

Supplementary Table 5: Cigarette Smoking and Reproductive Aging

Source	Chemical	Study Design	Main Finding
<b>Human</b>			
<b>Cochran et al., 2008</b>	<b>Cigarette smoke</b>	Women with and without hot flashes were recruited from Baltimore, Maryland and the surrounding counties; women were between 45 and 54 years of age, with at least three menstrual periods in the previous 12 months, and were not postmenopausal; study participants completed a questionnaire and gave a blood sample for hormone measurements	<ul style="list-style-type: none"> <li>• Current smokers had significantly lower progesterone levels compared to never-smokers</li> <li>• Former and current cigarette smokers had increased odds of experiencing hot flashes compared to never-smokers (Former: OR = 1.41, Current: OR = 2.43)</li> </ul>
<b>Gallicchio et al., 2006</b>	<b>Cigarette smoke</b>	Lifestyle information, hot flash information, and blood samples were collected from 611 women aged 45-54	<ul style="list-style-type: none"> <li>• Current and ever-smokers had higher odds than never-smokers of experiencing any and more severe hot flashes.</li> <li>• Positive association between frequency and duration of smoking and experiencing any and more severe hot flashes was observed</li> <li>• Smoking was not associated with estradiol or estrone levels in univariate analysis</li> </ul>
<b>Hyland et al., 2016</b>	<b>Cigarette smoke</b>	Information on smoking, lifetime fertility status, and age at natural menopause were collected from 93,676 postmenopausal women aged 50-79	<ul style="list-style-type: none"> <li>• Active ever-smokers had odds ratios of 1.14 for infertility and 1.26 for earlier menopause compared to never-smoking women</li> <li>• Active-ever smokers reached menopause 21.7 months earlier on average compared to never-smokers</li> <li>• Women exposed to high levels of secondhand smoke reached menopause 13.0 months earlier compared to women not exposed to secondhand smoke</li> </ul>
<b>Smith et al., 2015</b>	<b>Cigarette</b>	Cross-sectional study from the	<ul style="list-style-type: none"> <li>• Women who quit smoking</li> </ul>

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	<b>smoke</b>	<p>MWHS cohort; lifestyle and hot flash information were collected from 761 women aged 45 to 54</p>	<p>were less likely to experience hot flashes, less likely to have severe hot flashes, and less likely to have frequent hot flashes than women who continued to smoke (odds ratio = 0.55, 0.80, 0.76), but were more likely to experience any hot flashes, more severe hot flashes, and more frequent hot flashes than women who never smoked (odds ratio = 2.55, 1.68, 1.46)</p> <ul style="list-style-type: none"> <li>• Subset analysis of the 353 women who had ever smoked found that women who had quit smoking for longer than 5 years had significantly lower odds of severity and frequency of hot flashes than women who had continued smoking (odds ratio = 0.36, 0.62, 0.63) or women who had quit in the previous 5 years (odds ratio = 0.66, 0.77, 0.69)</li> </ul>
<b>Whitcomb et al., 2018</b>	<b>Cigarette smoke</b>	<p>Information regarding lifestyle behavior and medical conditions were collected from 106,256 female US registered nurses aged 25-42</p>	<ul style="list-style-type: none"> <li>• Current smokers had hazard ratios of 1.90 for early menopause compared to never-smokers</li> <li>• Former smokers had hazard ratios of 1.1 for early menopause compared to never-smokers</li> <li>• Increased risk was observed for current smokers who have smoked for 11-15 pack years (hazard ratio = 1.72) and more than 20 pack years (hazard ratio=2.42) compared to never-smokers</li> <li>• Women who smoked 10 or</li> </ul>

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			fewer cigarettes per day but quit before age 25 had comparable risk to non-smokers for early menopause (HR = 1.03)
<b>Whiteman et al., 2003</b>	<b>Cigarette smoke</b>	Lifestyle and hot flash information were collected from 1,087 women in the Baltimore metropolitan area	<ul style="list-style-type: none"> <li>• Current smokers were at an increased risk of moderate to severe hot flashes (OR = 1.9) and daily hot flashes (OR = 2.2) compared to never-smokers</li> <li>• Among current smokers, risk for hot flashes increased with greater amount smoked</li> </ul>