (TERT) and telomerase activity of the human telomerase complex. In addition, DEHP activates the PI3K/Akt signaling pathway in MCF-7 breast cancer cells. Qu et al. (2013) observed a reverse J-shaped association between LTL and breast cancer risk — both long and short LTL were associated with breast cancer risk in a large prospective study. Further studies are warranted to confirm the phthalate exposure-LTL association, especially in prospective, longitudinal studies.

## Conflicts of interest

The author declares no conflict of interest.

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