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Factors associated with the acquisition and retention of male-origin microchimerism in women

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ABSTRACT

Background: Natural microchimerism is the presence of cells at low concentrations in one individual originating from another. Although most cells are cleared from the maternal vascular system shortly after delivery, microchimeric cells - presumably of fetal origin - can be detected in many women decades after pregnancy.
Method: This cross-sectional study includes 774 women who participated in the Danish Diet, Cancer, and Health cohort sampled from 1993 to 1997. We investigate sources of male-origin microchimerism related to childbearing in maternal peripheral blood and its association with lifestyle using logistic regression. Guided by previous reports, we distinguish between sources of acquisition and retention of male-origin microchimerism.
Results: Women who had given birth to a male fetus had significantly increased odds of testing positive for male-origin microchimerism compared with women who had never given birth to a male fetus (OR = 1.61, 95 % CI [1.12; 2.33]). Compared with current users of hormone replacement treatment, women who reported no or former use of hormone replacement treatment had increased odds of testing positive for male-origin microchimerism (OR = 1.57, 95 % CI [1.12; 2.21]; OR = 1.89, 95 % CI [1.14; 3.13]). Furthermore, women who reported having formerly smoked had increased odds of testing positive for male-origin microchimerism, compared with women who reported current smoking (OR = 1.77, 95 % CI [1.15; 2.75]).
Conclusions: We find that the acquisition of male-origin microchimerism is associated with pregnancy with a male fetus, and retention may be linked to external factors, including smoking.

1. Introduction

During pregnancy, there is an exchange of oxygen and nutrients across the placenta between mother and fetus [1]. Recently, however, it has been convincingly demonstrated that there is also a bidirectional exchange of cells during gestation [2]. Such cell exchange gives rise to natural microchimerism, which is the presence of cells at low concentrations in one individual that originate from another. Although cell exchange occurs in all pregnancies, most cells are cleared from the maternal vascular system shortly after delivery [2]. However, in many females, microchimeric cells – presumably of fetal origin – can be detected decades after pregnancy [3]. Intriguingly, male-origin cells are also detectable in young girls [4,5] and in some females with no known history of pregnancy [3].

In females, considerable associations between male-origin microchimerism (MOMc) and health outcomes, including cancer and autoimmune diseases, have been repeatedly demonstrated [6–9]. Yet, the sources of MOMc are very scarcely described [10]. Most often, the presence of MOMc in females is attributed to a previous birth of a male fetus [11]. However, since MOMc has been detected in young girls [5] and females without an earlier known pregnancy [4], other possible sources of MOMc likely exist. Small studies have proposed that male cells originate from early miscarriage of a male embryo [12], a vanished male twin [13], and an older brother [6]. In this large-scale cross-sectional study, we investigate a range of reproductive, lifestyle, and other factors and their association with MOMc. Guided by previous reports [14,15], we distinguish between sources of acquisition and retention of MOMc. Whereas acquisition is likely attributed to pregnancy with a male fetus, retention may be linked to external factors such as smoking, hormone replacement treatment, and breastfeeding. Based on an

Abbreviations: MOMc, male-origin microchimerism.

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unprecedented sample size, we are, to the best of our knowledge, the first to carry out a study using such distinction.

2. Methods

The present cross-sectional study is based on data from the Diet, Cancer, and Health cohort sampled from 1993 to 1997 [16]. A total of 57,053 Danish men and women participated in the cohort. All participants were between 50 and 64 years old at baseline, had no diagnosis of cancer, and were all living in one of Denmark's two biggest cities, Copenhagen and Aarhus [17]. At enrolment into the Diet, Cancer, and Health cohort, all participants filled in questionnaires regarding lifestyle factors known or thought to be associated with the development of cancer [16]. Furthermore, at study centers, 30 ml of blood was drawn from all participants. Blood samples were separated into plasma, serum, erythrocytes, and buffy coat by centrifugation, and frozen at minus 20 °C within 2 h of phlebotomy [16]. To maximize the use of previously collected blood samples, we reused laboratory test results for a subset of females in the Diet, Cancer, and Health cohort. Data from this subset of females was originally obtained for two case-cohort studies by Hallum et al. [7] and Kamper-Jørgensen et al. [10], respectively. In both studies, the sub-cohorts were randomly selected at baseline among all females in the Diet, Cancer, and Health cohort, and therefore, the two sub-cohorts together make up an unbiased group of females to examine factors that are associated with the acquisition and retention of MOMc. Together, the two sub-cohorts comprised 895 females after removing duplicate records, which were sampled for both control groups (n = 5). Blood samples from all 895 females were tested in a laboratory for the presence of MOMc. In short, we used probe-based Quantitative Polymerase Chain Reaction (qPCR) to determine the presence and concentration of the Y-specific gene sequence DYS14 [18]. All tests were carried out by female laboratory technicians at the Department of Clinical Immunology, Odense University Hospital, Denmark [19]. For each female, DNA was divided into six wells with approximately 30,000 cells in each well [19]. We set the threshold cycle to 40, and if the intensity of the fluorescent light from a minimum of one of six wells crossed the threshold, the test was considered positive for the presence of MOMc. If the DNA quantity was insufficient, tests were not performed and were recorded as 'missing'. 'Inconclusive' results occurred in cases with signs of contamination in control wells, or amplification curves showing signs of irregularities, raising doubts about the reliability of the result. Blood samples from a total of 121 (13.5 %) females were inconclusive when tested for the presence of MOMc. These females were excluded, leaving us with a study population of 774 females.

We separated the analysis according to the acquisition and retention of microchimerism, respectively. Whereas acquisition is likely attributed to pregnancy with a male fetus and potentially lost and/or terminated pregnancy with a male fetus, retention is likely linked to external factors such as smoking and breastfeeding. We considered two self-reported acquisition-related variables, namely birth of a male fetus (no vs. yes) and lost and/or terminated one or more pregnancies (no vs. yes). Fetal sex was not registered for multiple pregnancies and for lost and/or terminated pregnancies. Pregnancy complications like preeclampsia [20] have been described to be associated with microchimerism, however, we did not have detailed data on pregnancy complications available.

As retention-related variables, we considered five self-reported covariates, namely age at enrolment (≤54, 55–59, ≥60 years), maximum breastfeeding duration (0, 1–2, 3–5, ≥6 months), hormone replacement therapy status (never, former, current), cigarette smoking status (never, former, current), and alcohol consumption (0, 1–10, ≥11 units per week). Hormone replacement therapy includes all types of hormone therapies aimed at relieving symptoms of menopause. The alcohol consumption variable describes the intake between the ages of 40 and 50 years, and categorization follows the guidelines of the National Board of Health, advising against a weekly consumption of more than 10 units per week [21].

For the statistical analysis, we first characterized the study population by tabulating frequencies and column percentages of all variables (Table 1). To examine the association between the acquisition- and retention-related variables, respectively, and MOMc, we estimated crude odds ratios (OR) with associated 95 % confidence intervals (95 % CI) using univariate logistic regression models (Table 2). Next, using a similar approach, we tested the possible interaction of acquisition-related variables and retention-related variables on the association with MOMc (Tables 3 and 4). Interactions were evaluated based on p-values from Wald tests of homogeneity. Statistical significance was evaluated at the 5 % level. The study was approved by the Danish Committee on Health Research Ethics (H-16021411) and the Danish Data Protection Agency through the joint notification of the Faculty of Health and Medical Sciences at the University of Copenhagen. The work described has furthermore been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. All data management and analyses were done using SPSS version 28.0.0.0.

3. Results

Among the 774 eligible females, 550 (71.1 %) tested positive, and 224 (28.9 %) tested negative for MOMc (Table 1). The covariates are divided into acquisition- and retention-related factors. Of the 774 females, 455 (70.5 %) had given birth to one or more male fetuses, and 236 (32.9 %) had lost and/or terminated one or more pregnancies. The median age at enrolment was 56 years, both among females testing

Table 1
Baseline characteristics of the study population (column%).

Variable	Frequency (n = 774)
Male origin microchimerism	
Positive	550 (71.1 %)
Negative	224 (28.9 %)
Acquisition-related variables	
Given birth to a male fetus [a]	
No	190 (29.5 %)
Yes	455 (70.5 %)
Lost and/or terminated pregnancy [b]	
No	481 (67.1 %)
Yes	236 (32.9 %)
Retention-related variables	
Age at enrolment (years)	
≤54	316 (40.8 %)
55–59	259 (33.5 %)
≥60	199 (25.7 %)
Duration of breastfeeding (months) [c]	
0	43 (6.2 %)
1–2	178 (25.7 %)
3–5	237 (34.2 %)
≥ 6	235 (33.9 %)
Hormone replacement therapy status	
Never	419 (54.1 %)
Former	117 (15.1 %)
Current	238 (30.7 %)
Smoking status[d]	
Never	331 (42.8 %)
Former	179 (23.2 %)
Current	263 (34.0 %)
Alcohol consumption (units per week)[e]	
0	105 (13.6 %)
1–10	563 (73.0 %)
≥ 11	103 (13.4 %)

[a] Information on fetal sex was not available for 129 participants.
[b] Information on lost and/or terminated pregnancies was not available for 57 participants.
[c] Information on the duration of breastfeeding is not available for 81 participants.
[d] Information on smoking status and BMI not available for one participant.
[e] Information on alcohol consumption not available for three participants.

Table 2
Number of females (row%) and crude odds ratios (95 % CI) for testing positive for male-origin microchimerism (MOMc), according to covariates.

Variable	Negative for MOMc (n = 224)	Positive for MOMc (n = 550)	Crude OR (95 % CI)
Acquisition			
Birth of a male fetus [a]			
No	65 (34.2 %)	125 (65.8 %)	1 (Ref.)
Yes	111 (24.4 %)	344 (75.6 %)	1.61 (1.12; 2.33)
Lost and/or terminated pregnancy [b]			
No	130 (63.1 %)	351 (68.7 %)	1 (Ref.)
Yes	76 (36.9 %)	160 (31.3 %)	0.78 (0.56; 1.10)
Retention			
Age at enrolment (years)			
≤54	92 (29.1 %)	224 (70.9 %)	1.00 (0.68; 1.48)
55–59	74 (28.6 %)	185 (71.4 %)	1.03 (0.68; 1.55)
≥60	58 (29.1 %)	141 (70.9 %)	1 (Ref.)
Duration of breastfeeding[c] **(months)**			
0	19 (44.2 %)	24 (55.8 %)	0.48 (0.25; 0.94)
1–2	49 (27.5 %)	129 (72.5 %)	1.01 (0.65,1.56)
3–5	67 (28.3 %)	170 (71.7 %)	0.97 (0.65; 1.45)
≥ 6	65 (27.7 %)	170 (72.3 %)	1 (Ref.)
Hormone replacement therapy status			
Never	111 (26.5 %)	308 (73.5 %)	1.57 (1.12; 2.21)
Former	27 (23.1 %)	90 (76.9 %)	1.89 (1.14; 3.13)
Current	86 (36.1 %)	152 (63.9 %)	1 (Ref.)
Smoking status [d]			
Never	97 (29.3 %)	234 (70.7 %)	1.19 (0.84; 1.69)
Former	39 (21.8 %)	140 (78.2 %)	1.77 (1.15; 2.75)
Current	87 (33.1 %)	176 (66.9 %)	1 (Ref.)
Alcohol consumption (units per week) [e]			
0	26 (24.8 %)	79 (75.2 %)	1.43 (0.78; 2.63)
1–10	164 (29.1 %)	399 (70.9 %)	1.15 (0.73; 1.80)
≥ 11	33 (32.0 %)	70 (68.0 %)	1 (Ref.)

[a] Information on fetal sex was not available for 48 females who tested negative for MOMc and 81 females who tested positive for MOMc.
[b] Information on lost and/or terminated pregnancies was not available for 18 females who tested negative for MOMc and 39 females who tested positive for MOMc.
[c] Information on the duration of breastfeeding was not available for 24 women who tested negative for MOMc and 57 women who tested positive for MOMc.
[d] Information on smoking status was not available for one woman who tested negative for MOMc.
[e] Information on alcohol consumption was not available for one woman who tested negative for MOMc and two females who tested positive for MOMc.

Table 3
Crude OR (95 % CI) of testing positive for male origin microchimerism (MOMc), according to lost and/or terminated pregnancy and having given birth to a male fetus and retention-related variables shown in a bar chart with 95 % CI, and test of homogeneity.

Variable	Stratum-specific OR (95 % CI)	Test of homogeneity	
Birth of a male fetus [a]			
	No	**Yes**	
Lost and/or terminated pregnancy [b]			
No	1 (Ref.)	2.19 (1.35; 3.55)	P = 0.024*
Yes	2.04 (0.91; 4.55)	1.73 (1.13; 2.64)	

* Significant at 5 % significant level.
[a] Information on fetal sex was not available for 48 females who tested negative for MOMc and 81 females who tested positive for MOMc.
[b] Information on lost and/or terminated pregnancies was not available for 18 females who tested negative for MOMc and 39 females who tested positive for MOMc.

negative and positive for MOMc. A total of 238 (30.7 %) females were current users of hormone replacement therapy, 263 (34.0 %) were current smokers, and 103 (13.4 %) consumed 11 units of alcohol per week or more (Table 1).

The distribution of females and crude OR (95 % CI) between having given birth to a male fetus and having lost and/or terminated a pregnancy, respectively, and testing positive for MOMc are presented in Table 2. Furthermore, we present the distribution of females along with crude OR (95 % CI) between retention-related covariates and testing positive for MOMc. We demonstrate increased odds of testing positive for MOMc among females who had given birth to a male fetus (OR = 1.61, 95 % CI [1.12; 2.33]) compared with females who had not given birth to a male fetus. Additionally, the analysis showed reduced odds of testing positive for MOMc among females with one or more lost and/or terminated pregnancies compared with women who reported no lost and/or terminated pregnancies (OR = 0.78, 95 % CI [0.56; 1.10]). This result did not reach statistical significance. The crude analysis between the retention-related breastfeeding covariate and testing positive for MOMc showed reduced odds of testing positive for MOMc among females who had never breastfed (OR = 0.48, 95 % CI [0.25; 0.94]) compared to having breastfed six months or more as their maximum breastfeeding period. Furthermore, we found increased odds for testing positive for MOMc among females who reported to be never (OR = 1.57, 95 % CI [1.12; 2.21]) or former users of hormone replacement therapy (OR = 1.89, 95 % CI [1.14; 3.13]), compared to current users of hormone replacement therapy. In addition, we demonstrated increased odds of testing positive for MOMc among females who reported to be former smokers at baseline (OR = 1.77, 95 % CI [1.15; 2.75]), compared with current smokers at baseline. A similar tendency was observed among females who had never smoked (OR = 1.19, 95 % CI [0.84; 1.69]), although this result did not reach statistical significance. We found insignificantly increased odds among females who consumed 0 (OR = 1.43, 95 % CI [0.78; 2.63]), or 1–10 alcoholic units per week (OR = 1.15, 95 % CI [0.73; 1.80]), compared with females who consumed 11 or more alcoholic units per week (Table 2).

Table 4
Crude OR (95 % CI) of testing positive for male origin microchimerism (MOMc), according to having given birth to a male fetus and retention-related variables, and test of homogeneity.

Variable	Stratum-specific OR (95 % CI)	Test of homogeneity
Birth of male fetus		
No	**Yes**	
Age at enrolment (years)		
≤54	1 (Ref.)	1.28 (0.72; 2.27)	P = 0.036*
55–59	1 (Ref.)	1.11 (0.57; 2.17)	
≥60	1 (Ref.)	3.68 (1.77; 7.67)	
Duration of breastfeeding (months)		
0	1 (Ref.)	0.27 (0.03; 2.56)	P = 0.283
1–2	1 (Ref.)	1.55 (0.63; 3.80)	
3–5	1 (Ref.)	2.62 (1.24; 5.52)	
≥ 6	1 (Ref.)	1.81 (0.87; 3.78)	
Hormone replacement therapy		
Never	1 (Ref.)	1.87 (1.15; 3.05)	P = 0.561
Former	1 (Ref.)	1.56 (0.48; 5.09)	
Current	1 (Ref.)	1.20 (0.62; 2.31)	
Smoking status		
Never	1 (Ref.)	1.26 (0.72; 2.20)	P = 0.098
Former	1 (Ref.)	3.64 (1.59; 8.29)	
Current	1 (Ref.)	1.42 (0.76; 2.65)	
Alcohol consumption (units per week)		
0	1 (Ref.)	0.98 (0.33; 2.89)	P = 0.087
1–10	1 (Ref.)	2.10 (1.36; 3.24)	
≥ 11	1 (Ref.)	0.72 (0.27; 1.90)	

* Significant at 5 % significant level.

In a sub-analysis of the interaction between having given birth to a male fetus and having lost and/or terminated one or more pregnancies, we tested for homogeneity and demonstrated the presence of interactions. Compared with females who had not given birth to a male fetus and had no lost or terminated pregnancies, the odds of testing MOMc-positive were markedly increased among females who had given birth to a male fetus and had not lost and/or terminated one or more pregnancies (OR = 2.19, 95 % CI [1.35; 3.55]) (Table 3). Among females who had not given birth to a male fetus and had lost and/or terminated one or more pregnancies, the OR was 2.04 (95 % CI [0.91; 4.55]). Females who had given birth to a male fetus as well as had lost and/or

terminated one or more pregnancies had an OR of 1.73 (95 % CI [1.13; 2.64]). All the above groups were compared with females who had never given birth to a male fetus and never had lost and/or terminated one or more pregnancies (Table 3).

Table 4 presents the crude OR of testing positive for MOMc, according to having given birth to a male fetus, and the retention-related variables. For this analysis, the birth of a male fetus was associated with increased odds of testing MOMc-positive among females aged 60 years or older (OR = 3.68, 95 % CI [1.77; 7.67]). None of the remaining retention-related variables interacted with giving birth to a male fetus (Table 4).

4. Discussion

In accordance with the research hypothesis, we report 61 % increased odds of testing positive for MOMc in females who had given birth to a male fetus compared with females who had not. This association may not have been apparent in earlier studies due to smaller study populations, as the biggest study in this field of research, to our knowledge, included 272 females [10]. The association, however, was most pronounced among females who reported not having lost and/or terminated one or more pregnancies. Although the results were not statistically significant, women who had experienced a pregnancy loss and/or termination but had not given birth to a male fetus appeared more likely to test positive compared to women with no sons and no history of pregnancy loss or termination. This suggests that lost or terminated pregnancies could potentially be a source of male cells. This is in accordance with an earlier study by Peterson et al. [12] that reports significant fetal cell transfer during miscarriage and termination of pregnancy. Further examination is needed to support the associations, however, this could arguably contribute to the understanding of studies showing that females who have not given birth to a male fetus often test positive for MOMc [22].

In the literature, MOMc has been detected in breast tissue in a high percentage of women. Both breastfeeding and microchimerism have been reported to be associated with breast cancer [9,23–25]. This led us to hypothesize a potential connection between breastfeeding and the retention of MOMc in peripheral blood. Our findings suggest a reduced likelihood of testing positive for MOMc among females who did not breastfeed. However, in our stratum-specific analysis, which explored the relationship between breastfeeding and MOMc based on whether the female gave birth to a male fetus, we did not observe any significant association. In both the crude and stratum-specific analyses, any duration of breastfeeding under six months was not associated with MOMc when compared to six months or more. We defined breastfeeding duration as the maximum duration across all pregnancies, but to further assess the appropriateness of this approach, we conducted a sub-analysis using the average and minimum breastfeeding durations. However, the association did not differ between these different measures of breastfeeding duration (data not shown).

We also examined the association between smoking and MOMc presence, and our findings suggest that smoking may be a retention-related factor for MOMc. Microchimeric cells are believed to home to anatomical sites such as the bone marrow, where stem cells are typically found. These cells may possess multilineage potential, enabling them to differentiate into various lineages, and could represent early-stage stem cells [26]. This hypothesis aligns with previous studies [14,27], which suggest that microchimeric cells might migrate to damaged tissues. In our study, we found reduced odds of testing positive for MOMc among females who were current smokers, compared to non-smokers. This reduction in odds is consistent with the findings of Vogelgesang et al. [15], who reported that smoking alters the distribution of fetal cells in the mother, attracting these cells to the lungs where inflammation and injury occur, as seen in mouse models. Since we assessed MOMc presence in peripheral blood, the reduced odds observed among current smokers could indicate that microchimeric cells are being recruited to other tissues.

Additionally, we observed increased odds of testing positive for MOMc among females who had never used or were former users of hormone replacement therapy, compared to current users. This finding is interesting in the context of prior studies that have shown a lower risk of ovarian cancer among women who test positive for MOMc in peripheral blood [7], together with previous research indicating that reduced exposure to hormone replacement treatment is associated with a lower risk of ovarian cancer [28,29]. Considering these findings, we believe the negative association between hormone replacement treatment use and MOMc observed in our study warrants further exploration. Future research may help to understand the underlying mechanisms linking MOMc, hormone replacement treatment, and ovarian cancer risk.

Based on our findings, we believe the retention-related variables smoking, hormone replacement treatment, and breastfeeding are worth further examination. Specifically, the possible interaction between the retention-related factors. Future studies could also benefit from examining the retention-related exposures prospectively. Measuring MOMc before, during, and after retention-related exposures would provide further insight into the retention of MOMc.

Female bioanalysts performed all blood sampling and laboratory tests, so contamination with Y-chromosome-specific genes of the blood samples is most unlikely. Further, we evaluated whether the timing of blood sampling and the brand of the sample kits used were associated with MOMc. We found no indication of such differences (data not shown). Comparing the prevalence with those reported in existing literature, particularly studies using qPCR targeting Y-chromosome markers (such as DYS14 or SRY) to detect MOMc, the prevalence of MOMc varies widely, generally ranging from 31 % to 85 % [25,30–32]. This variation could be influenced by factors such as the assay used, the age of participants, their pregnancy history, and the number of cells screened. For instance, our findings are notably higher than those of Yan et al. (2005), who found MOMc in 21 % of their participants, however, Yan et al. (2005) studied MOMc in females with no history of birthing a male fetus [22]. Furthermore, our study screened a total of 180,000 cells, whereas some studies have reported screening 100,000 cells [33]. Additionally, the assay used in our study is highly sensitive, with strict controls to minimize the risk of non-specific amplification or contamination.

Self-reported data were obtained in similar ways for all participants before conducting the laboratory analysis. Thus, considerable differential misclassification is highly unlikely. Still, measurement uncertainties from the self-reported data may have affected the baseline characteristics; for example, females may have underreported unhealthy lifestyles, thereby possibly introducing social desirability bias, or not accurately remembered their breastfeeding duration [34–36]. For example, the high prevalence of females reporting having never smoked may indicate social desirability bias. However, this can also reflect that the examined population is healthier than the general population. This is supported by findings from Larsen et al. (2012), showing that the participants in the Diet, Cancer, and Health cohort are healthier than the general Danish population [37]. Besides the possible information bias, we may not have been aware of important confounders affecting the studied associations, because research on factors predisposing to MOMc is scarce. However, the crude associations reported in the current study were not affected by adjustment for other available variables (data not shown).

In conclusion, the present work supports that male pregnancies are the primary source of MOMc acquisition and that external factors, including smoking, breastfeeding, and hormone replacement treatment, may impact the retention of MOMc. Further examination is needed to support the associations and to provide deeper insight into the mechanisms of the retention of MOMc.

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CRediT authorship contribution statement

Tine Dreier Bille: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Laura Brasen Kidmose:** Writing – original draft, Methodology, Formal analysis, Conceptualization. **Cindy Melanie Krøyer:** Writing – original draft, Methodology, Formal analysis, Conceptualization. **Anne Tjønneland:** Writing – review & editing, Validation, Data curation. **Mads Kamper-Jørgensen:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] M.-C. Maurel, C. Kanellopoulos-Langevin, Heredity—venturing beyond genetics, Biol. Reprod. 79 (2008) 2–8, https://doi.org/10.1095/biolreprod.107.065607.
[2] S. Shrivastava, R. Naik, H. Suryawanshi, N. Gupta, Microchimerism: a new concept, J. Oral Maxillofac. Pathol. 23 (2019) 311, https://doi.org/10.4103/jomfp.JOMFP_85_17.
[3] D.W. Bianchi, G.K. Zickwolf, G.J. Weil, S. Sylvester, M.A. DeMaria, Male fetal progenitor cells persist in maternal blood for as long as 27 years postpartum, Proc. Natl. Acad. Sci. U. S. A. 93 (1996) 705–708, https://doi.org/10.1073/pnas.93.2.705.
[4] T.D. Pan, S.B. Kanaan, N.R. Lee, J.L. Avila, J.L. Nelson, D.T.A. Eisenberg, Predictors of maternal-origin microchimerism in young women in the Philippines, Am. J. Phys. Anthropol. 174 (2021) 213–223, https://doi.org/10.1002/ajpa.24191.
[5] A.C. Müller, M.A. Jakobsen, T. Barington, A.A. Vaag, L.G. Grunnet, S.F. Olsen, et al., Microchimerism of male origin in a cohort of Danish girls, Chimerism 6 (2015) 65–71, https://doi.org/10.1080/19381956.2016.1218583.
[6] M.A. Knippen, Microchimerism: sharing genes in illness and in health, ISRN Nurs 2011 (2011) 893819, https://doi.org/10.5402/2011/893819.
[7] S. Hallum, M.A. Jakobsen, T.A. Gerds, A. Pinborg, A. Tjønneland, M. Kamper-Jørgensen, Male origin microchimerism and ovarian cancer, Int. J. Epidemiol. 50 (2021) 87–94, https://doi.org/10.1093/ije/dyaa019.
[8] V. Cirello, C. Colombo, M. Perrino, S. De Leo, M. Muzza, M.A. Maffini, et al., Fetal cell microchimerism in papillary thyroid cancer: a role in the outcome of the disease: microchimerism in thyroid cancer, Int. J. Cancer 137 (2015) 2989–2993, https://doi.org/10.1002/ijc.29653.
[9] M. Kamper-Jørgensen, R.J. Biggar, A. Tjønneland, H. Hjalgrim, K. Rostgaard, C. L. Stamper, et al., Opposite effects of microchimerism on breast and colon cancer, Eur. J. Cancer 48 (2012) 2227–2235, https://doi.org/10.1016/j.ejca.2012.02.006.
[10] M. Kamper-Jørgensen, L.H. Mortensen, A.-M.N. Andersen, H. Hjalgrim, V.K. Gadi, A. Tjønneland, Predictors of male microchimerism, Chimerism 3 (2012) 51–58, https://doi.org/10.4161/chim.21968.
[11] N.C. Lambert, J.M. Pang, Z. Yan, T.D. Erickson, A.M. Stevens, D.E. Furst, et al., Male microchimerism in women with systemic sclerosis and healthy women who have never given birth to a son, Ann. Rheum. Dis. 64 (2005) 845–848, https://doi.org/10.1136/ard.2004.029314.
[12] S.E. Peterson, J.L. Nelson, K.A. Guthrie, V.K. Gadi, T.M. Aydelotte, D.J. Oyer, et al., Prospective assessment of fetal–maternal cell transfer in miscarriage and pregnancy termination, Hum. Reprod. 27 (2012) 2607–2612, https://doi.org/10.1093/humrep/des244.
[13] L.M. de bellefon, P. Heiman, S.B. Kanaan, D.F. Azzouz, J.M. Rak, M. Martin, et al., Cells from a vanished twin as a source of microchimerism 40 years later in a male with a scleroderma-like condition, Chimerism 1 (2010) 56–60, https://doi.org/10.4161/chim.1.2.14294.
[14] Y. Fujiki, K.L. Johnson, H. Tighiouart, I. Peter, D.W. Bianchi, Fetomaternal trafficking in the mouse increases as delivery approaches and is highest in the maternal Lung 1, Biol. Reprod. 79 (2008) 841–848, https://doi.org/10.1095/biolreprod.108.068973.
[15] A. Vogelgesang, C. Scapin, C. Barone, E. Tam, A. Blumental Perry, C.E. L. Dammann, Cigarette smoke exposure during pregnancy alters fetomaternal cell trafficking leading to retention of microchimeric cells in the maternal lung, PLoS One 9 (2014) e88285, https://doi.org/10.1371/journal.pone.0088285.
[16] A. Tjønneland, A. Olsen, K. Boll, C. Stripp, J. Christensen, G. Engholm, et al., Study design, exposure variables, and socioeconomic determinants of participation in Diet, Cancer and Health: a population-based prospective cohort study of 57,053 men and women in Denmark, Scand. J. Publ. Health 35 (2007) 432–441, https://doi.org/10.1080/14034940601047986.
[17] K.E.N. Petersen, J. Halkjær, S. Loft, A. Tjønneland, A. Olsen, Cohort profile and representativeness of participants in the Diet, cancer and health—next generations cohort study, Eur. J. Epidemiol. 37 (2022) 117–127, https://doi.org/10.1007/s10654-021-00832-7.
[18] N.C. Lambert, Y.M.D. Lo, T.D. Erickson, T.S. Tylee, K.A. Guthrie, D.E. Furst, et al., Male microchimerism in healthy women and women with scleroderma: cells or circulating DNA? A quantitative answer, Blood 100 (2002) 2845–2851, https://doi.org/10.1182/blood-2002-01-0295.
[19] S.D.H. Olsen, A.M. Kolte, N. Bang, M.C. Krog, R. Steffensen, H.S. Nielsen, et al., The development of an indel panel for microchimerism detection, Exp. Mol. Pathol. 127 (2022) 104804, https://doi.org/10.1016/j.yexmp.2022.104804.
[20] D.P. Jacobsen, H.E. Fjeldstad, M.B. Olsen, M. Sugulle, A.C. Staff, Microchimerism and pregnancy complications with placental dysfunction, Semin. Immunopathol. 47 (2025) 21, https://doi.org/10.1007/s00281-025-01045-w.
[21] Danish National Board of Health, 10-4 – National Board of Health reports new guidelines for alcohol consumption, Last seen 14th of august 2023, https://www.sst.dk/da/nyheder/2022/10-4-sundhedsstyrelsen-melder-nye-genstandsgraenser-ud, 2022. (Accessed 14 August 2023).
[22] Z. Yan, N.C. Lambert, K.A. Guthrie, A.J. Porter, L.S. Loubiere, M.M. Madeleine, et al., Male microchimerism in women without sons: quantitative assessment and correlation with pregnancy history, Am. J. Med. 118 (2005) 899–906, https://doi.org/10.1016/j.amjmed.2005.03.037.
[23] E. Dhimolea, V. Denes, M. Lakk, S. Al-Bazzaz, S. Aziz-Zaman, M. Pilichowska, et al., High male chimerism in the female breast shows quantitative links with cancer, Int. J. Cancer 133 (2013) 835–842, https://doi.org/10.1002/ijc.28077.
[24] V.K. Gadi, Fetal microchimerism in breast from women with and without breast cancer, Breast Cancer Res. Treat. 121 (2010) 241–244, https://doi.org/10.1007/s10549-009-0548-1.
[25] V.K. Gadi, J.L. Nelson, Fetal microchimerism in women with breast cancer, Cancer Res. 67 (2007) 9035–9038, https://doi.org/10.1158/0008-5472.CAN-06-4209.
[26] L. Fugazzola, V. Cirello, P. Beck-Peccoz, Microchimerism and endocrine disorders, J. Clin. Endocrinol. Metabol. 97 (2012) 1452–1461, https://doi.org/10.1210/jc.2011-3160.
[27] R.J. Kara, P. Bolli, I. Matsunaga, O. Tanweer, P. Altman, H.W. Chaudhry, A mouse model for fetal maternal stem cell transfer during ischemic cardiac injury, Clin. Translat. Sci. 5 (2012) 321–328, https://doi.org/10.1111/j.1752-8062.2012.00424.x.
[28] B. Zhou, Q. Sun, R. Cong, H. Gu, N. Tang, L. Yang, et al., Hormone replacement therapy and ovarian cancer risk: a meta-analysis, Gynecol. Oncol. 108 (2008) 641–651, https://doi.org/10.1016/j.ygyno.2007.12.003.
[29] L.S. Mørch, Hormone therapy and ovarian cancer, JAMA 302 (2009) 298, https://doi.org/10.1001/jama.2009.1052.
[30] J.K. Eun, K.A. Guthrie, G. Zirpoli, V.K. Gadi, In situ breast cancer and microchimerism, Sci. Rep. 3 (2013) 2192, https://doi.org/10.1038/srep02192.
[31] P.C. Evans, N. Lambert, S. Maloney, D.E. Furst, J.M. Moore, J.L. Nelson, Long-term fetal microchimerism in peripheral blood mononuclear cell subsets in healthy women and women with scleroderma, Blood 93 (1999) 2033–2037, https://doi.org/10.1182/blood.V93.6.2033.406k18_2033_2037.
[32] L.S. Loubière, N.C. Lambert, L.J. Flinn, T.D. Erickson, Z. Yan, K.A. Guthrie, et al., Maternal microchimerism in healthy adults in lymphocytes, monocyte/macrophages and NK cells, Lab. Invest. 86 (2006) 1185–1192, https://doi.org/10.1038/labinvest.3700471.
[33] V.K. Gadi, J.L. Nelson, Fetal microchimerism in women with breast cancer, Cancer Res. 67 (2007) 9035–9038, https://doi.org/10.1158/0008-5472.CAN-06-4209.
[34] E. Bertol, F. Vaiano, R. Boscolo-Berto, A. Fioravanti, D. Palumbo, V. Catalani, et al., Alcohol, caffeine, and nicotine consumption in adolescents: hair analysis versus self-report, Am. J. Drug Alcohol Abuse 43 (2017) 341–349, https://doi.org/10.1080/00952990.2016.1216556.
[35] R.A. Knibbe, K. Bloomfield, Alcohol consumption estimates in surveys in europe: comparability and sensitivity for gender differences, Subst. Abuse 22 (2001) 23–38, https://doi.org/10.1080/08897070109511443.
[36] L. Midanik, The validity of self-reported alcohol consumption and alcohol problems: a literature review, Addiction 77 (1982) 357–382, https://doi.org/10.1111/j.1360-0443.1982.tb02469.x.
[37] S.B. Larsen, S.O. Dalton, J. Schüz, J. Christensen, K. Overvad, A. Tjønneland, et al., Mortality among participants and non-participants in a prospective cohort study, Eur. J. Epidemiol. 27 (2012) 837–845, https://doi.org/10.1007/s10654-012-9739-x.