Cosmetics use and age at menopause: is there a connection?

Erika T. Chow, M.S.[a] and Shruthi Mahalingaiah, M.D., M.S.[a,b]

[a] Department of Obstetrics and Gynecology, Boston University School of Medicine; and [b] Department of Epidemiology, Boston University School of Public Health, Boston, Massachusetts

Cosmetics contain a vast number of chemicals, most of which are not under the regulatory purview of the Food and Drug Administration. Only a few of these chemicals have been evaluated for potential deleterious health impact: parabens, phthalates, polycyclic aromatic hydrocarbons, and siloxanes. A review of the ingredients in the best-selling and top-rated products of the top beauty brands in the world, as well as a review of highlighted chemicals by nonprofit environmental organizations, reveals 11 chemicals and chemical families of concern: butylated hydroxyanisole/butylated hydroxytoluene, coal tar dyes, diethanolamine, formaldehyde-releasing preservatives, parabens, phthalates, 1,4-dioxane, polycyclic aromatic hydrocarbons, siloxanes, talc/asbestos, and triclosan. Age at menopause can be affected by a variety of mechanisms, including endocrine disruption, failure of DNA repair, oxidative stress, shortened telomere length, and ovarian toxicity. There is a lack of available studies to make a conclusion regarding cosmetics use and age at menopause. What little data there are suggest that future studies are warranted. Women with chronic and consistent use of cosmetics across their lifespan may be a population of concern. More research is required to better elucidate the relationship and time windows of vulnerability and the effects of mixtures and combinations of products on ovarian health. (Fertil Steril® 2016;106:978–90. ©2016 by American Society for Reproductive Medicine.)

Key Words: Menopause, cosmetics, personal care products, ovarian aging, reproductive senescence

Discuss: You can discuss this article with its authors and with other ASRM members at https://www.fertstertdialog.com/posts/11408-cosmetics-use-and-age-at-menopause-is-there-a-connection

Women are susceptible to the societal pressures of using cosmetics to beautify themselves (1–3). One theory behind the origins of the ♀ symbol used to denote "woman" is that it represents the hand mirror used by the Roman goddess Venus or the Greek goddess Aphrodite (4). In their efforts to look beautiful, both men and women apply cosmetics to hide their flaws and accentuate their features. Cosmetics have been a part of human history as far back as the ancient Egyptians (5). The ancient Egyptians, Romans, and Greeks used various ingredients to soften, improve, exfoliate, and detoxify skin (5). The ancient Romans and Greeks used walnut extracts as hair dye, antimony (a known toxic heavy metal) as eye shadow, white lead carbonate as a skin lightener, charcoal crocodile excrement as a skin darkener, and cinnabar as rouge (5).

The present article broadly addresses the question, "Cosmetics use and menopause—is there a connection?" The Oxford English Dictionary defines "cosmetics" as "A preparation intended to beautify the hair, skin, or complexion" (6). The word comes from the Greek word *kosmetikos* ("relating to adornment"), which is taken from the Greek word *kosmein* ("to arrange, adorn"), which itself is taken from the Greek word *kosmos* ("order, adornment") (6). For the purposes of this review, we define cosmetics as any product applied to the skin to enhance and beautify, i.e., products often labeled as "makeup." In 2014, the revenue of the cosmetics industry in the United States alone was 56.63 billion dollars (7), compared with the global oral contraceptive pills market which was valued at 5.236 billion that same year (8). Companies sell a broad spectrum of cosmetic items, each item containing a huge variety of chemicals that all contribute to the color, texture, patina (sheen vs. matte), odor, preservation, suspension, lubrication, thermal stability, and finishing texture of the cosmetic. Given the widespread and frequent personal use of cosmetics containing classes of compounds that are endocrine disrupters, it is of great importance for women and health care providers to understand the potential harm that ingredients in cosmetics can have on women's reproductive health and reproductive aging. In a survey administered to pregnancy planners and pregnant women regarding risk perception of cosmetic use, out of 128 respondents (68 of whom were pregnant), 39.5% thought

Received April 30, 2016; revised and accepted August 8, 2016; published online August 18, 2016.
E.T.C. has nothing to disclose. S.M. is supported by the Reproductive Scientist Development Program from the National Institute of Child Health and Human Development, National Institutes of Health, grant K12 HD000849.
Reprint requests: Shruthi Mahalingaiah, M.D. M.S., Department of Obstetrics and Gynecology, Boston Medical Center/Boston University, 85 East Concord St., 6th Floor, Boston, Massachusetts 02118 (E-mail: shruthi.mahalingaiah@bmc.org).

Fertility and Sterility® Vol. 106, No. 4, September 15, 2016 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2016.08.020

that cosmetics outside of pregnancy were "fairly safe" and 37.7% thought that cosmetics were "not really safe" (9). Despite this fairly high level of concern, most women did not intend to/had not changed their cosmetics use during pregnancy (9).

THE ROLE OF THE FOOD AND DRUG ADMINISTRATION IN COSMETICS

While the United States Food and Drug Administration (FDA) closely monitors the chemicals that go into foods, drugs, and medical devices, cosmetics are not subjected to similar scrutiny. The FDA does not have to approve any cosmetics that go on the market unless the product claims to treat or prevent disease or alter the body in any way (in which case the product is classified as a drug) (10). There are only 11 chemicals that are outright prohibited or restricted for use in cosmetics: bithionol, chlorofluorocarbon propellants, chloroform, halogenated salicylanilides, hexachlorophene, mercury compounds, methylene chloride, cattle materials, sunscreens, vinyl chloride, and zirconium-containing complexes (11). Of note, color additives must be approved by the FDA before use in any cosmetics (12). The exception to this rule is color additives derived from mineral, plant, or animal sources, or additives derived from coal tar or petroleum (12). However, coal tar dyes, especially para-phenylenediamine, have been linked to DNA damage (13–15). This paper describes the chemicals that cosmetics contain and discusses the few studies that address how these chemicals can potentially affect human physiology, especially in relation to menopause.

METHODS

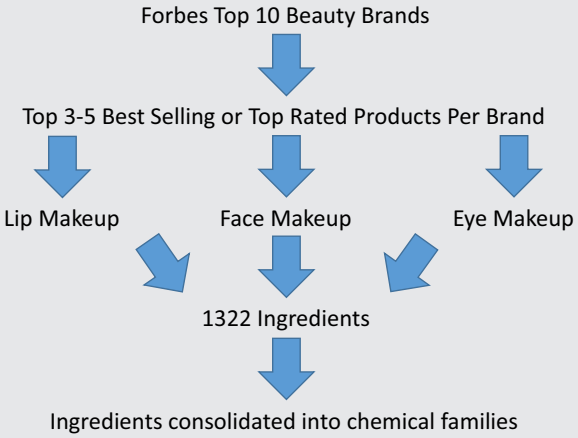
Selection of Cosmetics and Their Ingredients

Owing to the vast number of chemical ingredients in cosmetics, we devised the following methodology to identify chemicals for which to conduct our literature review (Fig. 1). Once these chemicals were identified, we generated a word cloud to visualize the frequency of chemicals and undertook a literature review. To summarize our identification methodology, we began by using the Forbes list of top ten global beauty brands in 2012 (16). We did not use the top-grossing global beauty companies, because many companies own several brands. From the top ten beauty brand list, we went to the websites of the top five. These brands are denoted by symbolic letters X, A, B, C, and D (in order from largest to smallest global brand revenue) (16). On each site, we looked at lip makeup, face makeup, and eye makeup products of each company and extracted the ingredient list of the top three to five best-selling or top-rated products in each category, depending on the company (Table 1 provides a complete list of the products assessed in this paper). Brands X and D carry only skin care products and no makeup, so they were not included in the table.

Definitions

We defined face makeup as any product that is applied to the skin for enhancing purposes. Eye makeup encompassed any makeup that is applied near the eye, including eye liners, mascaras, eye shadows, and brow liners. Lip makeup is any lip color–or shape–enhancing makeup, therefore not including lip balms.

FIGURE 1



Path of determination of ingredients most commonly found in beauty products.

Chow. Cosmetics use and menopause. Fertil Steril 2016.

Chemical Families and Their Ingredients

Because several ingredients are in the same chemical family but have different names, we simplified the list of ingredients by replacing some with their chemical family name (e.g., paraben in place of methylparaben and ethylparaben) to better isolate which chemical families most commonly appear in the ingredients. Table 2 presents the ingredients and their associated chemical family names. Because different companies named some ingredients differently (e.g., "safflower seed oil" vs. "*Carthamus tinctorius* [safflower] seed oil"), we also standardized the names, but we did not include the standardizations in Table 2. The simplified ingredient list was then inserted into a word cloud generator to visualize which chemical families appeared the most (Fig. 2). There are two algorithms used in word cloud generation: One is a direct correlate of the count data and the other is a log function of the count. We used the direct correlation to best represent what cosmetic users may be most concerned about. From the word cloud, it was immediately apparent that coal tar dyes, siloxanes, and parabens were the most frequent chemical exposures from cosmetics application. Iron oxide and titanium dioxide color dyes appeared with high frequency, but because they are inorganic compounds that have little dermal penetration we did not include them in our literature search (17). A total of 1,322 ingredients were compiled for the word cloud. Of the 1,322 ingredients, we consolidated chemicals into nine chemical families. Of the three largest chemical families, 145 ingredients were classified into the family of coal tar

TABLE 1

Complete list of products examined for the major ingredients in cosmetics as shown in the word cloud in Figure 2.

Brand A			Brand B			Brand C		
Face	**Lip**	**Eye**	**Face**	**Lip**	**Eye**	**Face**	**Lip**	**Eye**
Smooth Minerals Blush	Ultra Luxury Lip Liner	Glimmersticks Brow Definer	Visible Lift Blur Concealer	Colour Riche Lipcolour	Studio Secrets Professional Eye Shadow Duos	Shine Control Liquid Makeup	MoistureShine Gloss	Nourishing Long Wear Eye Shadow + Built-in Primer
Smooth Minerals Powder Foundation	Mark. Gloss Gorgeous Stay On Lip Stain	Glimmersticks Eye Liner	Infallible Pro-Matte Foundation	Colour Riche La Lacque Lip Pen	Brow Stylist Plumper	Shine Control Primer	Revitalizing Lip Balm SPF 20	Nourishing Eye Liner
Invisible Coverage Liquid Foundation	Mark. Lipstick Full Color Lipstick	Ultra Luxury Brow Liner	True Match Concealer	Infallible Pro-Matte Gloss	Infallible 24 Hour Eye Shadow	SkinClearing Mineral Powder	MoistureSmooth Color Stick	Healthy Lengths Mascara
Ideal Flawless Invisible Coverage Cream-to-Powder Foundation		Ultra Luxury Eye Liner	Infallible Pro-Matte Powder	Colour Riche Collection Exclusive Red Lipcolor	HiP High Intensity Pigments Matte Shadow Duos	Mineral Sheers Loose Powder Foundation	MoistureShine Lip Soother SPF 20	Healthy Skin Brightening Eye Perfector Broad Spectrum SPF 25
Ideal Luminous Blush		SuperShock Mascara in Black	Infallible Pro Contour Palette		Infallible Matte-Matic Liner	Nourishing Long Wear Liquid Makeup Broad Spectrum SPF 20		Healthy Volume Mascara Regular

Chow. Cosmetics use and menopause. Fertil Steril 2016.

TABLE 2

Chemicals assigned to a chemical family for the word cloud.

Label used	Replaced names
Alpha-hydroxy acid	Citric acid
	Lactic acid
Beta-hydroxyl acid	Salicylic acid
Coal tar dye	Blue 1/CI 42090
	Blue 1 Lake/CI 42090
	Brown 1/CI 20170
	Green 5/CI 61570
	Green 6/CI 61565
	Orange 4/CI 15510
	Orange 5/CI 45370
	Orange 5 Lake/CI 45370
	Red 4/CI 14700
	Red 7/CI 15850
	Red 7 Lake/CI 15850
	Red 6/CI 15850
	Red 6 Lake/CI 15850
	Red 17/CI 26100
	Red 21/CI 45380
	Red 21 Lake/CI 45380
	Red 22/CI 45380
	Red 22 Lake/CI 45380
	Red 30/CI 73360
	Red 33/CI 17200
	Red 33 Lake/CI 17200
	Red 34/CI 15880
	Red 34 Lake/CI 15880
	Red 36/CI 12085
	Red 36 Lake/CI 12085
	Red 40/CI 16035
	Red 40 Lake/CI 16035
	Violet 2/CI 60725
	Ext. Violet 2/CI 60730
	Yellow 5/CI 19140
	Yellow 5 Lake/CI 19140
	Yellow 7/CI 45350
	Ext. Yellow 7/CI 10316
	Yellow 8/CI 45350
	Yellow 10/CI 47005
	Yellow 10 Lake/CI 47005
Ethylenediaminetetraacetic acid (EDTA)	Disodium EDTA
	Tetrasodium EDTA
	Trisodium EDTA
Paraben	Butylparaben
	Ethylparaben
	Isobutylparaben
	Isopropylparaben
	Methylparaben
	Propylparaben
Phthalate	Polyethylene terephthalate
	Terephthalate
Polyethylene glycol (PEG)	PEG-6 beeswax
	PEG-9
	PEG-40 stearate
Pyroglutamic acid (PCA)	Calcium PCA
	Lauryl PCA
	Sodium PCA
	Zinc PCA
Siloxane	Bis-PEG/PPG-14/14 dimethicone
	Bis-PEG-12/dimethicone beeswax
	C30–45 alkyl cetearyl dimethicone crosspolymer
	Caprylyl trimethicone
	Cetearyl dimethicone crosspolymer
	Cetyl dimethicone
	Cetyl PEG/PPG-10/1 dimethicone
	Cyclohexasiloxane
	Cyclopentasiloxane
	Methicone
	Dimethicone
	Dimethicone crosspolymer
	Dimethicone/PEG-10/15 crosspolymer
	Dimethicone/Vinyl dimethicone crosspolymer
	Diphenyl dimethicone
	Ethyl trisiloxane
	Hexamethyldisiloxane/disiloxane
	Lauryl PEG-9 polydimethylsiloxyethyl dimethicone
	Methyl trimethicone
	Nylon-611/dimethicone copolymer
	PEG/PPG-18/18 dimethicone
	PEG/PPG-20/23 dimethicone
	PEG-9 polydimethylsiloxyethyl dimethicone
	PEG-10 dimethicone
	Phenyl trimethicone
	Steardimonium hydroxypropyl panthenyl PEG-7 dimethicone phosphate chloride
	Stearoxymethicone/ dimethicone copolymer
	Stearyl dimethicone
	Trimethylsiloxyphenyl dimethicone
	Vinyl dimethicone/methicone silsequioxane crosspolymer
Chemicals of concern that do not appear in the word cloud	Beta-hydroxyl acid
	Sodium laureth sulfate
Chemical families commonly found in cosmetics not found in the products in Table 1	Butylated hydroxyanisole
	Triclosan

Note: All ingredients were taken from the ingredients list of the products mentioned in Table 1. Chemicals that were part of the same family were replaced with the family name (e.g., Blue 1/CI 42090 is a coal tar dye and was replaced with "coal tar dye" for the word cloud), making sure to preserve the frequency of appearance for each ingredient.

Chow. Cosmetics use and menopause. Fertil Steril 2016.

dyes, 95 into siloxanes, and 39 into parabens. Of the remaining 1,043 individual chemicals we identified that could not be consolidated into chemical families, we cross-referenced our list of chemicals with websites detailing chemicals of concern. From that, we identified an additional 12 chemicals to assess for ovarian toxicity and age at menopause.

Chemicals of Concern

To determine if there were any remaining chemicals that were not identified through the methods above in our definition of makeup, we turned to the David Suzuki Foundation (a Canadian environmental nonprofit organization; www.davidsuzuki.org) and the cosmetics branch of the FDA (www.fda.gov/Cosmetics). In 2010, the David Suzuki Foundation investigated a list of "dirty dozen" cosmetics ingredients that contained butylated hydroxyanisole/butylated hydroxytoluene, coal tar dyes, diethanolamine compounds, dibutyl phthalate, formaldehyde-releasing preservatives,

FIGURE 2

Word cloud of ingredients most commonly found in the top-selling/best-rated products of brands A, B, and C listed in Table 1.

Chow. Cosmetics use and menopause. Fertil Steril 2016.

parabens, parfum, polyethylene glycol compounds, petrolatum, siloxanes, sodium laureth sulfate, and triclosan (18). The FDA website highlights certain additional cosmetic ingredients, which are alpha-hydroxy acids, beta-hydroxy acids, phthalates, and talc (19). However, beta-hydroxy acids were an infrequent ingredient and did not appear in the word cloud. Based on our inclusion criteria for the word cloud, some other ingredients did not appear in the word cloud: diethanolamine (only triethanolamine appeared in the ingredients; ethanolamine compounds are used mostly in moisturizers or shampoos/soaps, which were not included in this review), butylated hydroxyanisole (used mostly in lipsticks and eye shadow but did not appear as an ingredient in any of the products we assessed), sodium laureth sulfate (infrequent in cosmetics—it is used mostly in shampoos/soaps, which were not included in this paper), and triclosan (used mostly in personal hygiene and deodorant products, which were not included in this paper). After identification of the final list, Pubmed was used to conduct a literature review with the chemical of interest and the following other search terms: "menopause," "reproductive senescence," and "ovarian failure." To assess the toxicity and endocrine disruption of each chemical, we used the United States National Library of Medicine's Toxicology Data Network (http://toxnet.nlm.nih.gov/), Cosmetic Ingredient Review's safety assessment reports (http://www.cir-safety.org/ingredients), the Endocrine Disruption Exchange's list of potential endocrine disruptors (http://endocrinedisruption.org/endocrine-disruption/tedx-list-of-potential-endocrine-disruptors/), and Pubmed searches for the chemical of interest and the following other search terms: "genotox*," "carcino*," "endocrine," "estrogen," and "androgen."

Supplemental Table 1 (available online at www.fertstert.org) is a compilation of all of these chemicals, along with their primary use and their known toxicity to the human body (some ingredients have not been shown to be toxic to humans, but for the sake of completion we have listed all ingredients as well as all known information about relevant toxicity). We will focus on those chemicals that have relevant toxicities to humans.

CHEMICALS IN COSMETICS AND THEIR DETECTION

Some studies have examined the relationship between use of personal care products and serum or urinary concentrations of the ingredients. Because very few studies specifically examined the association between cosmetics use and ingredients absorption, we also included studies that examine topical

personal care product use to provide a better picture of how these ingredients can be absorbed through the skin. This section discusses the studies that have been published on siloxanes, diethanolamine, phthalates, and parabens.

Siloxanes

One study looked at use of personal care products in a cohort of 94 postmenopausal women in Norway and serum levels of estrogenic (20) and antiandrogenic (21) cyclic volatile methylsiloxane (cVMS) (22). Sources of exposure to cVMS are generally through cVMS present in personal care products, inhalation due to the volatility of the compounds, or cVMS contained in breast implants (22). None of the women in the cohort had breast implants, and 90.5% of the women creamed more than 10% of their skin area each day (22). cVMS also has a low blood:air partition coefficient, and therefore inhalation exposure would have only had a minor contribution to serum levels of cVMS unless there was risk of workplace air exposure (22). Unfortunately, because different products carry varying levels of cVMS, no direct correlation was drawn between serum levels and specific personal care product use (22). Of the 94 women examined, 85% of the women exceeded the limit of quantification for octamethylcyclotetrasiloxane, 18% for decamethylcyclopentasiloxane, and 5% for dodecamethylcyclohexasiloxane (22).

Diethanolamine

A study provided three premenopausal women with lotion containing 1.8 mg diethanolamine/gram of lotion and instructed them to apply the lotion every day for a month (23). Diethanolamine is a compound that is antiestrogenic, antiandrogenic, and possibly carcinogenic (24–26). Blood samples of the subjects revealed detectable plasma concentrations of diethanolamine after lotion application (23).

Phthalates and Parabens

An extensive study of personal care product use among pregnant women revealed significant associations between product use and urinary concentrations of phthalate metabolites and antiandrogenic (27) and estrogenic (28) parabens. Phthalates are a class of chemicals that have different hormonal activities depending on the congener's compound structure (29). Braun et al. found that cosmetics users had 53% more urinary monoethyl phthalate (MEP; 95% confidence interval [CI] 9%–113%), 89% more butylparaben (BP; 95% CI 21%–198%), 66% more methylparaben (MP; 95% CI 17%–137%), and 105% more propylparaben (PP; 95% CI 31%–220%) than noncosmetics users (30).

A study with 332 postmenopausal women in Norway examined the association between serum paraben levels and personal care product use (31). Median serum levels of MPs were correlated with increasing percentage of skin area creamed per day (31). The observed trend was also significant for the total combination of MPs, PPs, and ethylparabens ($P<.001$), but increases in ethylparabens and PPs were observed in participants creaming more than 100% of their skin surface per day (i.e., multiple applications) (31).

A study of 337 women at follow-up visits 3–36 months after their pregnancies found that use of basic makeup (including eye makeup, foundation, and lipstick) was associated with increased urinary concentrations of MEP ($\beta = 0.054$; $P=.029$) and monomethyl phthalate ($\beta = 0.040$; $P=.023$) (32).

MENOPAUSE

Naturally occurring menopause is defined as amenorrhea for 12 full months (33). The current established average age at menopause in the United States is 51.4 years (33). In utero, the ovarian reserve of primordial follicles is built from ovarian germ cells. At 4 months postconceptional age, the ovary peaks at 6–7 million oocytes (34). Owing to apoptosis, at birth only 1–2 million primordial follicles remain (34). Primordial follicle numbers continue to fall exponentially, albeit less rapidly, until menarchal onset when the ovary has 300,000–400,000 follicles remaining (34). At menopause, fewer than 1,000 follicles remain (34). Natural menopause is a physiologic manifestation of a depleted follicular pool. Elevated FSH and LH levels, and low antimüllerian hormone (AMH; a hormone used to estimate ovarian reserve ß (35)) are hallmark biochemical signs of menopause (33, 36). Menopause is preceded by a transition period (perimenopause) that can last several years starting from when a woman enters her fifth decade of life (33). Perimenopause is associated with changes in a woman's reproductive hormones and is associated with waist thickening, vaginal dryness, and irregular periods (33). Other symptoms include hot flashes, irritability, and sleep disturbance (33).

Age at Menopause: Potential Mechanisms

Age at menopause can be affected by various aspects, such as race, family history, smoking history, genetic predisposition, fragile X syndrome, and autoimmune disorders (8, 37–44). There is some evidence that chemical exposure can affect age at menopause, but little research has been done directly linking exposure to chemicals in cosmetics with age at menopause. We therefore discuss the potential mechanisms by which cosmetics ingredients may have an effect on age at menopause.

Onset of reproductive senescence is due to depletion of primordial follicles. It is thought that prenatal follicle assembly and rate of recruitment of primordial follicles are factors in the rate of depletion (45–47). Lower ovarian follicle reserves, increased number of follicles recruited for maturation per cycle, and absence of corpora lutea (CL) development indicate onset of reproductive senescence. Because the hypothalamic-pituitary-ovarian axis is crucial to the maintenance of reproductive organs as well as the menstrual cycle in females, any chemicals that disrupt the axis may also cause early reproductive senescence (48). Endocrine-disrupting chemicals (EDCs) are a class of exogenous chemicals that disrupt some aspect of a hormone's

mechanism (49). EDCs that are either estrogenic or antiandrogenic seem to play the largest role in this process of premature reproductive senescence (45) (See Supplemental Text for a summary of known estrogenic or antiandrogenic EDCs and reproductive senescence; available online at www.fertstert.org).

Failure of DNA repair mechanisms may lead to failure in ovarian follicle reserves and earlier age at menopause. Ovarian follicle aging has been linked to lower expression of DNA double strand break repair genes BRCA1, MRE11, Rad51, and ATM (50). Women with BRCA1 mutations have shown significantly lower concentrations of AMH and earlier age at menopause (50–52). A meta-analysis of 22 genome-wide association studies in 38,968 women found additional associations between age at menopause and genes implicated in DNA repair (EXO1, HELQ, UIMC1, FAM175A, FANCI, TLK1, POLG, and PRIM1) (53). Another study found an association between a variant in the mismatch repair gene MSH6 with age at menopause (54).

Shortened leukocyte telomere length may be associated with age at menopause, although the mechanisms are still unclear. It should be noted that DNA repair mechanisms and telomere length are mechanistically related (55), and telomere length can be affected by many elements, such as telomerase activity, oxidative stress, antioxidant activity, inflammation, the hypothalamus-pituitary-adrenal axis (glucocorticoid levels), and mitochondria regulation (56). One study found that among non-Hispanic white women, one standard deviation in longer leukocyte telomere length was associated with 0.43 year later age at menopause (57). Among Mexican-American women, one standard deviation in shorter leukocyte telomere length was associated with 1.56 years earlier age at menopause, and among non-Hispanic black women, no association was found (57). Another study with a cohort of 486 white women found that for every 1-kilobase increase in leukocyte telomere length, average age at natural menopause increased by 10.2 months (95% CI 1.3–19.0 mo), with no association seen in women with surgical menopause (58).

Oxidative stress can affect the ovarian reserve in other ways as well. Reactive oxygen species (ROS) can induce primordial follicle loss and apoptosis in the ovary (59). ROS can also deplete glutathione, which then leads to atresia of antral follicles and apoptosis of granulosa cells (59). Oxidative stress also increases permeability in mitochondria (60), which exposes mitochondrial DNA to damaging elements (61). Damaged mitochondrial DNA has been linked to reproductive aging (55, 62). Mice lacking the glutamate cysteine ligase modifier subunit, the rate-limiting enzyme in production of the most abundant intracellular antioxidant, glutathione, showed increased oxidative stress, apoptosis in follicles, and accelerated age-related decline in primordial follicles compared with wild-type mice (63).

Direct ovarian toxicity accelerates reproductive senescence. There is extensive evidence of environmental toxins and their effect on the ovaries (64), and the effect of iatrogenic chemicals (chemotherapy and radiotherapy) is very well documented. Women who have undergone anticancer treatment, especially in adolescence, show accelerated depletion in ovarian reserve, decreased AMH levels, decreased ovarian volume, and early age at menopause (65–67).

Some of the chemicals in cosmetics have known carcinogenic effects. Studies of age at menopause and cancer in humans examine cohorts of patients that have undergone gonadotoxic chemotherapy. There is one study that demonstrated reproductive senescence due to the presence of cancer alone in rats. In that study, only 49% of female Wistar rats with administered neoplasms had regular estrous cycles by 30 weeks of age, and at 112 weeks of age only 24% of female rats were still cycling and the majority of those individuals had major cycle abnormalities (68).

The contribution of these mechanisms to early reproductive aging means that chemicals that are either antiandrogenic or estrogenic EDCs, that damage DNA repair mechanisms, that affect telomere length, that increase oxidative stress or reduce antioxidant activity, that increase ovarian toxicity, or that are carcinogenic have the potential to contribute to premature age at menopause. Although the present review examines the limited data on cosmetics use and age at menopause, it should be noted that there are a handful of articles that have published data indicating that there is a secular trend toward later age at menopause (69–72). This trend toward later age at menopause is associated with increasing physical activity and education level, as well as better childhood nutrition and health in the general population, but those studies do not also examine this secular trend according to cosmetics use (69, 72).

COSMETICS EXPOSURE AND MENOPAUSE

We present here the research on exposure to cosmetics ingredients/cosmetic use and age at menopause. Unfortunately, most of the chemicals that we mention in this review have not been evaluated in relation to age at menopause, and of the chemicals that have been studied, there are very little published data. Owing to the limited amount of studies, we expanded our literature search to include studies examining topical personal care product use. The studies noted below were found with the same search terminology reported in the methods section and represent the complete set of articles in that search.

One study examined phthalate levels in the personal care products of 195 women aged 45–54 years, urinary phthalate levels, and self-reported hot flashes history (73). Phthalate concentrations in personal care products were estimated by summing the metabolite molar concentrations of monobutyl phthalate and MEP (73). The sum of personal care product urine phthalate levels was associated with: 1) ever experiencing hot flashes (odds ratio [OR] 1.45, CI 1.07–1.96); 2) experiencing moderate/severe hot flashes (OR 1.31, CI 0.95–1.82), 3) experiencing hot flashes in the past 30 days (OR 1.43, CI 1.04–1.96); and 4) experiencing daily hot flashes (OR 1.47, CI 1.06–2.05) (73). Previous research has linked hot flash severity in the perimenopausal transition to earlier age at menopause (74).

Another study of urinary paraben levels in 192 women presenting for fertility care in the Boston, Massachusetts, area found MP and PP in more than 99% of urine samples and BP in more than 75% (75). That study found a trend toward decreased antral follicle counts and increased day 3 FSH levels with increasing PP tertiles (75). However the study did not achieve statistical significance (75). No other consistent associations were found with the other parabens or with ovarian volume (75).

Exposure to polycyclic aromatic hydrocarbons (PAHs), which are a known contaminant of inadequately refined petrolatum, has been shown to increase proapoptotic gene expression in the ovary and to induce oocyte depletion via p53 (76). There is some evidence that the ovarian toxicity of PAHs work through the aromatic hydrocarbon receptor, which induces Bax gene expression which induces apoptosis (77). Benzo[a]pyrene (BaP), a PAH contaminant sometimes detected in cosmetics (78), also induced significant DNA damage in oocytes and cumulus cells (79), as well as decreased CL counts and ovarian volume in mice (80). A study of BaP and two other PAHs in mice and rats found that exposure to all three PAHs resulted in drastically lower numbers of primordial and primary follicles (81). Surprisingly, that study also found that chronic low-dose exposure to the three PAHs was more toxic compared with acute high-dose exposure (81). PAHs have also been found to be antiandrogenic, estrogenic, carcinogenic, and potentially genotoxic (79, 82–84).

A study examined how gestational exposure of Wistar rats to a mixture of proven human EDCs (di-n-butyl phthalate, di-(2-ethylhexyl) phthalate, vinclozolin, prochloraz, procymidone, linuron, epoxiconazole, octyl methoxycinnamate, dichlorodiphenyl-dichloroethylene (p,p′-DDE), 4-methyl-benzylidene camphor, BPA, butyl paraben, and paracetamol; italics indicate that the compounds or their metabolites have been found in cosmetics) affected ovarian follicle reserves and reproductive aging (85). The study examined the effects of subjecting the rats to a mix of all the EDCs (Totalmix), to a mix of the antiandrogenic EDCs (4-methyl-benzylidene camphor, octyl methoxycinnamate, BPA, and BP; AAmix), and to a mix of the estrogenic EDCs (di-*n*-butyl phthalate, di-(2-ethylhexyl) phthalate, vinclozolin, prochloraz, procymidone, linuron, epoxiconazole, and p,p′-DDE; Emix) (85). Rats exposed to AAmix had significantly reduced numbers of primordial follicles (78.2% of control values; $P=.02$) (85). Rats exposed to AAmix also had significantly lower percentages of primordial follicles ($P=.005$) and significantly higher percentages of secondary ($P=.05$) and tertiary follicles ($P=.04$) out of the total number of follicles (85). The number of total recruited follicles was also significantly higher in rats exposed to AAmix ($P=.01$) (85). At 12 months of age, rats exposed to Totalmix had a significant increase in irregular estrous cycles ($P=.041$), and those exposed to Totalmix and AAmix had significantly lower ovarian weights (85). In addition, at 13 months of age, rats exposed to AAmix had a significant increase in incidence of complete absence of CL ($P=.033$), and a reduction in mean number of CL that approached significance in the AAmix group ($P=.056$) and was significant (55% of control) in the Totalmix group ($P=.04$) (85).

CONSIDERATIONS OF OTHER PERSONAL CARE PRODUCTS

We have examined the ingredients in cosmetics, specifically limited to face makeup, eye makeup, and lip makeup, but these products are but a subset of personal care products. This paper does not extensively cover the hazards of sunscreen, hair dye, makeup remover, lotion, skin lightener, anti-aging/antiwrinkle creams, and chemicals associated with nail embellishment, to name a few. Another subset of products we do not address that is gaining particular traction is that of "fountain of youth" agents, which often contain hydroquinone, retinol, sunscreen, antioxidants, and alpha-hydroxyl acids. Here we give a brief overview of some of these products in the hope that future research will take these areas into consideration as well.

The Braun et al. study mentioned above also found several associations between the use of different personal care products and increased urinary phthalate and paraben levels. Users of shampoo, conditioner, and nail polish had significantly higher urinary levels of phthalates (30). Users of hair gel had higher urinary levels of parabens (30). Finally, users of lotion and cologne/perfume had higher urinary levels of both pthalates and parabens (30). Perfume, lotion, deodorant, hair spray, crème rinse, other hair products, and bar soap were all positively and significanty associated with urinary MEP levels (32). There was also a significant association between total number of personal care products used in the 24 hours before the urine spot test and median creatinine-adjusted $\log_{10}$-transformed MEP concentrations. In a study of 108 women in Mexico, increased use of body lotion, deodorant, perfume, and antiaging facial cream use was associated with increased median urinary phthalate concentrations (86). A study of 186 minority pregnant women in New York City revealed that women who used perfume had 2.3 times higher urinary MEP concentrations (95% CI 1.6–3.3) (87).

Suntan and sunscreen products also are particularly harmful. Polyaromatic hydrocarbons (78) as well as benzophenones are used as ingredients in these products (88). Benzophenone passes through the skin and enters the blood stream (89), along with other sunscreen chemicals such as octyl-methoxycinnamate and 3-(4-methylbenzylidene) camphor (90). Benzophenone has been shown to be endocrine disrupting in nonhuman animals (91, 92), positively associated with women who have uterine leiomyomas and endometriosis (93, 94) and with increased oxidative stress and genotoxicity (95, 96). Benzophenones are not just limited to sunscreen products. They are found in makeup, lotion, and hair products to protect consumers from the sun (97).

Skin lighteners are commonly used in minority races/ethnicities (98–101), and as a result this population of women are at particular risk of exposure to toxic chemicals that are in skin-lightening products, such as mercury, hydroquinone, and steroids (102, 103). Vaginal

douching, which a study on the National Health and Nutrition Examination Survey (NHANES) 2001–2004 found to be more common among black women than among white or Mexican-American women, is significantly associated with higher urinary concentrations of MEP (104). Hair products, which contain a significant amount of phenylenediamine, a coal tar dye, also contain formaldehyde-releasing chemicals (105, 106).

The Madrid Statement is a document released in 2015 by more than 200 scientists worldwide calling to limit the use of fluorinated chemicals in everyday products (19), and it has previously been shown that fluorinated chemicals are pervasive in personal care products (107). A database compiled by the Green Science Policy Institute, a group of scientists based in California dedicated to promoting responsible use of chemicals, reveals that there are several perfluorinated and polyfluorinated chemicals that are used in a variety of cosmetics (108). Although there are too many to examine individually, one chemical, polytetrafluoroethylene (PTFE), popularly known as Teflon, is of particular concern. It is used in a variety of products, including face makeup, eye makeup, men's shaving cream, and sunscreen, as a bulking agent and slip modifier (17, 108). PTFE is traditionally produced by using perfluorooctanoic acid (PFOA) as a surfactant during emulsion polymerization of PTFE, leading to concerns that PTFE is contaminated with PFOA (109). The adverse health effects of PFOA have been numerously studied. In relation to menopause, a study of 25,957 women aged 18–65 years found that the odds of having experienced menopause were significantly higher in the highest quintile of exposure to estrogenic PFOA and perfluorooctane sulfonate (PFOS) compared with the lowest quintile of exposure in women aged 42–51 years (PFOS OR 1.4, CI 1.1–1.8; PFOA OR 1.4, CI 1.1–1.8) and in women aged $\geq$52 years (PFOS OR 2.1, CI 1.6–2.8; PFOA OR 1.7, CI 1.3–2.3) (110). In the NHANES cohort, women in the second and third tertiles of serum levels of estrogenic polyfluoroalkyl chemicals had significantly higher incidences of menopause than women in the first tertile (hazard ratio [HR] 1.23, 95% CI 1.04–1.44 for tertile 2; HR 1.16, 95% CI 0.91–1.48 for tertile 3) (111). For women in the third tertile of serum levels of perfluorooctanoate, perfluorononanoate, and perfluorohexane sulfonate compared with women in the first tertile, the adjusted HRs were 1.36 (95% CI 1.05, 1.75), 1.47 (95% CI 1.14, 1.90), and 1.70 (95% CI 1.36, 2.12), respectively (111). For women in the second tertile of serum levels of perfluorooctanoate, perfluorononanoate, and perfluorohexane sulfonate compared with women in the first tertile, the adjusted HRs were 1.22 (95% CI 0.92–1.62), 1.43 (95% CI 1.07–1.91), and 1.42 (95% CI 1.08–1.87), respectively (111). However, a study evaluating serum levels of PFOA from environmental exposure and age at menopause in women aged 40 years and above in the Mid-Ohio Valley community demonstrated no statistically significant associations (112). Owing to the known health hazards of PFOA, PTFE is now produced by many manufacturers with chemicals other than PFOA (113); however, cosmetic companies do not specify how they manufacture the PTFE that they use.

CONCLUSION

Again, although we have examined the ingredients in cosmetics, specifically limited to face makeup, eye makeup, and lip makeup, those products are but a subset of personal care products. This paper does not extensively cover the hazards of sunscreen, hair dye, makeup remover, lotion, skin lightener, antiaging/antiwrinkle creams, and chemicals associated with nail embellishment, to name a few. Another subset of products we do not address that is gaining particular traction is that of "fountain of youth" agents, which often contain hydroquinone, retinol, sunscreen, antioxidants, and alpha-hydroxyl acids. As such, evaluation of other personal care products and use of mixtures in relation to ovarian health is very important.

Most of the reviewed chemicals have demonstrated dermal absorption. Certain chemicals have limited dermal absorption, such as formaldehyde (23, 114). However, studies evaluating formaldehyde are limited by studying the exposure for as short as 1 month. Other limitations include no evaluation of body repositories of these chemicals, such as visceral and subcutaneous fat compartments. Women apply these products to their face daily, sometimes even more than once daily, which can lead to several grams of exposure per product per day over the course of a woman's life (115–118). As noted above, chronic low-dose exposure to PAHs is more toxic to the ovaries than acute high-dose exposure (81), and future studies need to explore if this is true for other chemicals.

In addition, although studies have examined the impact of these chemicals individually, little work has been done on the potential interactions that these chemicals can have with each other and how these mixtures can then affect human physiology. Women generally use more than one product (115–117), and the ingredients that are contained in different products can interact with each other. In addition, although one product may contain a level of these ingredients that has been deemed to be safe, continuous use and use of several products containing these ingredients can easily expose a woman to levels that are beyond what has been defined as safe. Another consideration that must be taken into account is the packaging for these cosmetics. Packaging and plastic materials have been shown to have toxins that can leach into products and adversely affect human health (119–121). It would be reasonable to extrapolate that the plastic packaging of many cosmetics may leach additional toxins into the products, which are then applied to the skin. These are considerations that need to be taken seriously as we continue to evaluate the long-term adverse impact that cosmetics use has on a woman.

One final consideration is incomplete reporting of ingredients. Although cosmetics companies are for the most part required to report all of the ingredients they use, there are still some exceptions. As mentioned before, all chemicals that are

used as fragrance do not need to be reported and can simply be listed as "parfum" or "fragrance." The same applies for cosmetics that have flavors, most often found in lipstick. Some of the cosmetics we looked at simply had "Flavor" written, with no indication of what ingredients this broad term referred to. In addition, a couple of the brand A products that we examined contained "Shimmer Shades," which was followed by a note that said "Shimmer Shades may contain:" with potential ingredients listed. Consumers have no way of knowing the exact composition of ingredients of the Shimmer Shades owing to the vague wording. Finally, brand B products have several ingredients in their products that are listed as FIL D*****/2, with * representing a number. Our search for what these ingredients may be revealed nothing.

Currently, limited evidence has demonstrated that few patients are counseled regarding safe cosmetics use. A study found that only 23.4% of 128 women surveyed had received advice about personal care product use, and only 18.9% of them had received advice about make-up product use (9). Health care providers should make attempts to make their patients aware of the developing literature around the chemicals used in cosmetics and help educate their patient population to make more informed personal care product choices. Many groups are now disseminating information in hopes of making consumers aware of the toxins in these cosmetics, such as the Environmental Working Group (EWG), Campaign for Safe Cosmetics, and the David Suzuki Foundation. In addition, the EWG has created a Skin Deep Cosmetics Database that allows consumers to search for personal care products and determine the hazard level of each product.

Limitations of this review are in large part due to our inability to assess each and every ingredient and their mixture effects, as well as the lack of available data regarding the vast number of chemicals that are in cosmetics and their relationship to age at menopause. A more comprehensive investigation of cosmetics and their effects on menopause, reproductive health, and the health of other organ systems needs to be undertaken.

REFERENCES

1. Barker DJ, Barker MJ. The body as art. J Cosmet Dermatol 2002;1:88–93.
2. Hill SE, Rodeheffer CD, Griskevicius V, Durante K, White AE. Boosting beauty in an economic decline: mating, spending, and the lipstick effect. J Pers Soc Psychol 2012;103:275–91.
3. Ehlinger-Martin A, Cohen-Letessier A, Taieb M, Azoulay E, du Crest D. Women's attitudes to beauty, aging, and the place of cosmetic procedures: insights from the QUEST Observatory. J Cosmet Dermatol 2016; 15:89–94.
4. Stearn WT. The origin of the male and female symbols of biology. Taxon 1962;11:109–13.
5. Oumeish OY. The cultural and philosophical concepts of cosmetics in beauty and art through the medical history of mankind. Clin Dermatol 2001;19:375–86.
6. Oxford English Dictionary. Cosmetic, adj. and n. Oxford: Oxford University Press. Available at: http://www.oxforddictionaries.com/us/definition/american_english/cosmetic. Last accessed August 30, 2016.
7. Dawber TR, Kannel WB, Lyell LP. An approach to longitudinal studies in a community: the Framingham Study. Ann N Y Acad Sci 1963;107:539–56.
8. Daan NM, Fauser BC. Menopause prediction and potential implications. Maturitas 2015;82:257–65.
9. Marie C, Cabut S, Vendittelli F, Sauvant-Rochat MP. Changes in cosmetics use during pregnancy and risk perception by women. Int J Environ Res Public Health 2016;13:383.
10. U.S. Food and Drug Administration. Is it a cosmetic, a drug, or both? (or is it soap?). 2002 [Updated April 30, 2012–April 5, 2016]. Available at: http://www.fda.gov/Cosmetics/GuidanceRegulation/LawsRegulations/ucm074201.htm. Last accessed August 23, 2016.
11. Butler MG, McGuire A, Manzardo AM. Clinically relevant known and candidate genes for obesity and their overlap with human infertility and reproduction. J Assist Reprod Genet 2015;32:495–508.
12. U.S. Food and Drug Administration. Color additives and cosmetics. 2006. [Updated April 29, 2007–April 5, 2016]. Available from: http://www.fda.gov/ForIndustry/ColorAdditives/ColorAdditivesinSpecificProducts/InCosmetics/ucm110032.htm. Last accessed August 23, 2016.
13. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, ed. Occupational exposures of hairdressers and barbers and personal use of hair colourants; some hair dyes, cosmetic colourants, industrial dyestuffs and aromatic amines. Lyon, France: International Agency for Research on Cancer, 1993.
14. Zanoni TB, Hudari F, Munnia A, Peluso M, Godschalk RW, Zanoni MV, et al. The oxidation of *p*-phenylenediamine, an ingredient used for permanent hair dyeing purposes, leads to the formation of hydroxyl radicals: oxidative stress and DNA damage in human immortalized keratinocytes. Toxicol Lett 2015;239:194–204.
15. Reena K, Ng KY, Koh RY, Gnanajothy P, Chye SM. *para*-Phenylenediamine induces apoptosis through activation of reactive oxygen species-mediated mitochondrial pathway, and inhibition of the NF-kappaB, mTOR, and Wnt pathways in human urothelial cells. Environ Toxicol 2016 Jan 19; http://dx.doi.org/10.1002/tox.22233. [Epub ahead of print.]
16. Goudreau J. The top 10 global beauty brands. Forbes Magazine, 2012. Available at: http://www.forbes.com/sites/jennagoudreau/2012/04/20/the-top-10-global-beauty-brands/#4b034f99ec55. Last accessed August 23, 2016.
17. Environmental Working Group. Skin Deep Cosmetic Database. 2004. Available at: http://www.ewg.org/skindeep/. Accessed April 15, 2016.
18. David Suzuki Foundation. The "dirty dozen" ingredients investigated in the David Suzuki Foundation survey of chemicals in cosmetics. 2010. Available at: http://www.davidsuzuki.org/issues/downloads/Dirty-dozen-backgrounder.pdf. Last accessed August 23, 2016.
19. Blum A, Balan SA, Scheringer M, Trier X, Goldenman G, Cousins IT, et al. The Madrid Statement on poly- and perfluoroalkyl substances (PFASs). Environ Health Perspect 2015;123:A107–11.
20. Quinn AL, Regan JM, Tobin JM, Marinik BJ, McMahon JM, McNett DA, et al. In vitro and in vivo evaluation of the estrogenic, androgenic, and progestagenic potential of two cyclic siloxanes. Toxicol Sci 2007;96: 145–53.
21. McKim JM Jr, Wilga PC, Breslin WJ, Plotzke KP, Gallavan RH, Meeks RG. Potential estrogenic and antiestrogenic activity of the cyclic siloxane octamethylcyclotetrasiloxane (D4) and the linear siloxane hexamethyldisiloxane (HMDS) in immature rats using the uterotrophic assay. Toxicol Sci 2001;63: 37–46.
22. Hanssen L, Warner NA, Braathen T, Odland JO, Lund E, Nieboer E, et al. Plasma concentrations of cyclic volatile methylsiloxanes (cVMS) in pregnant and postmenopausal Norwegian women and self-reported use of personal care products (PCPs). Environ Int 2013;51:82–7.
23. Craciunescu CN, Niculescu MD, Guo Z, Johnson AR, Fischer L, Zeisel SH. Dose response effects of dermally applied diethanolamine on neurogenesis in fetal mouse hippocampus and potential exposure of humans. Toxicol Sci 2009;107:220–6.
24. Kassotis CD, Klemp KC, Vu DC, Lin CH, Meng CX, Besch-Williford CL, et al. Endocrine-disrupting activity of hydraulic fracturing chemicals and adverse health outcomes after prenatal exposure in male mice. Endocrinology 2015;156:4458–73.
25. Kassotis CD, Tillitt DE, Davis JW, Hormann AM, Nagel SC. Estrogen and androgen receptor activities of hydraulic fracturing chemicals and surface and ground water in a drilling-dense region. Endocrinology 2014;155: 897–907.

26. Health and Human Services, National Institutes of Health. Toxicology Data Network. 2014. Available at: http://toxnet.nlm.nih.gov/. Accessed April 15, 2016.
27. Chen J, Ahn KC, Gee NA, Gee SJ, Hammock BD, Lasley BL. Antiandrogenic properties of parabens and other phenolic containing small molecules in personal care products. Toxicol Appl Pharmacol 2007;221:278–84.
28. Routledge EJ, Parker J, Odum J, Ashby J, Sumpter JP. Some alkyl hydroxy benzoate preservatives (parabens) are estrogenic. Toxicol Appl Pharmacol 1998;153:12–9.
29. Parveen M, Inoue A, Ise R, Tanji M, Kiyama R. Evaluation of estrogenic activity of phthalate esters by gene expression profiling using a focused microarray (EstrArray). Environ Toxicol Chem 2008;27:1416–25.
30. Braun JM, Just AC, Williams PL, Smith KW, Calafat AM, Hauser R. Personal care product use and urinary phthalate metabolite and paraben concentrations during pregnancy among women from a fertility clinic. J Expo Sci Environ Epidemiol 2014;24:459–66.
31. Sandanger TM, Huber S, Moe MK, Braathen T, Leknes H, Lund E. Plasma concentrations of parabens in postmenopausal women and self-reported use of personal care products: the NOWAC postgenome study. J Expo Sci Environ Epidemiol 2011;21:595–600.
32. Parlett LE, Calafat AM, Swan SH. Women's exposure to phthalates in relation to use of personal care products. J Expo Sci Environ Epidemiol 2013;23:197–206.
33. National Institutes of Health. Menopause: time for a change. 2008. Available at: https://www.nia.nih.gov/health/publication/menopause-time-change/introduction. Last accessed August 23, 2016.
34. Broekmans FJ, Soules MR, Fauser BC. Ovarian aging: mechanisms and clinical consequences. Endocr Rev 2009;30:465–93.
35. Iwase A, Osuka S, Nakamura T, Kato N, Takikawa S, Goto M, et al. Usefulness of the ultrasensitive anti-müllerian hormone assay for predicting true ovarian reserve. Reprod Sci 2015.
36. Cui L, Qin Y, Gao X, Lu J, Geng L, Ding L, et al. Antimüllerian hormone: correlation with age and androgenic and metabolic factors in women from birth to postmenopause. Fertil Steril 2016;105:481–5.e1.
37. Henderson KD, Bernstein L, Henderson B, Kolonel L, Pike MC. Predictors of the timing of natural menopause in the Multiethnic Cohort Study. Am J Epidemiol 2008;167:1287–94.
38. Gold EB, Crawford SL, Avis NE, Crandall CJ, Matthews KA, Waetjen LE, et al. Factors related to age at natural menopause: longitudinal analyses from SWAN. Am J Epidemiol 2013;178:70–83.
39. Bromberger JT, Matthews KA, Kuller LH, Wing RR, Meilahn EN, Plantinga P. Prospective study of the determinants of age at menopause. Am J Epidemiol 1997;145:124–33.
40. Voorhuis M, Onland-Moret NC, Janse F, Ploos van Amstel HK, Goverde AJ, Lambalk CB, et al. The significance of fragile X mental retardation gene 1 CGG repeat sizes in the normal and intermediate range in women with primary ovarian insufficiency. Hum Reprod 2014;29:1585–93.
41. Mayorga J, Alpizar-Rodriguez D, Prieto-Padilla J, Romero-Diaz J, Cravioto MC. Prevalence of premature ovarian failure in patients with systemic lupus erythematosus. Lupus 2015.
42. Torgerson DJ, Thomas RE, Reid DM. Mothers and daughters menopausal ages: is there a link? Eur J Obstet Gynecol Reprod Biol 1997;74:63–6.
43. Snieder H, MacGregor AJ, Spector TD. Genes control the cessation of a woman's reproductive life: a twin study of hysterectomy and age at menopause. J Clin Endocrinol Metab 1998;83:1875–80.
44. Fenton AJ. Premature ovarian insufficiency: pathogenesis and management. J Midlife Health 2015;6:147–53.
45. Uzumcu M, Zachow R. Developmental exposure to environmental endocrine disruptors: consequences within the ovary and on female reproductive function. Reprod Toxicol 2007;23:337–52.
46. Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, Hauser R, Prins GS, Soto AM, et al. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. Endocr Rev 2009;30:293–342.
47. Depmann M, Faddy MJ, van der Schouw YT, Peeters PH, Broer SL, Kelsey TW, et al. The relationship between variation in size of the primordial follicle pool and age at natural menopause. J Clin Endocrinol Metab 2015;100:E845–51.
48. Gore AC, Walker DM, Zama AM, Armenti AE, Uzumcu M. Early life exposure to endocrine-disrupting chemicals causes lifelong molecular reprogramming of the hypothalamus and premature reproductive aging. Mol Endocrinol 2011;25:2157–68.
49. Zoeller RT, Brown TR, Doan LL, Gore AC, Skakkebaek NE, Soto AM, et al. Endocrine-disrupting chemicals and public health protection: a statement of principles from The Endocrine Society. Endocrinology 2012;153:4097–110.
50. Titus S, Li F, Stobezki R, Akula K, Unsal E, Jeong K, et al. Impairment of BRCA1-related DNA double-strand break repair leads to ovarian aging in mice and humans. Sci Transl Med 2013;5:172ra21.
51. Finch A, Valentini A, Greenblatt E, Lynch HT, Ghadirian P, Armel S, et al. Frequency of premature menopause in women who carry a BRCA1 or BRCA2 mutation. Fertil Steril 2013;99:1724–8.
52. Wang ET, Pisarska MD, Bresee C, Chen YD, Lester J, Afshar Y, et al. BRCA1 germline mutations may be associated with reduced ovarian reserve. Fertil Steril 2014;102:1723–8.
53. Stolk L, Perry JR, Chasman DI, He C, Mangino M, Sulem P, et al. Meta-analyses identify 13 loci associated with age at menopause and highlight DNA repair and immune pathways. Nat Genet 2012;44:260–8.
54. Perry JR, Hsu YH, Chasman DI, Johnson AD, Elks C, Albrecht E, et al. DNA mismatch repair gene MSH6 implicated in determining age at natural menopause. Hum Mol Genet 2014;23:2490–7.
55. Liu L, Trimarchi JR, Smith PJ, Keefe DL. Mitochondrial dysfunction leads to telomere attrition and genomic instability. Aging Cell 2002;1:40–6.
56. Shalev I, Belsky J. Early-life stress and reproductive cost: a two-hit developmental model of accelerated aging? Med Hypotheses 2016;90:41–7.
57. Shenassa ED, Rossen LM. Telomere length and age-at-menopause in the US. Maturitas 2015;82:215–21.
58. Gray KE, Schiff MA, Fitzpatrick AL, Kimura M, Aviv A, Starr JR. Leukocyte telomere length and age at menopause. Epidemiology 2014;25:139–46.
59. Devine PJ, Perreault SD, Luderer U. Roles of reactive oxygen species and antioxidants in ovarian toxicity. Biol Reprod 2012;86:27.
60. Galluzzi L, Vitale I, Abrams JM, Alnemri ES, Baehrecke EH, Blagosklonny MV, et al. Molecular definitions of cell death subroutines: recommendations of the Nomenclature Committee on Cell Death 2012. Cell Death Differ 2012;19:107–20.
61. Kroemer G, Galluzzi L, Brenner C. Mitochondrial membrane permeabilization in cell death. Physiol Rev 2007;87:99–163.
62. Otten AB, Smeets HJ. Evolutionary defined role of the mitochondrial DNA in fertility, disease and ageing. Hum Reprod Update 2015;21:671–89.
63. Lim J, Nakamura BN, Mohar I, Kavanagh TJ, Luderer U. Glutamate cysteine ligase modifier subunit (Gclm) null mice have increased ovarian oxidative stress and accelerated age-related ovarian failure. Endocrinology 2015;156:3329–43.
64. Iorio R, Castellucci A, Ventriglia G, Teoli F, Cellini V, Macchiarelli G, et al. Ovarian toxicity: from environmental exposure to chemotherapy. Curr Pharm Des 2014;20:5388–97.
65. Krawczuk-Rybak M, Leszczynska E, Poznanska M, Zelazowska-Rutkowska B, Wysocka J. The progressive reduction in the ovarian reserve in young women after anticancer treatment. Horm Metab Res 2013;45:813–9.
66. Gracia CR, Sammel MD, Freeman E, Prewitt M, Carlson C, Ray A, et al. Impact of cancer therapies on ovarian reserve. Fertil Steril 2012;97:134–40.e1.
67. Sklar CA, Mertens AC, Mitby P, Whitton J, Stovall M, Kasper C, et al. Premature menopause in survivors of childhood cancer: a report from the childhood cancer survivor study. J Natl Cancer Inst 2006;98:890–6.
68. Mitchard TL, Klein S. Reproductive senescence, fertility and reproductive tumour profile in ageing female Han Wistar rats. Exp Toxicol Pathol 2016;68:143–7.
69. Dratva J, Gomez Real F, Schindler C, Ackermann-Liebrich U, Gerbase MW, Probst-Hensch NM, et al. Is age at menopause increasing across Europe?

Results on age at menopause and determinants from two population-based studies. Menopause 2009;16:385–94.
70. Rodstrom K, Bengtsson C, Milsom I, Lissner L, Sundh V, Bjourkelund C. Evidence for a secular trend in menopausal age: a population study of women in Gothenburg. Menopause 2003;10:538–43.
71. Nichols HB, Trentham-Dietz A, Hampton JM, Titus-Ernstoff L, Egan KM, Willett WC, et al. From menarche to menopause: trends among US women born from 1912 to 1969. Am J Epidemiol 2006;164:1003–11.
72. Pakarinen M, Raitanen J, Kaaja R, Luoto R. Secular trend in the menopausal age in Finland 1997–2007 and correlation with socioeconomic, reproductive and lifestyle factors. Maturitas 2010;66:417–22.
73. Ziv-Gal A, Gallicchio L, Chiang C, Ther SN, Miller SR, Zacur HA, et al. Phthalate metabolite levels and menopausal hot flashes in midlife women. Reprod Toxicol 2016;60:76–81.
74. Edwards BJ, Li J. Endocrinology of menopause. Periodontol 2000 2013;61:177–94.
75. Smith KW, Souter I, Dimitriadis I, Ehrlich S, Williams PL, Calafat AM, et al. Urinary paraben concentrations and ovarian aging among women from a fertility center. Environ Health Perspect 2013;121:1299–305.
76. Pru JK, Kaneko-Tarui T, Jurisicova A, Kashiwagi A, Selesniemi K, Tilly JL. Induction of proapoptotic gene expression and recruitment of p53 herald ovarian follicle loss caused by polycyclic aromatic hydrocarbons. Reprod Sci 2009;16:347–56.
77. Matikainen T, Perez GI, Jurisicova A, Pru JK, Schlezinger JJ, Ryu HY, et al. Aromatic hydrocarbon receptor–driven Bax gene expression is required for premature ovarian failure caused by biohazardous environmental chemicals. Nat Genet 2001;28:355–60.
78. Monarca S, Sforzolini GS, Fagioli F. Presence of benzo[a]pyrene and other polycyclic aromatic hydrocarbons in suntan oils. Food Chem Toxicol 1982;20:183–7.
79. Einaudi L, Courbiere B, Tassistro V, Prevot C, Sari-Minodier I, Orsiere T, et al. In vivo exposure to benzo[a]pyrene induces significant DNA damage in mouse oocytes and cumulus cells. Hum Reprod 2014;29:548–54.
80. Miller MM, Plowchalk DR, Weitzman GA, London SN, Mattison DR. The effect of benzo[a]pyrene on murine ovarian and corpora lutea volumes. Am J Obstet Gynecol 1992;166:1535–41.
81. Borman SM, Christian PJ, Sipes IG, Hoyer PB. Ovotoxicity in female Fischer rats and B6 mice induced by low-dose exposure to three polycyclic aromatic hydrocarbons: comparison through calculation of an ovotoxic index. Toxicol Appl Pharmacol 2000;167:191–8.
82. Hawliczek A, Nota B, Cenijn P, Kamstra J, Pieterse B, Winter R, et al. Developmental toxicity and endocrine disrupting potency of 4-azapyrene, benzo[b]fluorene and retene in the zebrafish *Danio rerio*. Reprod Toxicol 2012;33:213–23.
83. Sievers CK, Shanle EK, Bradfield CA, Xu W. Differential action of monohydroxylated polycyclic aromatic hydrocarbons with estrogen receptors alpha and beta. Toxicol Sci 2013;132:359–67.
84. Flesher JW, Lehner AF. Structure, function and carcinogenicity of metabolites of methylated and nonmethylated polycyclic aromatic hydrocarbons: a comprehensive review. Toxicol Mech Methods 2016;26:151–79.
85. Johansson HK, Jacobsen PR, Hass U, Svingen T, Vinggaard AM, Isling LK, et al. Perinatal exposure to mixtures of endocrine disrupting chemicals reduces female rat follicle reserves and accelerates reproductive aging. Reprod Toxicol 2016;61:186–94.
86. Romero-Franco M, Hernandez-Ramirez RU, Calafat AM, Cebrian ME, Needham LL, Teitelbaum S, et al. Personal care product use and urinary levels of phthalate metabolites in Mexican women. Environ Int 2011;37:867–71.
87. Just AC, Adibi JJ, Rundle AG, Calafat AM, Camann DE, Hauser R, et al. Urinary and air phthalate concentrations and self-reported use of personal care products among minority pregnant women in New York city. J Expo Sci Environ Epidemiol 2010;20:625–33.
88. Review CI. Final report on the safety assessment of benzophenones-1, -3, -4, -5, -9, and -11. J Am Coll Toxicol 1983;2:35–77.
89. Janjua NR, Kongshoj B, Andersson AM, Wulf HC. Sunscreens in human plasma and urine after repeated whole-body topical application. J Eur Acad Dermatol Venereol 2008;22:456–61.
90. Janjua NR, Mogensen B, Andersson AM, Petersen JH, Henriksen M, Skakkebaek NE, et al. Systemic absorption of the sunscreens benzophenone-3, octyl-methoxycinnamate, and 3-(4-methyl-benzylidene) camphor after whole-body topical application and reproductive hormone levels in humans. J Invest Dermatol 2004;123:57–61.
91. Watanabe Y, Kojima H, Takeuchi S, Uramaru N, Sanoh S, Sugihara K, et al. Metabolism of UV-filter benzophenone-3 by rat and human liver microsomes and its effect on endocrine-disrupting activity. Toxicol Appl Pharmacol 2015;282:119–28.
92. Kinnberg KL, Petersen GI, Albrektsen M, Minghlani M, Awad SM, Holbech BF, et al. Endocrine-disrupting effect of the ultraviolet filter benzophenone-3 in zebrafish, *Danio rerio*. Environ Toxicol Chem 2015;34:2833–40.
93. Pollack AZ, Buck Louis GM, Chen Z, Sun L, Trabert B, Guo Y, et al. Bisphenol A, benzophenone-type ultraviolet filters, and phthalates in relation to uterine leiomyoma. Environ Res 2015;137:101–7.
94. Kunisue T, Chen Z, Buck Louis GM, Sundaram R, Hediger ML, Sun L, et al. Urinary concentrations of benzophenone-type UV filters in U.S. women and their association with endometriosis. Environ Sci Technol 2012;46:4624–32.
95. Amar SK, Goyal S, Dubey D, Srivastav AK, Chopra D, Singh J, et al. Benzophenone 1 induced photogenotoxicity and apoptosis via release of cytochrome c and Smac/DIABLO at environmental UV radiation. Toxicol Lett 2015;239:182–93.
96. Zhao H, Wei D, Li M, Du Y. Substituent contribution to the genotoxicity of benzophenone-type UV filters. Ecotoxicol Environ Saf 2013;95:241–6.
97. Liao C, Kannan K. Widespread occurrence of benzophenone-type UV light filters in personal care products from China and the United States: an assessment of human exposure. Environ Sci Technol 2014;48:4103–9.
98. Peltzer K, Pengpid S, James C. The globalization of whitening: prevalence of skin lighteners (or bleachers) use and its social correlates among university students in 26 countries. Int J Dermatol 2016;55:165–72.
99. Hamed SH, Tayyem R, Nimer N, Alkhatib HS. Skin-lightening practice among women living in Jordan: prevalence, determinants, and user's awareness. Int J Dermatol 2010;49:414–20.
100. Kamagaju L, Morandini R, Gahongayire F, Stevigny C, Ghanem G, Pirotte G, et al. Survey on skin-lightening practices and cosmetics in Kigali, Rwanda. Int J Dermatol 2016;55:45–51.
101. Dlova NC, Hamed SH, Tsoka-Gwegweni J, Grobler A. Skin lightening practices: an epidemiological study of South African women of African and Indian ancestries. Br J Dermatol 2015;173(Suppl 2):2–9.
102. Agorku ES, Kwaansa-Ansah EE, Voegborlo RB, Amegbletor P, Opoku F. Mercury and hydroquinone content of skin toning creams and cosmetic soaps, and the potential risks to the health of Ghanaian women. Springerplus 2016;5:319.
103. Maneli MH, Wiesner L, Tinguely C, Davids LM, Spengane Z, Smith P, et al. Combinations of potent topical steroids, mercury and hydroquinone are common in internationally manufactured skin-lightening products: a spectroscopic study. Clin Exp Dermatol 2016;41:196–201.
104. Branch F, Woodruff TJ, Mitro SD, Zota AR. Vaginal douching and racial/ethnic disparities in phthalates exposures among reproductive-aged women: National Health and Nutrition Examination Survey 2001–2004. Environ Health 2015;14:57.
105. Boyer IJ, Heldreth B, Bergfeld WF, Belsito DV, Hill RA, Klaassen CD, et al. Amended safety assessment of formaldehyde and methylene glycol as used in cosmetics. Int J Toxicol 2013;32(6 Suppl):5S–32S.
106. Peteffi GP, Antunes MV, Carrer C, Valandro ET, Santos S, Glaeser J, et al. Environmental and biological monitoring of occupational formaldehyde exposure resulting from the use of products for hair straightening. Environ Sci Pollut Res Int 2016;23:908–17.
107. Fujii Y, Harada KH, Koizumi A. Occurrence of perfluorinated carboxylic acids (PFCAs) in personal care products and compounding agents. Chemosphere 2013;93:538–44.
108. Green Science Policy Institute. Fluorinated chemicals in cosmetics. Berkeley, California: Green Science Policy Institute; 2014. Available at: http://www.greensciencepolicy.org/wp-content/uploads/2014/10/Fluorinated-Chemicals-in-Cosmetics.xlsx. Last accessed August 23, 2016.

109. Lindstrom AB, Strynar MJ, Libelo EL. Polyfluorinated compounds: past, present, and future. Environ Sci Technol 2011;45:7954–61.
110. Knox SS, Jackson T, Javins B, Frisbee SJ, Shankar A, Ducatman AM. Implications of early menopause in women exposed to perfluorocarbons. J Clin Endocrinol Metab 2011;96:1747–53.
111. Taylor KW, Hoffman K, Thayer KA, Daniels JL. Polyfluoroalkyl chemicals and menopause among women 20–65 years of age (NHANES). Environ Health Perspect 2014;122:145–50.
112. Dhingra R, Darrow LA, Klein M, Winquist A, Steenland K. Perfluorooctanoic acid exposure and natural menopause: a longitudinal study in a community cohort. Environ Res 2016;146:323–30.
113. Gordon SC. Toxicological evaluation of ammonium 4,8-dioxa-3H-perfluorononanoate, a new emulsifier to replace ammonium perfluorooctanoate in fluoropolymer manufacturing. Regul Toxicol Pharmacol 2011;59:64–80.
114. Cosmetic Ingredient Review Expert Panel. Final report: triclosan. Washington, DC: Cosmetic Ingredient Review; 2010.
115. Chan LM, Chalupka SM, Barrett R. Female college student awareness of exposures to environmental toxins in personal care products and their effect on preconception health. Workplace Health Saf 2015;63:64–70.
116. Park JY, Lee K, Hwang Y, Kim JH. Determining the exposure factors of personal and home care products for exposure assessment. Food Chem Toxicol 2015;77:105–10.
117. Biesterbos JW, Dudzina T, Delmaar CJ, Bakker MI, Russel FG, von Goetz N, et al. Usage patterns of personal care products: important factors for exposure assessment. Food Chem Toxicol 2013;55:8–17.
118. Loretz L, Api AM, Barraj L, Burdick J, Davis de A, Dressler W, et al. Exposure data for personal care products: hairspray, spray perfume, liquid foundation, shampoo, body wash, and solid antiperspirant. Food Chem Toxicol 2006;44:2008–18.
119. Lee TW, Tumanov S, Villas-Boas SG, Montgomery JM, Birch NP. Chemicals eluting from disposable plastic syringes and syringe filters alter neurite growth, axogenesis and the microtubule cytoskeleton in cultured hippocampal neurons. J Neurochem 2015;133:53–65.
120. Xie M, Wu Y, Little JC, Marr LC. Phthalates and alternative plasticizers and potential for contact exposure from children's backpacks and toys. J Expo Sci Environ Epidemiol 2016;26:119–24.
121. Lin J, Chen W, Zhu H, Wang C. Determination of free and total phthalates in commercial whole milk products in different packaging materials by gas chromatography-mass spectrometry. J Dairy Sci 2015;98:8278–84.