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Article

ARTICLE

Prenatal Biochemical Screening and a Woman's Long-Term Risk of Cancer: A Population-Based Cohort Study

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Abstract

Background: Some hormones measured in pregnancy are linked to certain hormone-sensitive cancers. We investigated whether routine serum screening in pregnancy is associated with a woman's subsequent risk of hormone-sensitive cancer.
Methods: This population-based cohort study included women aged 12–55 years who underwent prenatal screening between 11 weeks + 0 days of gestation to 20 weeks + 6 days of gestation in Ontario, Canada, 1993–2011, where universal health care is available. The hazard ratio of newly diagnosed breast, ovarian, endometrial, and thyroid cancer—arising at 21 weeks + 0 days of gestation or thereafter—was estimated in association with an abnormally low (≤5th) or high (>95th) percentile multiple of the median (MoM) for alpha-fetoprotein (AFP), total human chorionic gonadotropin (hCG), unconjugated estriol, pregnancy-associated plasma protein A, and dimeric inhibin A.
Results: Among 677 247 pregnant women followed for a median of 11.0 years (interquartile range = 7.5–16.1), 7231 (1.07%) developed breast cancer, 515 (0.08%) ovarian cancer, 508 (0.08%) endometrial cancer, and 4105 (0.61%) thyroid cancer. In multivariable adjusted models, abnormally high hCG greater than the 95th percentile MoM was associated with a doubling in the risk of endometrial cancer (adjusted hazard ratio [aHR] = 1.98, 95% confidence interval [CI] = 1.33 to 2.95), and abnormally low AFP at the fifth percentile or less MoM conferred a moderately greater risk of thyroid cancer (aHR = 1.21, 95% CI = 1.07 to 1.38). Abnormally low pregnancy-associated plasma protein A at the fifth percentile or less MoM was not statistically significantly associated with breast cancer after multivariable adjustment (aHR = 1.19, 95% CI = 0.98 to 1.36).
Conclusions: Women with abnormally high levels of serum hCG or low AFP in early pregnancy may be at a greater future risk of certain types of hormone-sensitive cancers.

Serum levels of steroid hormones can be 10–50 times higher in concentration at term gestation relative to the nonpregnant state (1,2). Steroid hormones are also important drivers in the pathogenesis of hormone-sensitive cancers (3) and have been implicated in the association between pregnancy and breast (4,5), endometrial (6), and ovarian cancer (7,8). Human chorionic gonadotropin (hCG) and alpha-fetoprotein (AFP) also rise dramatically in early pregnancy and have been shown to be protective of breast cancer, though not consistently (9). Less is known about other pregnancy hormones, such as maternal serum pregnancy-associated plasma protein A (PAPP-A) and dimeric inhibin A (DIA). However, it is feasible that maternal serum PAPP-A is involved in maternal cancer through its regulation of the insulin-like growth factor-1 axis, which has been implicated in breast (10) and ovarian cancer (11).

Maternal serum screening for trisomy 21 and 18 and for neural tube defects became universally available to all pregnant women in Ontario, Canada, starting in 1993. Triple-screening,

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collected in the second trimester at 15 weeks + 0 days of gestation (ie, 15^{+0}) to 20 weeks + 6 days of gestation (ie, 20^{+6}), included maternal serum AFP, total hCG, and unconjugated estriol (uE3). Around the year 2000, DIA was added to second trimester screening, and measurement of serum PAPP-A at 11^{+0} to 13^{+6} weeks was further added.

The current study examined whether abnormal prenatal concentrations of AFP, hCG, uE3, PAPP-A, or DIA were associated with an increased long-term risk of hormone-sensitive cancer.

Methods

Study Design and Data Sources

This population-based cohort study used administrative health-care datasets for the province of Ontario, Canada, where universal health care includes free prenatal screening. Prenatal biochemical screening records from seven regional laboratories (reduced to 5 as of 2007) were aggregated in the Ontario Maternal Multiple Marker Screening Database, 1993–2011. Datasets were linked using unique encoded identifiers and analyzed at Institute for Clinical Evaluative Sciences (ICES). Specifics about the ICES databases are provided in Supplementary Table 1 (available online) and described elsewhere (12–14). The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board.

Participants

Eligible females were aged 12–55 years, with prenatal serum screening done at 11–20 completed weeks' gestation between 1993 and 2011. All pregnancies were eligible regardless of the outcome, including live births or stillbirths at 21^{+0} weeks or later gestation, miscarriages and ectopic pregnancies at less than 21^{+0} weeks' gestation, and induced abortions at any gestation.

There were 1 380 840 initially eligible pregnancies (Figure 1). Of these, 430 984 pregnancies (31.2%) were excluded. Exclusions were predominantly due to having fewer than 5 years of provincial health insurance plan eligibility preceding time zero, which was necessary to ensure exclusion of women with preexisting cancer (Figure 1). The remaining 950 259 pregnancies had a measured AFP, hCG, uE3, PAPP-A, or DIA to form the screened cohort. To simplify the analyses, we randomly selected one pregnancy per woman as the index pregnancy (n = 677 247). Pregnancies lacking a serum AFP, hCG, uE3, PAPP-A, or DIA comprised the nonscreened cohort (n = 972 326). These pregnancies were analyzed in a supplementary manner as outlined below.

Exposures and Outcomes

The study exposure was each prenatal biochemical screening analyte—AFP, hCG, uE3, PAPP-A, and DIA—expressed as a multiple of the median (MoM) (Supplementary Table 1, available online). For each analyte, the MoM value was originally calculated at each respective laboratory by dividing the marker concentration of a woman by the normal median for women of the same gestational age. The MoM metric is commonly used in clinical reporting that standardizes test results between different laboratories, thus eliminating interlaboratory variation.

The primary outcome was the occurrence of each hormone-sensitive cancer—breast, ovarian, endometrial, and thyroid—diagnosed from at least 21^{+0} weeks' gestation ("time zero") and onward (Supplementary Table 1, available online). If the pregnancy ended in a miscarriage, ectopic pregnancy, or induced abortion before 21^{+0} weeks' gestation, time zero was calculated as the date at which gestation would have been 21^{+0} weeks had the woman remained pregnant. Starting the window of observation for the outcome at 21^{+0} weeks ensured that prenatal biochemical screening would have been completed for all pregnancies, yet a cancer could still be picked up in pregnancy or any time thereafter. For each type of hormone-sensitive cancer, a woman was followed either until that type of cancer was diagnosed or she was censored on death, loss of Ontario Health Insurance Plan (OHIP) eligibility, or arrival at the end of the study (March 31, 2017), whichever came first. Additional cancer-specific censoring was applied as follows: in the analysis of breast cancer, at bilateral mastectomy in women free of breast cancer at that time; in the analysis of ovarian cancer, at bilateral oophorectomy in women free of ovarian cancer at that time; in the analysis of uterine cancer, at hysterectomy in women free of endometrial cancer at that time; and in the analysis of thyroid cancer, at thyroidectomy in women free of thyroid cancer at that time. For each given cancer type, a woman was not censored on the other three types of cancer.

Statistical Analysis

The association between each analyte (in MoM) and the log hazard of each cancer was explored using univariate fractional polynomial regression (15,16). Best-fitting plots were generated based on all prenatal screening results except for those resulting in a live birth or stillbirth affected by a congenital or chromosomal anomaly, or outliers of MoM beyond the 0.2nd or 99.8th percentiles (17,18) (Supplementary Figure 1, available online). Inspection of each individual plot enabled us to identify whether the risk of each type of cancer was more pronounced at a low or high concentration of each analyte: for AFP, this was the 5th or less percentile MoM; for hCG and DIA, it was the fifth or less MoM for breast and thyroid cancers, and greater than 95th percentile for ovarian and endometrial cancers; for uE3, it was the fifth or less percentile MoM for ovarian cancer and greater than the 95th percentile for the other cancers; for PAPP-A, it was the 5th or less percentile MoM for breast, endometrial, and thyroid cancer, and greater than the 95th percentile for ovarian cancer.

The main model assessed each cancer outcome in association with a potentially harmful MoM cutpoint of each analyte vs normal (referent) using multivariable Cox regression models to generate a hazard ratio (HR) and 95% confidence interval (CI) for each cancer outcome, with time-on-study as the time scale. Hazard ratios were adjusted for maternal characteristics measured at the time of the prenatal biochemical screening, including age (continuous), parity (0, ≥1, unknown), neighborhood income quintile (1, 2, 3, 4, 5, unknown), rural residence (rural, urban, unknown), ethnicity (Asian, black, Caucasian, other, unknown), gestational age (continuous), and year (continuous) as well as diabetes mellitus, chronic kidney disease, and illicit drug or tobacco use within 365 days preceding the 21^{+0} gestational week of pregnancy (ie, preceding "time zero").

In stratified analyses of the main model, each analyte was then reevaluated in the copresence of characteristics measured at the time of the prenatal screening that might influence a biochemical analyte and/or a woman's cancer risk, including: 1)

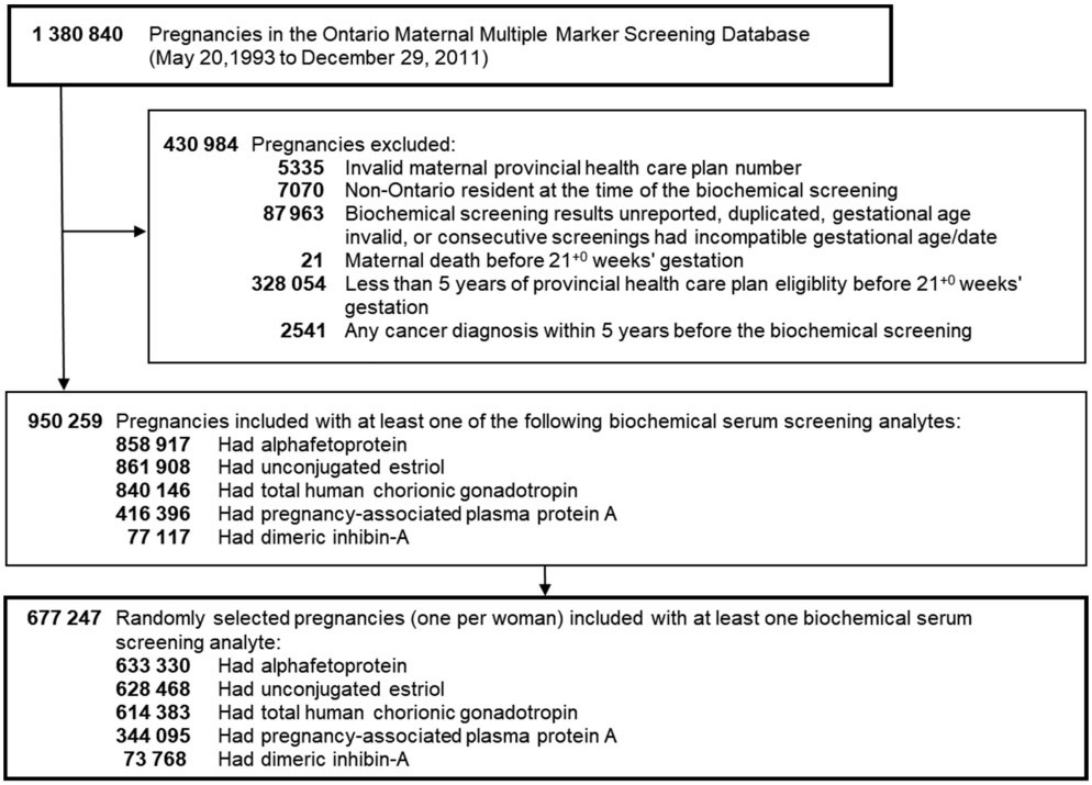

Figure 1. Flowchart describing cohort creation.

advanced maternal age 35 years or younger, and 2) nulliparity; as well as characteristics measured at the time of a live birth or stillbirth, including; 3) a maternal placental syndrome—pre-eclampsia, gestational hypertension, or placental abruption or infarction; and 4) a recognized chromosomal or congenital anomaly; and 5) fetal growth restriction at the time of live birth; and 6) a pregnancy ending with a non–live birth.

Additional analyses 1–7 (Supplementary Methods, available online) considered the possible effects of maternal weight, infant feeding, previous analyte abnormalities, more extreme levels of less than or equal to the first and greater than 99th percentiles MoM, re-setting time zero to 365 days after the index delivery in case the abnormal prenatal screening result was due to an undetected cancer, more refined categories of quintile MoM, and to characterize women who did and did not undergo prenatal serum screening.

Statistical significance was set at P less than .05 without correction for multiple comparisons. All statistical analyses were performed using SAS version 9.4 for UNIX (SAS Institute Inc). All tests were two-sided.

Results

Among the 677 247 randomly selected pregnancies included in the analysis, AFP was the most frequently measured analyte (633 330 pregnancies), and DIA was the least frequent (73 768 pregnancies) due to its introduction in later years (Table 1). The mean (SD) age at delivery was 30.3 (5.4) years.

The median (interquartile range [IQR]) duration of follow-up was 11.0 (7.5–16.1) years and was shortest for pregnancies with DIA (8.2 years, IQR = 6.4–10.6) and longest for pregnancies with uE3 (12.3 years, IQR = 8.3–17.2). There was a total of 8 116 631 person-years of follow-up among all of the randomly selected pregnancies, primarily from women with measured AFP, hCG, or uE3.

Of 677 247 pregnancies in the randomly selected screened cohort, 7231 (1.07%) women were subsequently diagnosed with breast cancer, 515 (0.08%) with ovarian cancer, 508 (0.08%) with endometrial cancer, and 4105 (0.61%) with thyroid cancer. The mean (SD) age a diagnosis of cancer was 43.0 (6.0) years for cancer of the breast, 42.0 (7.1) years for ovarian, 45.4 (6.6) years for endometrial, and 39.4 (6.4) years for thyroid.

In the main model, for the outcome of breast cancer, women with an abnormally low serum PAPP-A had an increased rate compared with women whose concentration was the 5th percentile or higher (8.9 vs 7.5 per 10 000 person-years), although the risk was no longer statistically significant after adjusting for covariates (adjusted hazard ratio [aHR] = 1.19, 95% CI = 0.98 to 1.36) (Figure 2A). The risk of ovarian cancer was not associated with any of the abnormal analytes. Women with abnormally high hCG greater than the 95th percentile had an increased rate of endometrial cancer compared with those below that cut-point (0.9 vs 0.6 per 10 000 person-years) (aHR = 1.98, 95% CI = 1.33 to 2.95) (Figure 2B). The rate of thyroid cancer was increased in women with an abnormally low AFP relative to those whose AFP was above the 5th percentile (5.7 vs 4.7 per 10 000 person-years) (aHR = 1.21, 95% CI = 1.07 to 1.38). Additionally, women with abnormally low DIA had a marginally greater risk of thyroid cancer compared with other women (6.7 vs 4.6 per 10 000 person-years) (aHR = 1.50, 95% CI = 1.00 to 2.26).

The rate of breast cancer did not vary by the presence or absence of each abnormal analyte among women aged 35 years or older or among those younger than 35 years, although an effect of older age in the index pregnancy was observed (Figure 3A). Compared with parous women with a normal level of each analyte, nulliparous women had a decreased crude rate of breast

Table 1. Characteristics of pregnancies with prenatal biochemical screening, by analyte*

Characteristic	Biochemical serum screening analyte				
	Alpha-fetoprotein (N = 633 330)	Unconjugated estriol (N = 628 468)	Total human chorionic gonadotropin (N = 614 383)	Pregnancy-associated plasma protein A (N = 344 095)	Dimeric inhibin A (N = 73 768)
At the time of maternal serum screening					
Mean (SD) age, y	30.3 (5.4)	30.2 (5.4)	30.2 (5.3)	31.2 (5.3)	29.2 (5.8)
Age, y					
12 to 19	3.7	3.7	3.7	2.3	5.9
20 to 24	11.1	11.4	11.3	8.8	15.9
25 to 29	26.5	26.9	26.8	24.3	28.3
30 to 34	37.0	37.1	37.2	37.3	30.7
35 to 39	18.6	18.0	18.1	22.7	16.1
40 to 44	3.0	2.8	2.8	4.3	3.0
45 to 55	0.1	0.1	0.1	0.2	0.2
Ethnicity					
Caucasian	70.6	71.3	70.9	69.7	62.5
Black	5.8	5.7	5.8	5.2	9.1
Asian	16.8	16.6	16.8	18.2	19.5
Other	2.2	2.2	2.2	3.0	4.8
Unknown	4.7	4.3	4.3	3.9	4.2
Income quintile (Q)					
Q1 (lowest)	19.5	19.6	19.6	16.8	26.1
Q5 (highest)	17.7	17.6	17.6	19.8	12.8
Unknown	0.3	0.3	0.3	0.3	0.7
Residence					
Urban	91.8	91.5	91.7	93.7	88.0
Rural	8.1	8.4	8.2	6.2	11.9
Unknown	0.1	0.1	0.1	0.0	0.0
Median (IQR) gravidity	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)
Gravidity					
1	36.5	36.5	36.5	36.0	33.1
2	35.4	35.3	35.4	34.5	32.2
3 or more	26.9	27.0	26.9	27.3	33.0
Unknown	1.2	1.2	1.2	2.2	1.7
Median (IQR) parity	1 (0–1)	1 (0–1)	1 (0–1)	1 (0–1)	1 (0–1)
Parity					
0	49.6	49.4	49.4	47.1	43.7
1	33.6	33.7	33.8	34.4	33.2
2 or more	15.2	15.3	15.3	15.0	20.5
Unknown	1.6	1.6	1.6	3.5	2.6
Mean (SD) maternal weight, kg	67.3 (17.2)	67.3 (17.2)	67.4 (17.2)	67.4 (21.6)	66.0 (20.2)
Unknown maternal weight	10.5	10.0	10.2	16.5	13.0
Type of pregnancy					
Singleton	95.0	96.0	95.9	86.3	98.8
Multifetal	1.3	0.6	0.6	0.0	0.2
Unknown	3.7	3.3	3.4	13.7	1.0
Mean (SD) weeks' gestation at screening	16.7 (1.1)	16.7 (1.1)	16.7 (1.1)	12.5 (0.5)	17.0 (1.3)
Year of screening					
1993–2002	43.9	43.6	44.7	3.8	0.0
2003–2011	56.1	56.4	55.3	96.2	100.0
Outcome of index pregnancy					
Live birth	97.0	97.0	97.0	96.1	96.8
Stillbirth	0.5	0.5	0.5	0.4	0.6
Miscarriage or ectopic pregnancy	0.3	0.3	0.3	0.6	0.4
Induced abortion	0.3	0.3	0.3	0.6	0.4
Unknown outcome	1.9	1.9	1.9	2.2	1.7
Conditions $\leq$1 year before 21^{+0} weeks' gestation					
Diabetes mellitus	2.4	2.3	2.3	2.7	2.6
Chronic kidney disease	0.2	0.2	0.2	0.2	0.2
Illicit drug or tobacco use	1.2	1.2	1.2	1.1	1.6

(continued)

Table 1. (continued)

Characteristic	Biochemical serum screening analyte				
	Alpha-fetoprotein (N = 633 330)	Unconjugated estriol (N = 628 468)	Total human chorionic gonadotropin (N = 614 383)	Pregnancy-associated plasma protein A (N = 344 095)	Dimeric inhibin A (N = 73 768)
Conditions at time of the index live birth or stillbirth delivery					
Congenital or chromosomal anomaly	3.9	3.9	3.9	3.1	2.9
Preeclampsia or eclampsia	2.0	2.0	2.0	1.2	1.2
Placental abruption	0.9	0.9	0.9	0.8	0.9
Placental infarction	0.6	0.6	0.6	0.4	0.3
Gestational hypertension	3.6	3.6	3.5	4.4	4.2
Conditions at time of index live birth delivery					
Fetal growth restriction	2.0	1.9	1.9	2.0	1.9
Preterm birth $<37^{+0}$ weeks' gestation	7.2	6.8	6.9	6.8	7.2
Infant feeding on discharge†					
Breast milk only	60.2	60.1	60.3	61.9	53.5
Formula	27.9	27.8	27.7	26.5	29.8
Combination	11.8	12.0	11.9	11.5	16.5
Other	0.1	0.1	0.1	0.1	0.2
Median (IQR) follow-up from $\geq 21^{+0}$ weeks' gestation in index pregnancy, y	11.8 (7.7–16.7)	12.3 (8.3–17.2)	12.1 (7.6–17.0)	8.2 (6.4–10.6)	9.9 (8.6–11.2)
Total person-years of follow-up from $\geq 21^{+0}$ weeks' gestation in index pregnancy	7 797 800	7 704 260	7 626 915	2 983 927	647 622
Prenatal biochemical screening percentiles‡					
No. of pregnancies included	873 852	868 685	846 884	456 107	78 995
1st percentile MoM	0.49	0.32	0.32	0.25	0.38
5th percentile MoM	0.60	0.50	0.49	0.38	0.50
95th percentile MoM	1.82	1.96	1.95	2.45	2.22
99th percentile MoM	2.51	2.92	2.78	3.51	3.24

*One pregnancy was allowed per woman. Values are percent age unless stated otherwise. IQR = interquartile range; MoM = multiple of the median.
†Available April 2006 to March 2012 only.
‡Percentiles calculated using all screened pregnancies resulting in live birth or stillbirth without a congenital or chromosomal anomaly diagnosis.

cancer but a greater adjusted risk, especially with an abnormally low PAPP-A (aHR = 1.37, 95% CI = 1.06 to 1.77) or an abnormally high uE3 (aHR = 1.19, 95% CI = 1.05 to 1.34) (Figure 3A). Women with a maternal placental syndrome had a reduced associated risk of breast cancer, particularly those with normal uE3 (Figure 3A). The risk of breast cancer was also reduced in women with fetal growth restriction and a normal AFP, HCG, or uE3 (Figure 3B).

For ovarian cancer, the risk was usually greatest in the co-presence of an abnormal analyte and advanced maternal age at the time of prenatal screening, except for an abnormally high PAPP-A, which conferred a greater risk among those aged younger than 35 years (aHR = 2.14, 95% CI = 1.03 to 4.45) (Figure 4). Nulliparous women with a high PAPP-A also displayed a greater risk of ovarian cancer (aHR = 2.33, 95% CI = 1.06 to 5.09) as did those whose AFP was normal in conjunction with a child affected by congenital or chromosomal anomaly (aHR = 1.48, 95% CI = 1.02 to 2.14).

The risk of endometrial cancer was not statistically significantly altered in the co-presence of an abnormal analyte and each co-factor when contrasted to that observed for the abnormal analyte or the cofactor in isolation (Figure 5). Even so, women with a maternal placental syndrome and abnormally high hCG had an aHR of 3.72 (95% CI = 1.53 to 9.03).

For thyroid cancer, the risk was noteworthy in the co-presence of abnormally low hCG and advanced maternal age relative to those with neither (aHR = 1.68, 95% CI = 1.29 to 2.20) (Figure 6). aHRs in the main model did not differ after adjusting for maternal weight, infant breastfeeding, or the presence of an abnormal prenatal screening result in a previous pregnancy (additional analyses 1–3, data not shown). At more extreme cutpoints set at less than or equal to the first or greater than the 99th percentile MoM to define each abnormal analyte, none of the adjusted models indicated a statistically significantly increased risk of cancer (additional analysis 4; Supplementary Figure 2, available online). Resetting time zero to start at 365 days after the index delivery did not change the previously noted increased risk of endometrial cancer with high hCG or of thyroid cancer with low AFP (additional analysis 5; Supplementary Figure 3, available online). An incremental increase in the risk for breast cancer was seen with decreasing quintile MoM of PAPP-A (quintile 1 vs 5: aHR = 1.29, 95% CI = 1.13 to 1.47) and was also greater among those in the lowest three quintiles of AFP and hCG (additional analysis 6; Supplementary Figure 4, available online).

There was a total of 950 259 biochemically screened pregnancies and 972 326 nonscreened pregnancies (additional analysis 7; Supplementary Table 2, available online). The risk of breast cancer (aHR = 1.12, 95% CI = 1.09 to 1.15) and thyroid cancer (aHR 1.25, 95% CI = 1.20 to 1.30) was greater in the screened cohort than the nonscreened cohort (Supplementary Table 2, available online). In contrast, the risk of endometrial cancer was decreased in the screened cohort (aHR = 0.89, 95% CI = 0.80 to 0.99).

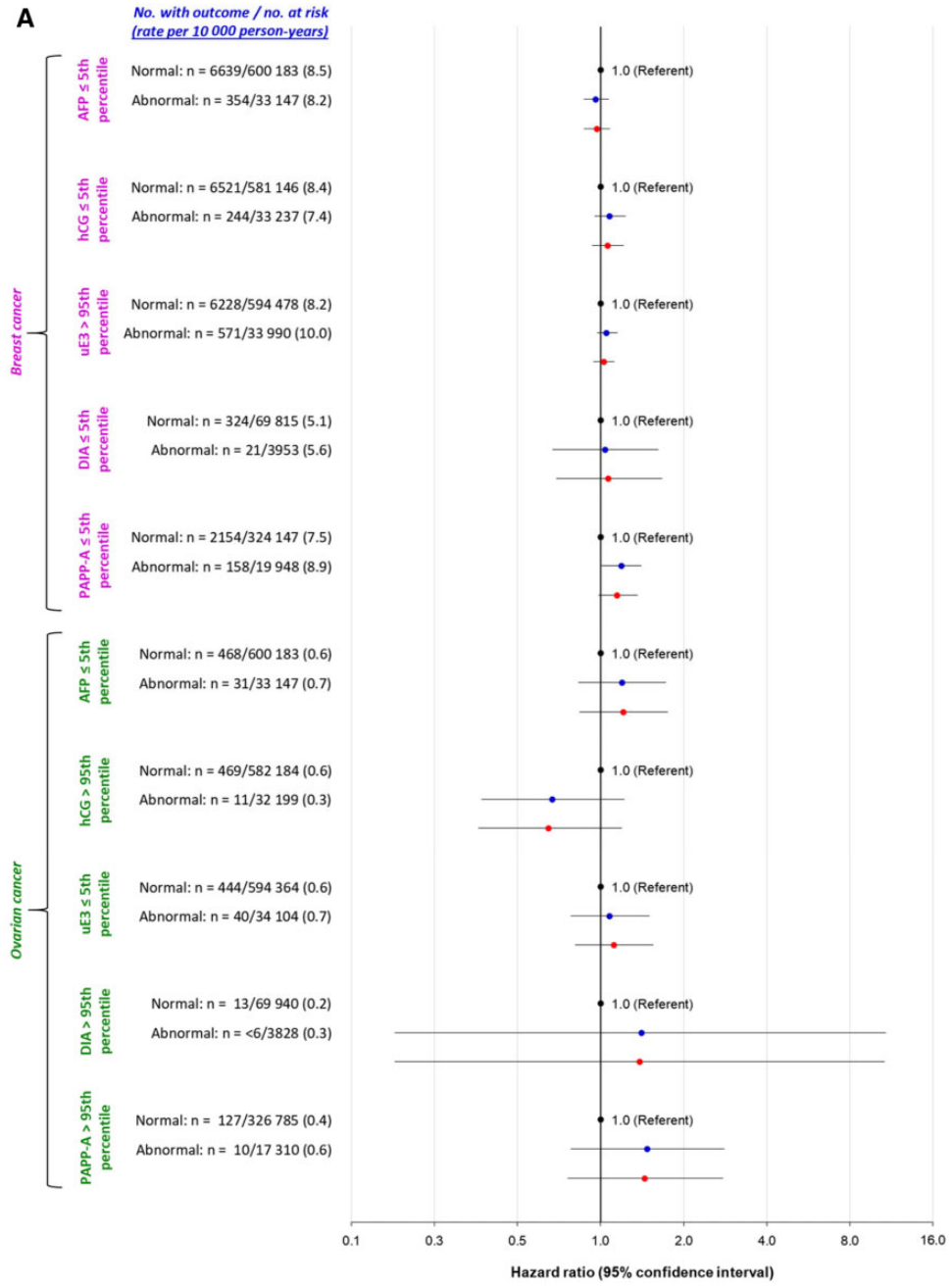

Figure 2. Risk of breast cancer (**A, upper**), ovarian cancer (A, **lower**), endometrial cancer (**B, upper**), and thyroid cancer (B, **lower**) arising from at least 21^{+0} weeks' gestation in the index pregnancy, associated with an abnormally low (≤5th vs >5th [referent]) or abnormally high (>95th vs ≤95th [referent]) percentile multiple of the median, depending on the given prenatal biochemical screening analyte and cancer. One pregnancy was allowed per woman. Shown are crude (**blue circles**) and adjusted (**red circles**) hazard ratios, the latter adjusted for maternal age, parity, income quintile, rural residence, ethnicity, gestational age, and year—each at the time of prenatal biochemical screening—as well as diabetes mellitus, chronic kidney disease, and illicit drug or tobacco use within 1 year before 21^{+0} weeks' gestation. Censoring was on death, end of Ontario Health Insurance Plan eligibility, or arrival at the end of study as well as bilateral mastectomy (for breast cancer), bilateral oophorectomy (for ovarian cancer), hysterectomy (for endometrial cancer), and thyroidectomy (for thyroid cancer). AFP, alpha-fetoprotein; hCG, total human chorionic gonadotropin; uE3, unconjugated estriol; DIA, dimeric inhibin A; PAPP-A, pregnancy-associated plasma protein A.

Discussion

Variation was observed in the risk of breast, ovarian, endometrial, and thyroid cancer in relation to five different prenatal serum screening analytes.

About one-half of pregnancies during the study period had prenatal biochemical screening, which was available within a universal health-care setting. This 50% rate of uptake may be partly explained by our inclusion of pregnancies ending before 20 weeks' gestation. Though the characteristics of the screened pregnancies differed minimally from the unscreened pregnancies, the uptake of prenatal screening was lower for rural than urban women (Supplementary Table 2, available online). This is consistent with previous reports (19,20). Also, rates of future breast and thyroid cancer were somewhat increased in unscreened pregnancies (Supplementary Table 2, available

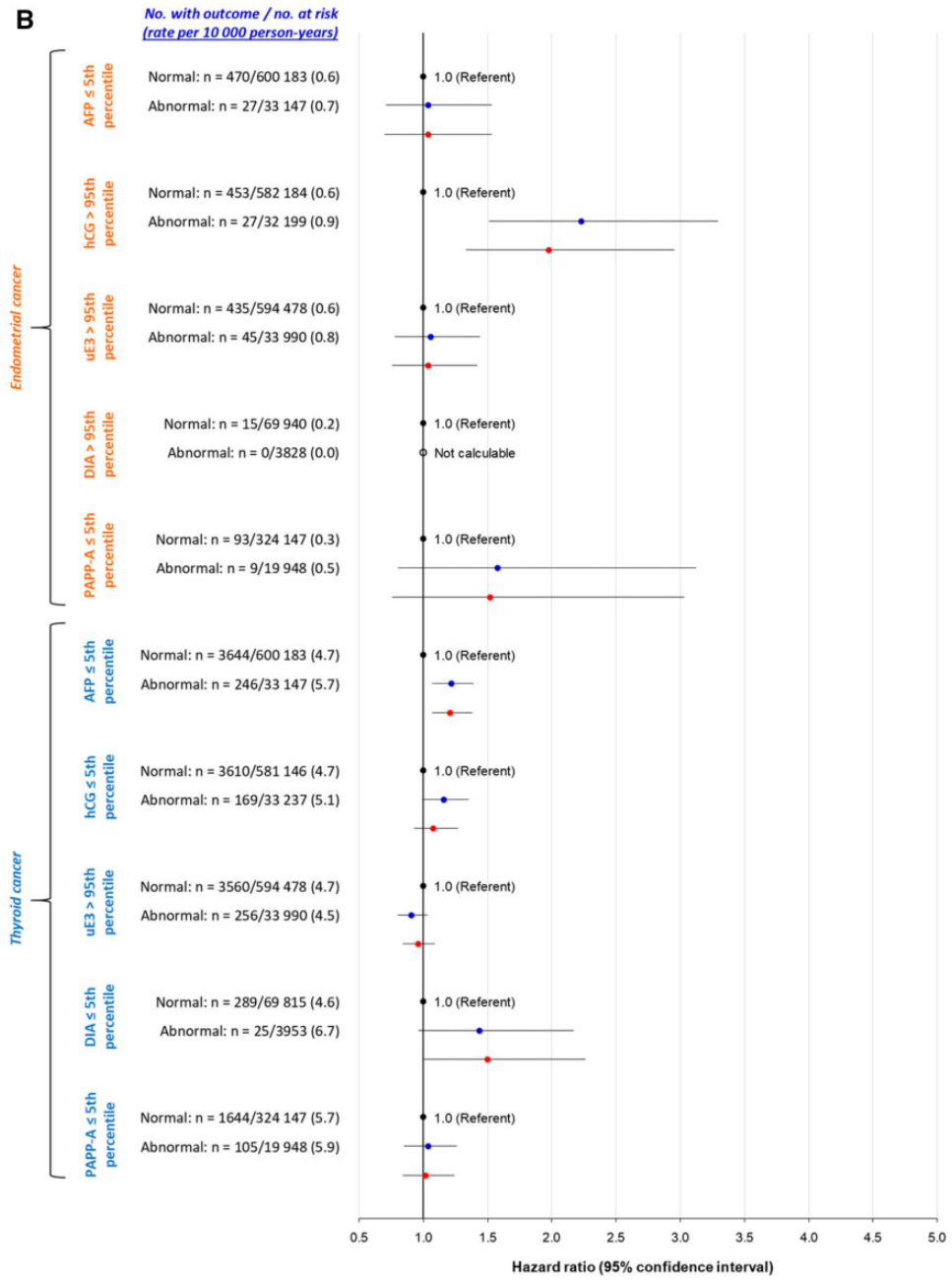

Figure 2b. Continued.

online). Cancer outcomes were identified from the Ontario Cancer Registry, which captures with a sensitivity of 98% all new cases of cancer in the entire province (21). The relation between a screening analyte and breast cancer may have differed by cancer stage or hormone receptor status, but these data were incomplete for most of the study period. Other potential confounders were considered herein, including age, parity, placental dysfunction, diabetes mellitus, fetal growth, and non-live birth pregnancy (22–24). We also considered breastfeeding status at hospital discharge and maternal weight (22). Unknown were menopausal status, oral contraceptive use, and hormone use after menopause.

Consistent with some previous studies, we found that the risk of breast cancer was lowest at the highest levels of maternal serum AFP (24,25) and hCG (26,27). The protective effect of AFP is presumably related to its antiestrogen properties (28), and hCG plays a role in cell proliferation and DNA repair (29). We did not find an association between second trimester uE3 and breast cancer, consistent with one other study (5). However, high third trimester E3 has been found protective of breast cancer (30), possibly by reducing accumulation of E1 and E2 by-products, which are carcinogenic (31). We found that lower levels of first trimester PAPP-A conferred a higher risk of breast cancer in the long term. This appears to contradict recent studies showing that PAPP-A outside of pregnancy is overexpressed in breast and other cancers, and high PAPP-A promotes tumor growth and invasion (32). We are unaware, however, of any study that has

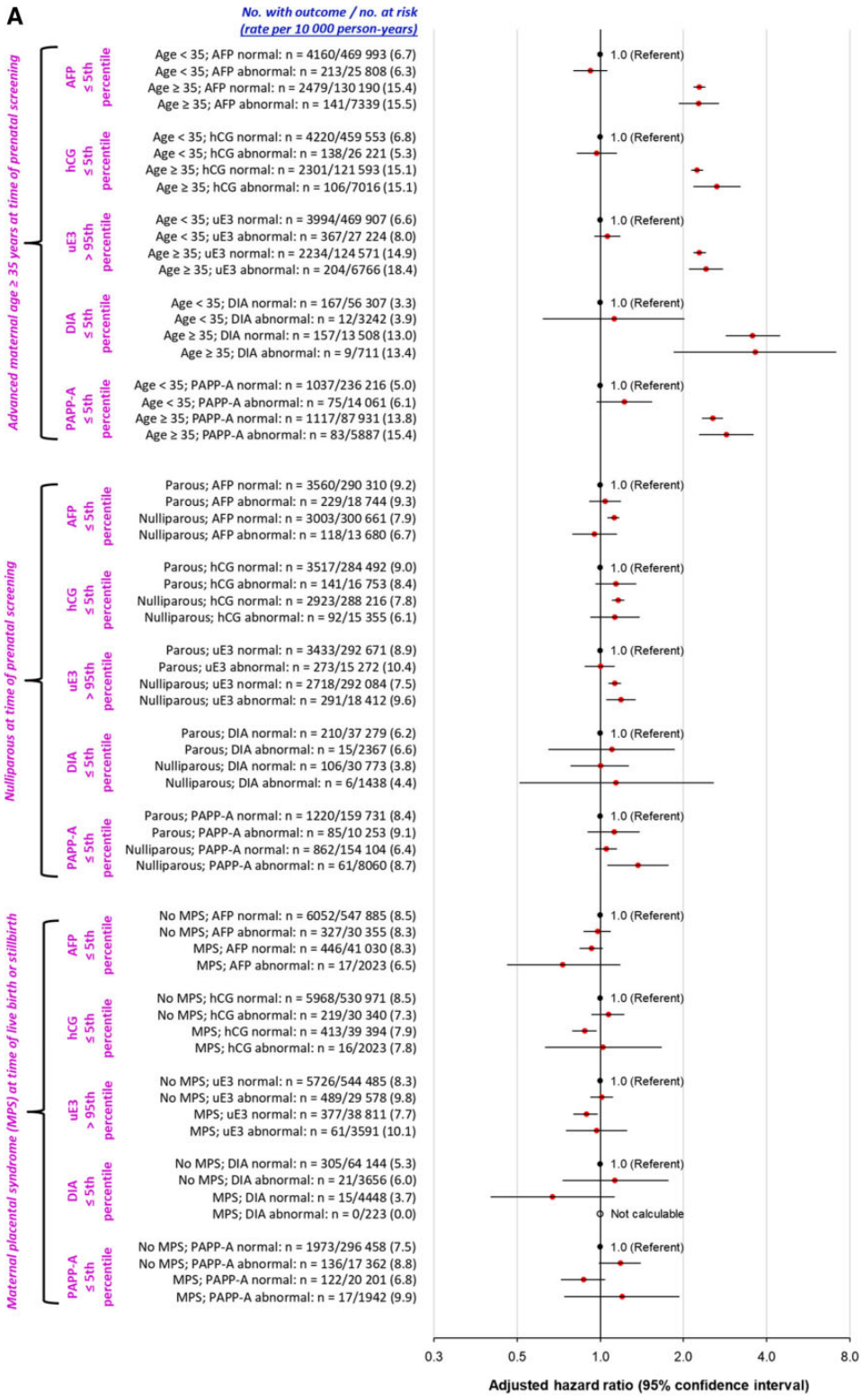

Figure 3. Risk of breast cancer arising from at least 21^{+0} weeks' gestation in the index pregnancy associated with an abnormally low alpha-fetoprotein (AFP), total human chorionic gonadotropin (hCG), dimeric inhibin A (DIA), or pregnancy-associated plasma protein A (PAPP-A) (≤5th vs >5th [referent]) or abnormally high unconjugated estriol (uE3) (>95th vs ≤95th [referent]) percentile multiple of the median, in the absence or copresence of advanced maternal age 35 years or older at time of prenatal screening (**A**, **upper**), nulliparous at time of prenatal screening (A, **middle**), maternal placental syndrome—preeclampsia, gestational hypertension, or placental abruption or infarction—at time of live birth or stillbirth (A, **lower**), chromosomal or congenital anomaly at time of live birth or stillbirth (**B**, **upper**), fetal growth restriction at time of live birth (B, **middle**), and pregnancy ending with a non-live birth outcome (B, **lower**). One pregnancy was allowed per woman. Models are adjusted for maternal age, parity, income quintile, rurality, ethnicity, gestational age, and year—each at the time of prenatal biochemical screening—as well as diabetes mellitus, chronic kidney disease, and illicit drug or tobacco use within 1 year before 21^{+0} weeks' gestation. The analysis of copresent advanced maternal age did not adjust for maternal age, and the analysis of copresent nulliparity did not adjust for parity. Censoring was on death, end of Ontario Health Insurance Plan eligibility, or arrival at the end of study as well as bilateral mastectomy.

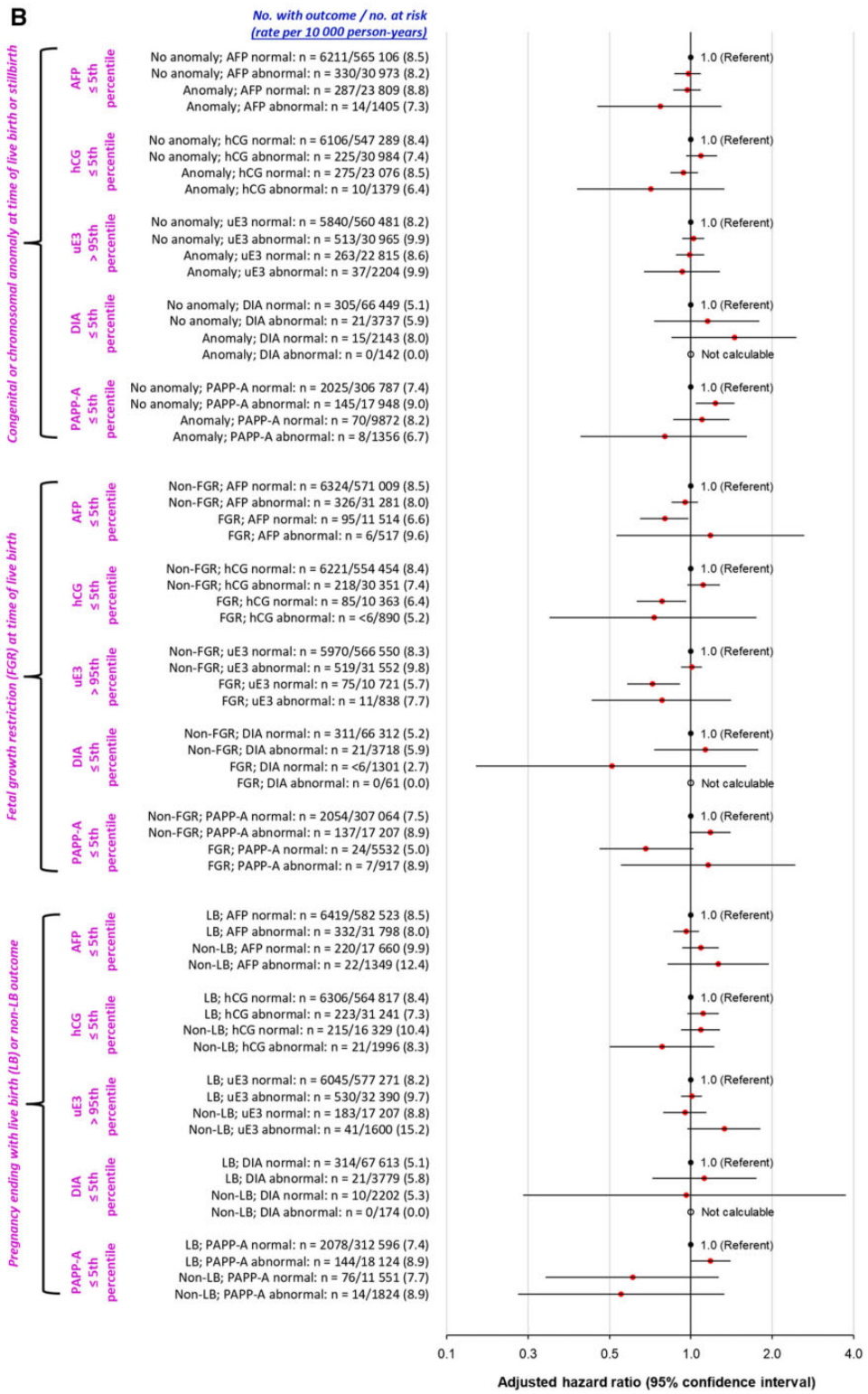

Figure 3b. Continued.

examined maternal serum PAPP-A and future cancer. Maternal placental syndrome was associated with a decreased risk of breast cancer, in line with one prior study (33) but not with another (34).

We did not find a statistically significant association between any of the hormones in this study and ovarian cancer. Maternal serum levels of certain sex steroids have been associated with a long-term risk of ovarian cancer (7,8), but little is

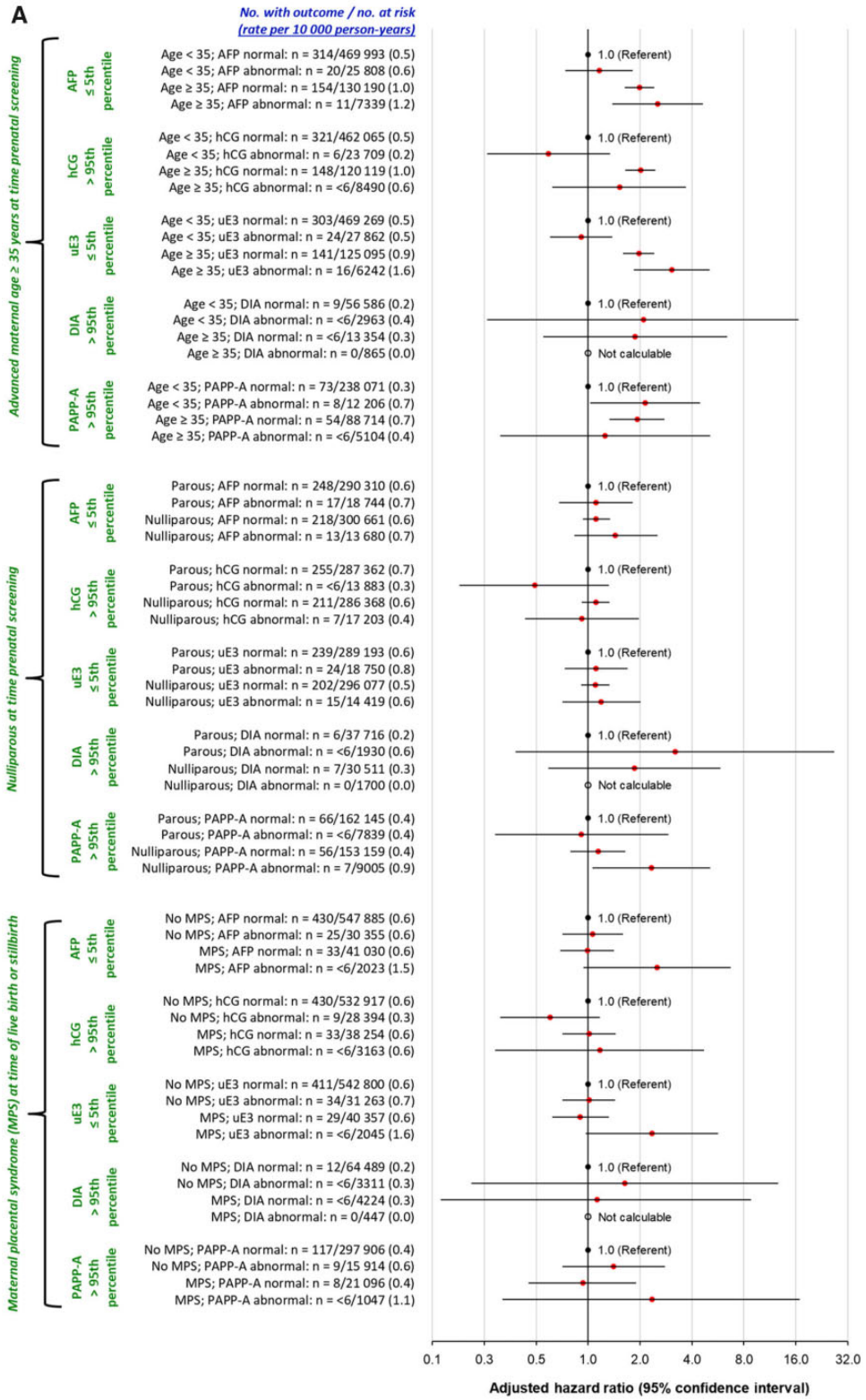

Figure 4. Risk of ovarian cancer arising from at least 21^{+0} weeks' gestation in the index pregnancy associated with an abnormally low alpha-fetoprotein (AFP) or unconjugated estriol (uE3) (≤5th vs >5th [referent]) or abnormally high total human chorionic gonadotropin (hCG), dimeric inhibin A (DIA), or pregnancy-associated plasma protein A (PAPP-A) (>95th vs ≤95th [referent]) percentile multiple of the median, in the absence or co-presence of advanced maternal age 35 years or older at time of prenatal screening (**A**, **upper**), nulliparous at time of prenatal screening (A, **middle**), maternal placental syndrome—preeclampsia, gestational hypertension, or placental abruption or infarction—at time of live birth or stillbirth (A, **lower**), chromosomal or congenital anomaly at time of live birth or stillbirth (**B**, **upper**), fetal growth restriction at time of live birth (B, **middle**), and pregnancy ending with a non-live birth outcome (B, **lower**). One pregnancy was allowed per woman. Models are adjusted for maternal age, parity, income quintile, rurality, ethnicity, gestational age, and year—each at the time of prenatal biochemical screening—as well as diabetes mellitus, chronic kidney disease, and illicit drug or tobacco use within 1 year before 21^{+0} weeks' gestation. The analysis of copresent advanced maternal age did not adjust for maternal age, and the analysis of copresent nulliparity did not adjust for parity. Censoring was on death, end of Ontario Health Insurance Plan eligibility, or arrival at the end of study as well as bilateral oophorectomy.

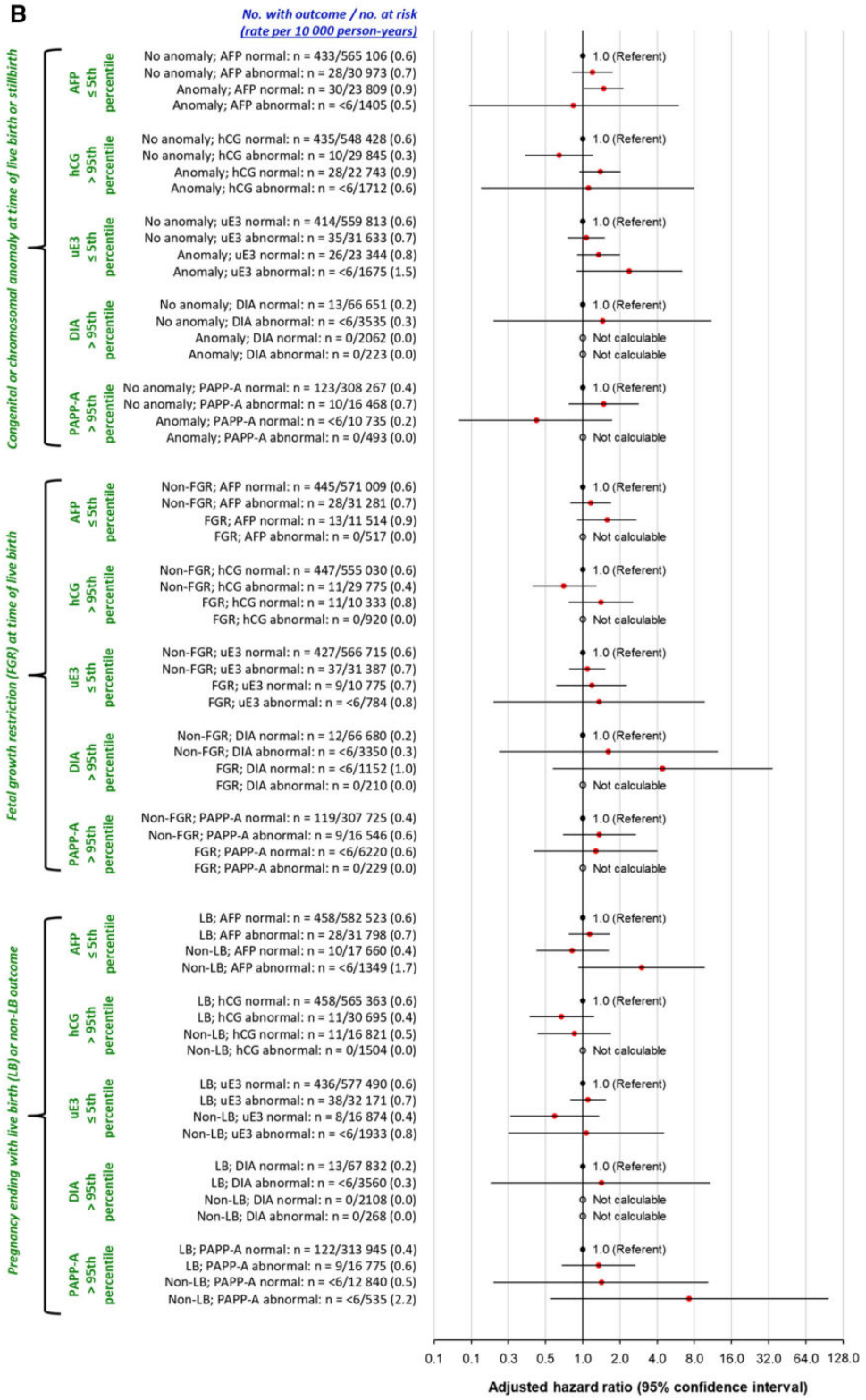

Figure 4b. Continued.

known about other maternal hormones and ovarian cancer risk. Although inhibin (35) and PAPP-A (32) may have some utility as biomarkers of some forms of ovarian cancer, their role in the pathogenesis of ovarian cancer is unknown.

Estriol was not associated with endometrial cancer in the current study. This discrepancy may be explained by varying levels of carcinogenicity between different estrogen types (30). High serum hCG conferred a greater risk of endometrial cancer

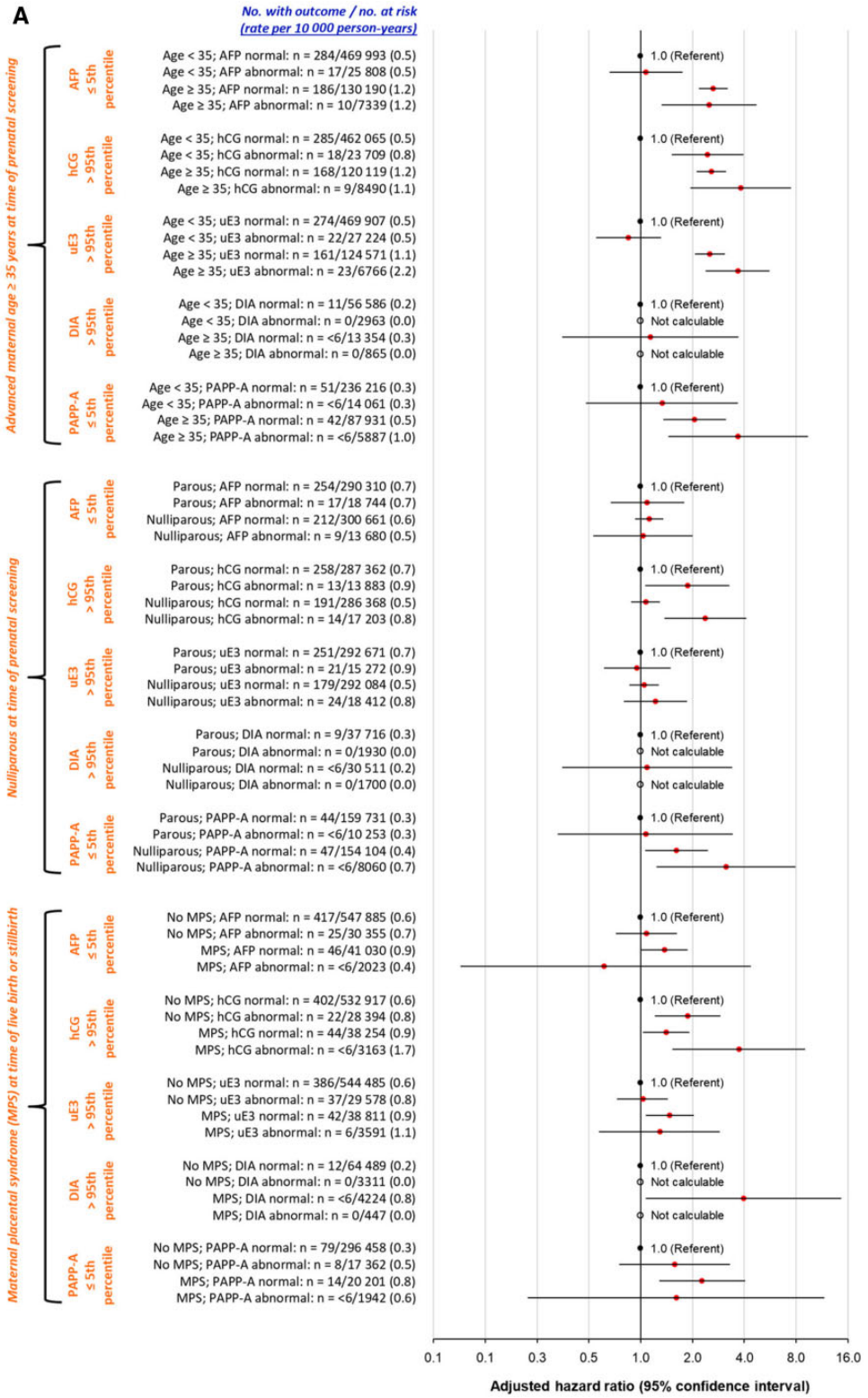

Figure 5. Risk of endometrial cancer arising from at least 21^{+0} weeks' gestation in the index pregnancy associated with an abnormally low alpha-fetoprotein (AFP) or pregnancy-associated plasma protein A (PAPP-A) (≤5th vs >5th [referent]) or abnormally high total human chorionic gonadotropin (hCG), unconjugated estriol (uE3), or dimeric inhibin A (DIA) (>95th vs ≤95th [referent]) percentile multiple of the median, in the absence or copresence of advanced maternal age 35 years or older at time of prenatal screening (**A**, **upper**), nulliparous at time of prenatal screening (A, **middle**), maternal placental syndrome—preeclampsia, gestational hypertension, or placental abruption or infarction—at time of live birth or stillbirth (A, **lower**), chromosomal or congenital anomaly at time of live birth or stillbirth (**B**, **upper**), fetal growth restriction at time of live birth (B, **middle**), and pregnancy ending with a non–live birth outcome (B, **lower**). One pregnancy was allowed per woman. Models are adjusted for maternal age, parity, income quintile, rurality, ethnicity, gestational age, and year—each at the time of prenatal biochemical screening—as well as diabetes mellitus, chronic kidney disease, and illicit drug or tobacco use within 1 year before 21^{+0} weeks' gestation. The analysis of copresent advanced maternal age did not adjust for maternal age, and the analysis of copresent nulliparity did not adjust for parity. Censoring was on death, end of Ontario Health Insurance Plan eligibility, or arrival at the end of study as well as hysterectomy.

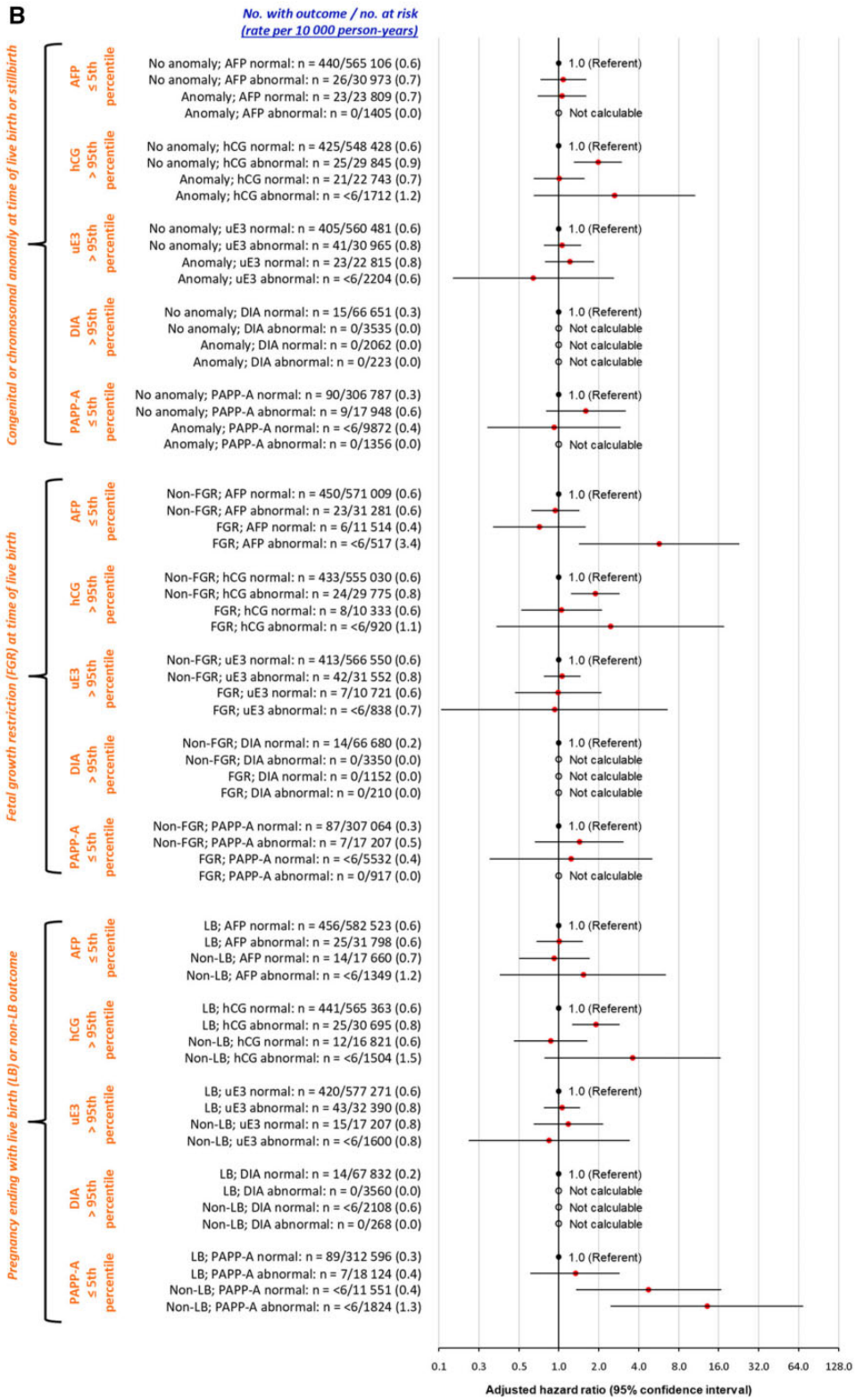

Figure 5b. Continued.

in the current study. Although the predictive value of maternal serum hCG in the long-term risk of endometrial cancer has not been widely explored, studies in women undergoing fertility treatment suggest an association between high hCG concentrations and uterine cancer (36). High hCG is also a biomarker for endometrial cancer and gestational trophoblastic disease. Even so, gestational trophoblastic disease or endometrial cancer at the time of biochemical screening could not

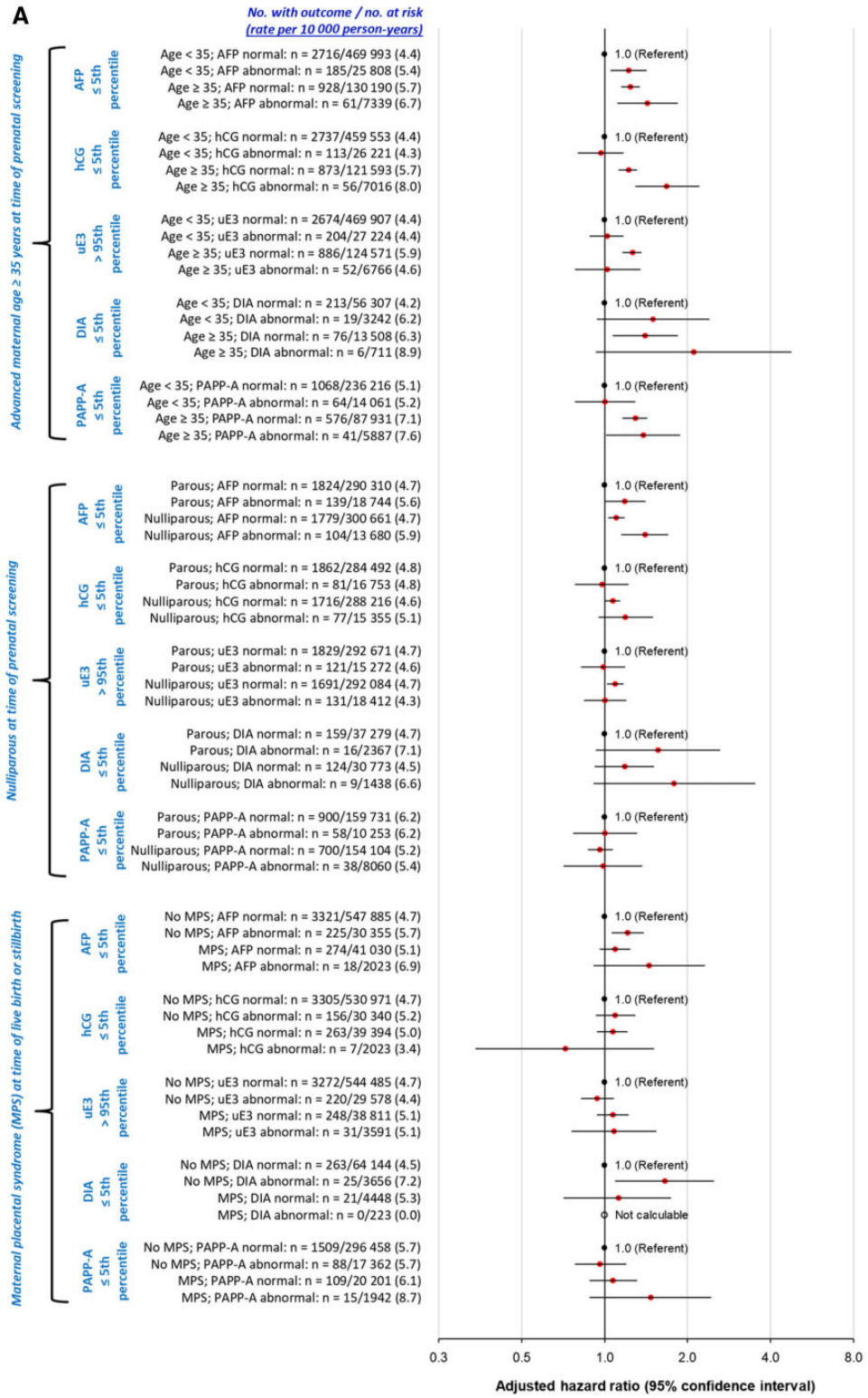

Figure 6. Risk of thyroid cancer arising from at least 21^{+0} weeks' gestation in the index pregnancy associated with abnormally low alpha-fetoprotein (AFP), total human chorionic gonadotropin (hCG), dimeric inhibin A (DIA), or pregnancy-associated plasma protein A (PAPP-A) (≤5th vs >5th [referent]) or abnormally high unconjugated estriol (uE3) (>95th vs ≤95th [referent]) percentile multiple of the median, in the absence or co-presence of advanced maternal age 35 years or older at time of prenatal screening (**A**, **upper**), nulliparous at time of prenatal screening (A, **middle**), maternal placental syndrome—preeclampsia, gestational hypertension, or placental abruption or infarction—at time of live birth or stillbirth (A, **lower**), chromosomal or congenital anomaly at time of live birth or stillbirth (**B**, **upper**), fetal growth restriction at time of live birth (B, **middle**), and pregnancy ending with a non–live birth outcome (B, **lower**). One pregnancy was allowed per woman. Models are adjusted for maternal age, parity, income quintile, rurality, ethnicity, gestational age, and year—each at the time of prenatal biochemical screening—as well as diabetes mellitus, chronic kidney disease, and illicit drug or tobacco use within 1 year before 21^{+0} weeks' gestation. The analysis of copresent advanced maternal age did not adjust for maternal age, and the analysis of copresent nulliparity did not adjust for parity. Censoring was on death, end of Ontario Health Insurance Plan eligibility, or arrival at the end of study as well as thyroidectomy.

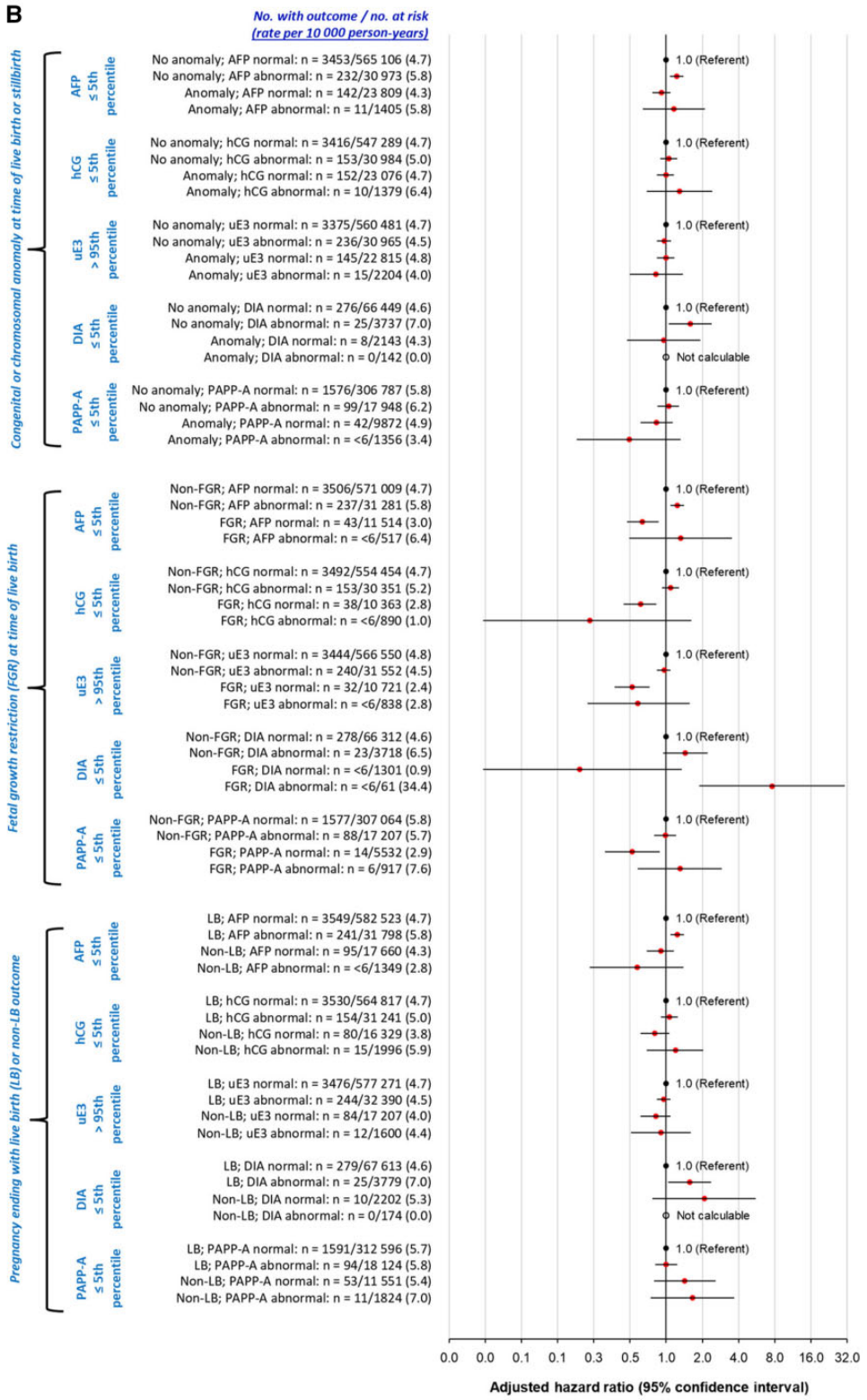

Figure 6b. Continued.

have accounted for our current findings, because the additional analysis excluding women with cancer up to 365 days after the index delivery showed a persistent greater risk of endometrial cancer with high hCG. Additionally, though rare, the joint presence of a maternal placental syndrome and abnormally high hCG was associated with a markedly greater risk of endometrial cancer. This finding is, however, inconsistent with findings from a Swedish cohort study (37) and

a Danish case-control study (38). Interestingly, the latter group did report a greater risk of endometrial cancer in association with early-onset preeclampsia at 22–33 weeks' gestation (38).

Although we are unaware of other studies on pregnancy hormones and long-term risk of maternal thyroid cancer, there is some evidence of a greater risk of thyroid carcinoma in women who had hyperemesis gravidarum, thought to be related to abnormally high levels of hCG (39).

Although the main purpose of prenatal biochemical screening has been to screen for fetal chromosomal and congenital anomalies, serum screening is also predictive of adverse pregnancy outcomes, such as preeclampsia, small-for-gestational age birthweight, and fetal death (18,23,40,41). As found herein, women with abnormal levels of hCG, AFP, or PAPP-A in early pregnancy also displayed some heightened future risk of certain types of hormone-sensitive cancers. Though appealing as a concept, the evidence to date does not support the use of prenatal serum screening to predict future cancer, and the biological mechanisms underlying these associations are not fully understood. Furthermore, whether these associations are reflective of the pregnancy state, or a perpetuated state of hormone dysregulation extending outside of pregnancy, remains to be determined.

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Notes

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A.L. Park had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: J.G. Ray, A.L. Park. Acquisition, analysis, or interpretation of data: all authors. Drafting of manuscript: J.G. Ray, A.L. Park. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: J.G. Ray, A.L. Park. Obtaining funding: J.G. Ray. Administrative, technical, or material support: J.G. Ray. Study supervision: J.G. Ray.

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