Biostatistics Project
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Review of Tubal ligation and risk of ovarian cancer data

Contraceptives are widely used and their use may span months or years, as they can be permanent (tubal ligation), and even a small effect on the risk of ovarian cancer may have a great impact on the incidence of disease in the general population. Women use contraceptives during their reproductive years; that is, between menarche and menopause. Ovarian cancer is generally a disease of post-menopausal women, with the highest incidence at ages 65 to 74 years. The age range, 35 to 69 years inclusive, captures the population that is most affected by ovarian cancer and, at the same time allows for the best recall of contraceptive usage. Ovarian cancer is related to age and the chances of having it get higher with the increase of age. As woman tend to do tubal ligation around their thirties and no other contraceptive method is usually used after that the association between ovarian cancer and tubal ligation could be an important fact. This case-control study checks if there is any association between tubal ligation (contraceptive method) and ovarian cancer.

The article by J. J. Chesang, A. K. Richardson, J. D. Potter, M. J. Sneyd and P.Coope, Association of partner vasectomy, depot medroxyprogesterone acetate and intrauterine contraceptive devices with ovarian cancer, Annals of Epidemiology. 60 (2021) 15-20 is the original article and research where all the data was collected and analyzed.

In October of 2021, Jacqueline Chesang, Ann Richardson, John Potter, Mary Sneyd, and Pat Coope of the School of Sciences of the University of Cantebury, New Zealand published a continuation of the study as at this time they added a more detailed analysis of the association of tubal ligation and the risk of ovarian cancer.

The data presented were obtained for a New Zealand nationwide population-based case-control analysis undertaken to assess the association between ovarian

cancer and depot medroxyprogesterone acetate (DMPA), intrauterine contraceptive devices (IUDs), and vasectomy of a woman's sexual partner (Chesang et al., 2021). The research involved women aged 35 to 69 years. Controls were randomly selected from the New Zealand electoral roll. Data collection was conducted between 1st May 2013 and 31st October, 2015. Data from analyses of the association between a history of tubal ligation and the risk of ovarian cancer are also presented. The researcher age-adjusted the participants for the multivariable analyses of the association between history of tubal ligation (TL) and the risk of ovarian cancer as ovarian cancer risk increase by age. *Cases* were women with newly diagnosed, histologically confirmed ovarian cancer, aged 35 to 69 years, at any stage of the disease. The *controls* consisted of women free from ovarian cancer with similar age restrictions. Controls were randomly selected from the General and Maori Electoral Rolls, frequency matched to cases by 5-year age groups.

In view of the small number of ovarian cancer cases, more controls than cases were recruited (a case-control ratio of 1:5) in order to enhance the statistical power of the study. Data were analysed using the IBM Statistical Package for the Social Sciences (IBM SPSS statis- tics 22). Descriptive statistics were used to compute frequencies and percentages. All variables collected in the study were assessed for association with the risk of ovarian cancer, adjusted for age in 5-year groups using the method of Mantel and Haenszel. When controlling for more than one variable, binary logistic regression was used. Odds ratios, 95% confidence intervals, and p-values were reported. All statistical tests were 2-sided and the risk estimates were considered statistically significant if the p-value was less than 0.05. Tests for trends were done using continuous rather than categorical variables. The collection of data were made through a questionary. Data were entered into an EXCEL spreadsheet. Frequency tables were constructed in order to aid in identifying data entry errors. These errors were corrected by referring to the answers in the questionnaires. In situations where values provided were considered unrealistic, these were treated as missing values. All identifying information was coded before analysis. To ensure that participants were at risk of first primary ovarian cancer, women with a prior history of ovarian cancer were excluded. Controls with a history of bilateral oophorectomy were also excluded because this effectively eliminates the risk of developing ovarian cancer.

Table 2
Risk of ovarian cancer in relation to specific exposures

	Cases		Controls			95% CI		
	No.	*(%)*[†]	*No.*	*(%)*[†]	OR[*]	*Lower*	*Upper*	*P*-value
Use of oral contraceptives	*(n = 152)*		*(n = 746)*					
Never	36	(24)	77	(10)	*1.00*			
Ever	116	(76)	669	(90)	0.35	0.22	0.55	<.01
Parity	*(n = 151)*		*(n = 735)*					
Nulliparous	32	(21)	85	(11)	*1.00*			
1	23	(15)	74	(10)	0.79	0.43	1.48	.57
2	44	(29)	276	(37)	0.40	0.24	0.67	<.01
3	36	(24)	188	(25)	0.53	0.30	0.94	.04
≥4	16	(11)	122	(16)	0.33	0.17	0.67	<.01
Trend test – per birth					*0.79*	*0.69*	*0.91*	*<.01*
Age at last delivery (y)	*(n = 151)*		*(n = 739)*					
Nulliparous	32	(21)	85	(12)	*1.00*			
≤25	26	(17)	98	(13)	0.80	0.43	1.51	.60
26–30	45	(30)	199	(27)	0.60	0.35	1.03	.09
31–35	29	(19)	216	(29)	0.34	0.19	0.60	<.01
>35	19	(13)	141	(19)	0.35	0.19	0.66	<.01
Trend test – per year of age					*0.94*	*0.90*	*0.97*	*<.01*
Breastfeeding (Parous)	*(n = 119)*		*(n = 655)*					
Never	16	(13)	46	(7)	*1.00*			
Ever	103	(87)	609	(93)	0.49	0.27	0.92	.04
Endometriosis	*(n = 150)*		*(n = 733)*					
No	126	(84)	687	(94)	*1.00*			
Yes	24	(16)	46	(6)	2.75	1.62	4.68	<.01
Infertility	*(n = 149)*		*(n = 730)*					
No	135	(91)	704	(96)	*1.00*			
Yes	14	(9)	26	(4)	3.05	1.52	6.12	<.01
Familial predisposition[‡]	*(n = 150)*		*(n = 737)*					
No	95	(63)	519	(70)	*1.00*			
Yes	55	(37)	218	(30)	1.43	0.98	2.08	.08
PMH[§] use	*(n = 151)*		*(n = 744)*					
No	117	(77)	627	(84)	*1.00*			
Yes	34	(23)	117	(16)	1.74	1.09	2.75	.03
Talcum use[‖]	*(n = 149)*		*(n = 740)*					
No	97	(65)	546	(74)	*1.00*			
Yes	52	(35)	194	(26)	1.54	1.05	2.25	.03
Tubal ligation	*(n = 149)*		*(n = 746)*					
No (None)	121	(82)	600	(80)	1.00			
Yes	27	(18)	146	(20)	0.98	0.62	1.57	.963

[*] Adjusted for age in 5-y groups
[†] Percentages are of total stated
[‡] Personal history and/or history of breast, ovarian, endometrial or colorectal cancer in a first-degree relative
[§] Post-menopausal hormone
[‖] Ever-use of talcum powder in the perineal area

Final analysis by researcher (1)

Ovarian Cancer Risk and Tubal Ligation – It was found that tubal ligation is not significant for the risk of Ovarian Cancer as the p-value associated with it was 0.963, higher than 0.05. The OR was 0.98.

Final analysis by researcher (2)

Table 4
Risk of ovarian cancer in women with history of tubal ligation.

	Cases		Controls			95% CI		
	No.	*(%)*[2]	*No.*	*(%)*[2]	OR[1]	*Upper*	*Lower*	*P*-value
Tubal Ligation								
No	121	(82)	600	(80)	1.00			
Yes	27	(18)	146	(20)	0.98	0.62	1.57	0.963
Age at TL								
Never had TL	121	(82)	600	(80)	1.00			
≤30 (22-30)	10	(7)	57	(8)	0.94	0.46	1.92	0.999
31-35	8	(5)	46	(6)	0.92	0.42	2.02	0.997
36-40	7	(5)	26	(3)	1.37	0.58	3.28	0.638
>40 (41-56)	2	(1)	17	(2)	0.581	0.13	2.54	0.673
Trend Test- per year					1.001	0.929	1.079	0.980
Years Since TL								
Never had TL	121	(82)	600	(80)	1.00			
≤10 (1-10)	2	(1)	10	(1)	1.01	0.21	4.76	0.697
11-20	6	(4)	18	(2)	1.40	0.53	3.66	0.675
21-30	9	(6)	54	(7)	0.88	0.42	1.86	0.877
>30 (31-45)	10	(7)	64	(9)	0.91	0.44	1.91	0.953
Trend Test – per year					*0.994*	*0.925*	*1.067*	*0.860*

[1] Adjusted for age in five-year groups
[2] Percentages are of total stated

Ovarian Cancer Risk and Tubal Ligation – It was found that tubal ligation is not significant for the risk of Ovarian Cancer as the p-value associated with it was 0.963, higher than 0.05. The OR was 0.98.

Stratified by age – It was found that tubal ligation is not significant for the risk of Ovarian Cancer as the p-value associated with it by the four divisions did not have a p-value lower than 0.05.

Review of Data Extraction

The raw data was consistent with 898 rows and 172 columns. The most important columns for this analysis were: StudyNo (ID), StudyArm (Case or Control), Tuballigation (presence or absence of tubal ligation), AgeTLGrouped (tubal ligation grouped by age). For the StudyArm, 0 = control and 1 = Cases. On Tuballigation 1 = yes, 2 = No, 888 = Missing. For TL age grouped 1 = 22-30, 2 = 31-35, 3 = 36-40, 4 = 41-56, 888 = no tubal ligation. We can visualize better in

Table 1 and Table 2. It was found 4 missing values, all of them were in the Case, which brings the total of 125 observations but they were not computed on the regression to not introduce bias.

Table 1 Risk of Ovarian Cancer

	CASE	CONTROL
TL = yes	121	600
TL = No	27	146
Total	148	746

Table2 Risk of Ovarian Cancer At Age of TL

	CASE	CONTROL	TOTAL
Age at TL			
22-30 years	10	57	67
31-35 years	8	46	54
36-40 years	7	26	33
41-56 years	2	17	19

Table3 Risk of Ovarian Cancer Since tubal ligation

	CASE	CONTROL	TOTAL
Years after TL			
1-10 years	2	10	12
years	6	18	24
36-40 years	9	54	63
41-56 years	10	64	74

Discussion of Findings

To account for the increasing risk of ovarian cancer with age, the data on “Age at tubal Ligation” was stratified into four age groups: 1 = 22-30, 2 = 31-35, 3 = 36-40, and 4 = 41-56. This stratification aimed to mitigate potential biases in the results by reducing confounding variables as much as possible. The “Age” variable was stratified into 7 groups, with a space of 5 years in between. Group 1 = 39-39, 2= 40-44, 3= 45-49, 4=50-54, 5=55-59, 6=60-64, 7=65-69.

The initial analysis of researcher 1 examines the association using odds ratios. Odds ratios were utilized to assess the strength of association between variables and the degree of their association. The results closely mirrored those of the original paper and are summarized in Table 4. While the article did not explicitly specify the overall alpha level used or the side of the side of the hypothesis, a default significance threshold of 0.05 was applied in my analysis.

Table 4

	Outcome + <S3: AsIs>	Outcome - <S3: AsIs>	Total <S3: AsIs>	Odds <S3: AsIs>
Exposed +	27	121	148	0.22 (0.14 to 0.32)
Exposed -	146	600	746	0.24 (0.20 to 0.29)
Total	173	721	894	0.24 (0.20 to 0.28)

Point estimates and 95% CIs:

Exposure odds ratio	0.92 (0.58, 1.44)
Attrib fraction (est) in the exposed (%)	-9.04 (-78.96, 31.70)
Attrib fraction (est) in the population (%)	-1.41 (-8.98, 5.63)

Uncorrected chi2 test that OR = 1: chi2(1) = 0.140 Pr>chi2 = 0.709
Fisher exact test that OR = 1: Pr>chi2 = 0.820
Wald confidence limits
CI: confidence interval

We are assessing if there is no difference between the proportions of ovarian cancer cases in the tubal ligation and non-tubal ligation groups (Pie1 = Pie2). As we are just reporting the OR the hypothesis is H0: OR=1 and H1: OR different from 1. However, the resulting p-value did not reach significance. Thus, we cannot conclude an association between ovarian cancer and tubal ligation.

This lack of association might stem from the fact that ovarian cancer incidence does not remain constant across age groups. Age serves as a confounding factor in this scenario. Therefore, the observed p-value might have been inflated due to the influence of age. To mitigate this issue and ascertain the true association, it would be prudent to control for age in further analyses.

As the data did not provide enough values to do a Mantel-Haenszel test and was stated in the article they adjusted for age in 5 years group (using MH), a logistic regression was made and the results were similar to the just OR. “Tuballigation” was found not significant when controlling for age-adjusted by 5 years group with a p-value of 0.757. “Age grouped” use as number and was not found significant as well when controlling tubal ligation. The OR for tubal ligation was 1.07. The article stated a OR of 0.98 and a p-value of 0.963. The regression coefficient was a little higher and p-value a little lower.

```
Call:
glm(formula = StudyArm ~ TubalLigation + AgeGrouped, family = "binomial",
    data = yrs_sincetl)

Coefficients:
             Estimate Std. Error z value Pr(>|z|)
(Intercept)   -1.69834    0.55740  -3.047  0.00231 **
TubalLigation  0.07405    0.23932   0.309  0.75701
AgeGrouped    -0.01125    0.05238  -0.215  0.82988
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 802.38  on 893  degrees of freedom
Residual deviance: 802.19  on 891  degrees of freedom
  (4 observations deleted due to missingness)
AIC: 808.19

Number of Fisher Scoring iterations: 3

  (Intercept) TubalLigation    AgeGrouped
    0.1829871     1.0768578     0.9888085
                   2.5 %    97.5 %
(Intercept)   0.06137051 0.5456086
TubalLigation 0.67367010 1.7213512
AgeGrouped    0.89232807 1.0957207
```

In the second section of Table 4 of the article, the aim was to explore the relationship between ovarian cancer and the age at tubal ligation controlling for age. The results found by the regression are very similar to the authors. The regression was made using Age at tubal ligation having never had TL as default group and controlling for age. I used AgeGrouped. The outcomes are presented in Table 5. Since none of the p-values were found to be significant across any age group, we can conclude, as the article, that there is no apparent association between ovarian cancer and the age at which tubal ligation occurs.

Table 5

Risk of Ovarian cancer in women at Age of TL

	CASE	CONTROL	OR	CI OR	P-value
Age at TL					
22-30	10	57	0.877	0.431 – 1.799	0.718
31-35	8	46	0.868	0.397 – 1.910	0.724
36-40	7	26	1.334	0.568 – 3.171	0.505
41-56	2	17	0.586	0.133 – 2.585	0.479
Never had TL	121	600	-	-	-

```
Call:
glm(formula = StudyArm ~ AgeGrouped + factor(AgeTLGrouped_new),
    family = "binomial", data = fit2_co_cancer)

Coefficients:
                          Estimate Std. Error z value Pr(>|z|)
(Intercept)              -1.560442   0.257389  -6.063 1.34e-09 ***
AgeGrouped               -0.008995   0.052561  -0.171    0.864
factor(AgeTLGrouped_new)2 -0.126766   0.364559  -0.348    0.728
factor(AgeTLGrouped_new)3 -0.137671   0.400480  -0.344    0.731
factor(AgeTLGrouped_new)4  0.294542   0.438560   0.672    0.502
factor(AgeTLGrouped_new)5 -0.530941   0.755576  -0.703    0.482
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 802.38  on 893  degrees of freedom
Residual deviance: 801.02  on 888  degrees of freedom
  (4 observations deleted due to missingness)
AIC: 813.02

Number of Fisher Scoring iterations: 4

             (Intercept)               AgeGrouped factor(AgeTLGrouped_new)2
factor(AgeTLGrouped_new)3 factor(AgeTLGrouped_new)4 factor(AgeTLGrouped_new)5
                0.2100431                 0.9910456                 0.8809394
0.8713854                 1.3425110                 0.5880513
                            2.5 %    97.5 %
(Intercept)               0.1268291 0.3478548
AgeGrouped                0.8940327 1.0985854
factor(AgeTLGrouped_new)2 0.4311544 1.7999449
factor(AgeTLGrouped_new)3 0.3974854 1.9102904
factor(AgeTLGrouped_new)4 0.5683483 3.1711821
factor(AgeTLGrouped_new)5 0.1337421 2.5856058
```

The last part of the article table 4 focuses on the risk of Ovarian cancer and the years after the tubal ligation controlling for age. The results found by the regression are very similar to the authors. The regression was made using Age since tubal ligation having never had TL as default group and controlling for age. I used AgeGrouped. The outcomes are presented in Table 6.

Table 6

Risk of Ovarian cancer in women with history of tubal ligation on Years since TL

	CASE	CONTROL	OR	OR CI	P-value
Years since TL					
1-10	2	10	0.9949	0.21 - 4.66	0.995
11-20	6	18	1.6539	0.64 - 4.25	0.297
21-30	9	54	0.8244	0.40 - 1.72	0.610
31-45	10	64	0.7712	0.39 - 1.55	0.484
Never had TL	121	600	-	-	-

One more time the results found by this second regression are similar to the authors. The results are found in table 6. No p-value associated to any strata was found. We can conclude that there is no association between ovarian cancer and years after the tubal ligation.

```
Call:
glm(formula = StudyArm ~ AgeGrouped + factor(YearsTLGrouped_new),
    family = "binomial", data = yrs_sincetl)

Coefficients:
                             Estimate Std. Error z value Pr(>|z|)
(Intercept)                -1.611350   0.266362  -6.049 1.45e-09 ***
AgeGrouped                  0.002251   0.054424   0.041    0.967
factor(YearsTLGrouped_new)2 -0.005031   0.784975  -0.006    0.995
factor(YearsTLGrouped_new)3  0.503170   0.482077   1.044    0.297
factor(YearsTLGrouped_new)4 -0.192988   0.377927  -0.511    0.610
factor(YearsTLGrouped_new)5 -0.259732   0.371153  -0.700    0.484
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 802.38  on 893  degrees of freedom
Residual deviance: 800.48  on 888  degrees of freedom
  (4 observations deleted due to missingness)
AIC: 812.48

Number of Fisher Scoring iterations: 4

               (Intercept)                 AgeGrouped factor(YearsTLGrouped_new)2
factor(YearsTLGrouped_new)3 factor(YearsTLGrouped_new)4 factor(YearsTLGrouped_new)5
                  0.1996179                  1.0022535                  0.9949819
1.6539567                  0.8244918                  0.7712585
                               2.5 %    97.5 %
(Intercept)                0.1184327 0.3364553
AgeGrouped                 0.9008480 1.1150740
factor(YearsTLGrouped_new)2 0.2136207 4.6343304
factor(YearsTLGrouped_new)3 0.6429529 4.2547021
factor(YearsTLGrouped_new)4 0.3930917 1.7293336
factor(YearsTLGrouped_new)5 0.3726266 1.5963422
```

Conclusion

I believe the concern of Age as a confounding factor in any cancer is legit and no one has double on it. For this particular study, it was found that tubal ligation and ovarian cancer have no association and the replication shows that the results found by the authors are valid unless you regress using age grouped by 5 years as a FACTOR.

The replication was made based on Age grouped into 5 years, as stated in Table 4 of the article. It was fitted Age at TL, and years since TL as a NUMERIC value. On this stance, NO significant difference was found. Only the crude radio was

computed and the difference is almost none between crude and controlling for Age-grouped.

An interesting finding was that when I regressed the age-grouped by 5 years as a FACTOR. I found Age group 4 (50 to 54 years) significant. The significance was at a p-value of 0.01 and its OR is 2. The same results were found in all regression using age-grouped as a factor. That contradicts the article that states that tubal ligation and Ovarian cancer it's not linked.

```
Call:
glm(formula = StudyArm ~ TubalLigation + factor(AgeGrouped),
    family = "binomial", data = yrs_sincetl)

Coefficients:
                   Estimate Std. Error z value Pr(>|z|)
(Intercept)        -2.41053    0.71071  -3.392 0.000695 ***
TubalLigation       0.01781    0.24086   0.074 0.941055
factor(AgeGrouped)2  0.75015    0.61078   1.228 0.219379
factor(AgeGrouped)3  0.69956    0.58637   1.193 0.232858
factor(AgeGrouped)4  1.35950    0.55994   2.428 0.015185 *
factor(AgeGrouped)5  0.69579    0.56224   1.238 0.215884
factor(AgeGrouped)6  0.65162    0.56637   1.151 0.249933
factor(AgeGrouped)7  0.59585    0.57126   1.043 0.296925
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 802.38  on 893  degrees of freedom
Residual deviance: 790.57  on 886  degrees of freedom
  (4 observations deleted due to missingness)
AIC: 806.57

Number of Fisher Scoring iterations: 4

       (Intercept)       TubalLigation factor(AgeGrouped)2 factor(AgeGrouped)3
factor(AgeGrouped)4 factor(AgeGrouped)5 factor(AgeGrouped)6 factor(AgeGrouped)7
        0.08976814          1.01796941          2.11732036          2.01285826
3.89422965          2.00530052          1.91863868          1.81457021
                        2.5 %     97.5 %
(Intercept)         0.02229267  0.3614784
TubalLigation       0.63491524  1.6321261
factor(AgeGrouped)2 0.63956905  7.0094785
factor(AgeGrouped)3 0.63781454  6.3523142
factor(AgeGrouped)4 1.29956674 11.6692926
factor(AgeGrouped)5 0.66619797  6.0360889
factor(AgeGrouped)6 0.63226393  5.8222116
factor(AgeGrouped)7 0.59227070  5.5593920
```