American Journal of Biochemistry and Biotechnology

Original Research Paper

Association Between Cancer Screening Results Using Single Nucleotide Polymorphism and Cancer Incidence Rate in Korean Women

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Article history
Received: 20-06-2023
Revised: 07-09-2023
Accepted: 09-09-2023

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Abstract: In this study, we investigated the usefulness of Single Nucleotide Polymorphism (SNP) testing in assessing cancer susceptibility in women by evaluating correlations between SNP testing results and cancer incidence rates. SNP testing was conducted on blood samples of women who underwent health examinations commissioned by medical institutions in the Republic of Korea in 2017 using real-time polymerase chain reaction with OpenArray testing. The SNP panel included susceptibility testing for lung, stomach, colorectal, breast, and thyroid cancers. By comparing the proportions of the normal, cautionary, and warning ranges for these five types of cancer obtained from OpenArray testing with the cancer incidence rates for women in 2017, as reported by the national cancer information center, the practical preventive potential of SNP-based testing was evaluated. Cancer susceptibility in women was the highest for breast cancer, followed by thyroid, colorectal, gastric, and lung cancers. These five types of cancer showed the same trend for cancer incidence in 2017. Based on cumulative percentages of the 5-year cancer prevalence (2013-2017) in Korean women, thyroid cancer ranked first, followed by breast, colon, gastric, and lung cancers. Although the breast and thyroid cancer ordinals differed, their proportion was 49.4% higher than that of the other three cancer types for both the 2017 and 5-year incidence. The high rate of 95.3% in the caution and warning intervals for breast and thyroid cancers in the OpenArray test results suggests a correlation with the reported cancer incidence in 2017. These results indicate that SNP testing, although not aimed directly at diagnosing specific diseases in direct-to-consumer tests or health check-ups, can help individuals identify their genetic susceptibility to cancer, thus allowing them to implement preventive measures.

Keywords: Cancer Risk, Genetic Testing, Single Nucleotide Polymorphism, Women, Korea

Introduction

Single-nucleotide polymorphisms (SNPs) are variations in bases in DNA sequences among individuals, which allow for the tracking of combinations of genes in individuals. To evaluate SNPs, genetic tests must be performed (Perkel, 2008). Among such tests, SNP testing using the OpenArray (OA) method is considered highly valuable. It surpasses the levels of existing Polymerase Chain Reaction (PCR) technologies, allowing for absolute quantification of DNA samples without the need for standard curves. It exhibits a sensitivity greater than 10^6 and enables extremely accurate absolute quantification per target reaction in each sample droplet. Hence, SNP testing using the OA method is highly useful (Dong *et al*., 2013).

This study aimed to investigate the utility of SNP testing by evaluating the correlation between testing for SNPs related to cancers i.e., cancer susceptibility and cancer incidence rates in women. We conducted SNP testing on health screening samples from women commissioned by medical institutions in the Republic of Korea in 2017. Herein, the Bio-core SNP female cancer susceptibility test panel was utilized. The panel employs

the OA method, which is a real-time PCR-based SNP genotyping technology developed by Thermo Fisher Scientific (Waltham, MA, USA). The assay utilizes a multi-well plate that integrates specific primers and two probes, each labeled with a different fluorescent dye, for a particular SNP region. After extracting DNA from blood, the DNA is mixed with the content of the OA plate that contains the specific primers and probes. The primers bind to the target SNP region and the amplified product binds to the probe labeled with a fluorescent dye, generating a signal. The signal is then measured using a laser and analyzed by software to determine the specific genotype at the targeted SNP (Genome Analysis, 2023) https://genolifecare.com/technology/1100_openarray.php).

The OA panel used in this study consists of susceptibility tests for five types of cancers: Lung, gastric, colorectal, breast, and thyroid cancer. By comparing the OA panel proportions of normal, cautionary, and warning ranges for these five types of cancer with the 2017 cancer incidence rates for women provided by the National Cancer Information Center, we aimed to analyze whether SNP testing could provide practically useful information for early diagnosis or prevention of cancer.

Materials and Methods

Study Subjects

The study involved analysis of 5,870 EDTA blood samples from female health-screening participants aged 20-85 years. These samples were obtained from affiliated medical institutions in the Republic of Korea that commissioned women's cancer susceptibility assessments from January 2, 2017, to December 31, 2017. This was a retrospective study that did not involve the use of patients' personal information and institutional IRB approval for waiver of consent was obtained. Data from the National Cancer Information Center for the year 2017 and the previous four years were collected for comparison purposes. The 2017 data from the National Cancer Information Center were publicly released in 2020.

OA Panel Composition

The panel for female cancer susceptibility testing was designed to examine SNPs for five types of cancer: Lung, gastric, colon, breast, and thyroid cancer (Table 1).

For lung cancer testing, three genes were examined. CHRNA5 not only directly influences lung cancer development but also contributes to lung cancer susceptibility through smoking habits and chronic obstructive pulmonary disease. ERBB2 is involved in overproduction of the HER2 protein and is associated with lung cancer development. CHRNA3 is a susceptibility gene for lung diseases, including lung cancer (Tatem *et al*., 2004; Amos *et al*., 2008; Young *et al*., 2008).

CDH1 is associated with susceptibility to gastric cancer and is related to tumor suppressor genes. ESR1 is associated with tumor necrosis factor and is over-expressed in gastric cancer patients. MDM2 is associated with p53 related to protein composition, involved in metabolic interactions, and linked with the development of gastric cancer (Grady *et al*., 2000; Moll and Petrenko, 2003).

For colorectal cancer susceptibility, the SNP rs961253 and the genes CDH1 and COLCA1 were analyzed. Rs961253 is a biomarker without a known gene; nevertheless, numerous studies have reported that it affects the development of colorectal cancer. CDH1 is related to E-cadherin and is involved in cell tissue formation; its expression is associated with colorectal cancer progression. COLCA1 has been associated with colorectal cancer susceptibility (Pittman *et al*., 2008; Zheng *et al*., 2012).

For breast cancer, the analysis included biomarkers rs13387042 and rs2046210 and variants in CASC16 and FGFR2. The biomarkers rs13387042 and rs2046210 do not have known genes associated with them, but several studies have shown that they influence the development of breast cancer. CASC16 is a Long, Non-Coding (LNC) RNA gene associated with breast cancer. FGFR2 is involved in cell growth and differentiation and affects breast cancer differentiation and progression (Easton *et al*., 2007; Han *et al*., 2011; Lin *et al*., 2014).

For thyroid cancer, variants in FOXE1, NRG1, and DIRC3 were analyzed. FOXE1 is associated with transcriptional activity and is involved in the genetic susceptibility and carcinogenic mechanisms of thyroid cancer. NRG1 is associated with signal transduction and plays a role in the susceptibility and expression of thyroid cancer. DIRC3 encodes a lncRNA that is associated with the onset of thyroid cancer (Jones *et al*., 2012; Estrada-Florez *et al*., 2016).

Table 1: Biomarkers and genes for five cancer types in women

Cancer	Biomarkers and genes			
Lung cancer	CHRNA3	CHRNA5	ERBB2	
Stomach cancer	CDH1	ESR1	MDM2	
Colorectal cancer	rs961253	CDH1	COLCA1	
Breast cancer	rs13387042	rs2046210	CASC16	FGFR2
Thyroid cancer	FOXE1	NRG1	DIRC3	

DNA Extraction

DNA extraction was performed using the Tianlong nucleic acid extraction kit (Xi'an, China) for whole-blood samples. Next, the estimation of DNA concentration was performed using a NanoDrop device.

OA Test Method

The OA test was conducted on a clean bench. Prior to the test, the frozen TaqMan OA Genotyping Plate was thawed at room temperature (18-24°C) for 20 min. TaqMan OA Genotyping Master Mix (2.6 μL) was dispensed into each well of the Accufill 384-well plate. Next, DNA samples (2.6 μL per well) prepared for testing were dispensed into each well. In the last well of the Accufill 384-well plate, the negative control and TaqMan OA genotyping master mix reagents were dispensed for quality control. Then, the plate was sealed with a 384-well sealing foil sheet and centrifuged at 1000 rpm for 3 min.

After centrifugation, the 384-well sealing foil sheet was removed from the Accufill 384-well plate, which was then inserted into the QuantStudio 12K Flex Accufill System. The packaging of the TaqMan OA genotyping plate (thawed) was carefully removed without touching the plate sub-array. It was attached to the QuantStudio 12K Flex Accufill System and the system was initiated.

The dispensed OA plate was positioned on the OA press using the QuantStudio 12k flex autofill system. After removing the vinyl inside the lid marked in red, the lid was placed in position and pressed using the press function for 10 sec to attach the lid to the OA plate. The OA plate with the lid attached was then tilted and the tip of the immersion fluid was positioned behind the plate opening. The immersion fluid was slowly injected. Once the fluid filled the OA plate, the injection was stopped and the opening was plugged to prevent leakage. Any fluid spilled from the OA plate was wiped off with gauze. The covered portion of the lid was not touched and it was kept as clean as possible.

The plate was attached to the OA plate holder of the QuantStudio 12K flex real-time PCR system and the barcode was scanned using the operating program. Once the recognition was complete, the “run" button was clicked to initiate real-time PCR. After the test was completed, a genotyping analysis was performed.

Genotyping Analysis

Analysis of the test results was conducted using the TaqMan Genotyper 1.3.1 program. The call rate was checked based on SNPs associated with the five types of cancer. Analysis was only carried out if the call rate was 100%; otherwise, a retest was performed. Call rate is a metric used in genetic panel testing to indicate how successfully genetic information has been called or identified during the testing process. It assesses the extent to which genetic data may be missing or inaccurately identified for various reasons during the test. A higher call rate, closer to 100%, signifies higher accuracy and reliability in the test results (Ragazzo *et al*., 2021).

For breast cancer, analysis was performed on SNPs rs2046210, rs13387042, rs1801157, rs3803662, and rs2981582. The signals for rs2046210 G > A, rs13387042 A > C·G > T, rs1801157 C > T, rs1801157 C > T, rs3803662 A > C·G and rs2981582 A > G were analyzed (Gu *et al*., 2013; Li *et al*., 2018; Thanh *et al*., 2018).

For thyroid cancer, analysis was performed on SNPs rs965513, rs2439302, rs1867277, rs966423 and rs116909374. The signals for rs965513 A > C·G·T, rs2439302 G > C, rs1867277 A > G, rs966423 C > G·T and rs116909374 C > T were analyzed (Wang *et al*., 2016; He *et al*., 2018; Jendrzejewski *et al*., 2019).

The SNPs analyzed for colorectal cancer were rs4444235, rs4939827, rs7014346, rs9929218, rs3802842, rs10411210, rs16892766, rs961253 and rs6983267. The specific variations for each SNP were as follows: rs4444235 T > C, rs4939827 T > A·C, rs7014346 A > C·G, rs9929218 G > A, rs3802842 C > A, rs10411210 C > T, rs16892766 A > C, rs961253 C > A and rs6983267 G > T (Liu *et al*., 2014; Yao *et al*., 2015).

The SNPs analyzed for gastric cancer were rs35572355, rs1800629, rs121964876, rs121964874, and rs1801133. The specific variations for each SNP were as follows: rs35572355 G > A·C·T, rs1800629 G > A, rs121964876 G > A·T, rs121964874 C > A·G·T and rs1801133 G > A·C (Lin *et al*., 2015).

The SNPs analyzed for lung cancer were rs1801133, rs16969968, rs121913469, rs3834129, rs1051730 and rs121434568. The specific variations for each SNP were as follows: rs1801133 G > A·C, rs16969968 G > A, rs121913469 TT > CC, rs3834129 DelAGTAAG >-, rs1051730 G > A and rs121434568 T > A·G (Pandey *et al*., 2017).

Results

The female cancer susceptibility test panel was used to examine the SNPs related to five types of cancer and the risk levels of the results were as follows. A range of 1.00-1.49 indicated normal, 1.50-1.99 indicated caution, and 2.00 or higher indicated warning. The cautionary interval indicates that the tested individual’s genotype shows a cancer development risk more than 1.5 times but less than 2 times higher than that of the average Korean population, signifying a level of concern and attention toward preventive measures. The warning interval indicates that the tested individual's genotype shows a cancer development risk more than 2 times higher than that of the average Korean population, signifying a significantly elevated genetic predisposition to cancer. Therefore, we strongly recommend seeking a specialist for medical

consultation, undergoing relevant tests and actively pursuing dietary and lifestyle adjustments for cancer and disease prevention.

Of the 29,350 single tests conducted for the five types of cancer, the results were as follows. For breast cancer tests, 3,942 cases were classified as normal, 1,840 cases as a caution, and 88 cases as a warning. For thyroid cancer, 4,422 cases were classified as normal, 1,196 cases as a caution, and 252 cases as a warning. For lung cancer, 5,861 cases were classified as normal, 7 cases as a caution, and 2 cases as a warning. For gastric cancer, 5,834 cases were classified as normal, 35 cases as a caution, and 1 case as a warning. For colorectal cancer, 5,748 cases were classified as normal, 121 cases as a caution, and 1 case as a warning. Ranking the results for the warning category showed that the top-ranked cancer type was thyroid cancer, with 252 cases, followed by breast cancer with 88 cases, lung cancer with two cases and gastric and colorectal cancer with one case each. In the caution category, breast cancer ranked first with 1,840 cases, followed by thyroid cancer with 1,196 cases, colorectal cancer with 121 cases, gastric cancer with 35 cases, and lung cancer with seven cases. In the normal category, lung cancer ranked first with 5,861 cases, followed by gastric cancer with 5,834 cases, colorectal cancer with 5,748 cases, thyroid cancer with 4,422 cases, and breast cancer with 3,942 cases (Table 2).

The overlap of caution and warning categories among the five types of cancer was investigated. Of the 1,840 cautions for breast cancer, there were 368 cautions for thyroid cancer, 75 warnings 1 caution for colorectal cancer, 1 caution for lung cancer, and 10 cautions and 1 warning for gastric cancer. Among the 88 warnings for breast cancer, there were 16 cautions and 4 warnings for thyroid cancer, 1 caution for colorectal cancer, and 1 caution for gastric cancer. Of the 1196 cautions for thyroid cancer, there were 368 cautions for breast cancer, 16 warnings and 19 cautions for colorectal cancer, 2 cautions for lung cancer, and 1 warning and 4 cautions for gastric cancer. Among the 252 warnings for thyroid cancer, there were 74 cautions for breast cancer, 2 warnings 7 cautions for colorectal cancer, and 2 cautions for gastric cancer. Regarding colorectal cancer, of the 121 warnings, there were 38 cautions 1 warning for breast cancer 19 cautions, and 7 warnings for thyroid cancer. There were 7 cautions for lung cancer, of which 5 were for breast cancer and 2 for thyroid cancer. Additionally, there were 2 warnings for lung cancer, 1 caution for breast cancer, and 1 caution for thyroid cancer. There were 35 cautions for gastric cancer, comprising 10 cautions for breast cancer, 1 warning 4 cautions for thyroid cancer, and 2 warnings. The 1 warning for gastric cancer was also a caution for breast cancer.

In our analysis of the data from 5,870 samples that were subjected to the OA test in 2017, when compared with the incidence of cancers in women in South Korea, as reported by the National Cancer Information Center, the following results were obtained for the major cancer types in women in 2017. The top five cancer incidence rates were ranked as follows (in descending order): Breast cancer with 22,300 cases, thyroid cancer with 20,135 cases, colorectal cancer with 11,458 cases, stomach cancer with 9,769 cases, and lung cancer with 8,328 cases. Expressed as percentages, breast cancer accounted for 20.3%, thyroid cancer 18.3%, colorectal cancer 10.4%, stomach cancer 8.9%, and lung cancer 7.6% of the total cases. The Crude Rate (CR) per 100,000 population was 86.9, 78.5, 10.4, 8.9, and 7.6 for breast, thyroid, colorectal, stomach, and lung cancers, respectively. The Age-Standardized Rates (ASR*) per 100,000 population were as follows: 68.9 ASR* for thyroid cancer, 63.0 ASR* for breast cancer, 23.0 ASR* for colorectal cancer, 21.1 ASR* for stomach cancer, and 15.8 ASR* for lung cancer (Table 3, Fig. 1).

For the top five cancer types, the 5-year cancer prevalence rates among women from 2013-2017 were as follows: Thyroid cancer ranked first, with 118,874 cases; breast cancer ranked second, with 94,601 cases; colorectal cancer ranked third, with 42,741 cases; stomach cancer ranked fourth, with 37,813 cases; and lung cancer ranked fifth, with 20,870 cases. When converted into percentages, thyroid cancer accounted for 27.5%, breast cancer 21.9%, colorectal cancer 9.9%, stomach cancer 8.7%, and lung cancer 4.8% of the total cases. The CR and ASR* were as follows: 463.4 and 373.9, 368.8 and 254.4, 166.6 and 86.9, 147.4 and 81.5, and 81.4 and 42.6 for thyroid, breast, colorectal, stomach and lung cancers, respectively (Table 4).

Table 2: OA panel test results of blood samples for five cancer types in women in 2017

Type of cancer	Normal	Caution	Warning
Breast	3,942	1,840	88
Thyroid	4,422	1,196	252
Lung	5,861	7	2
Gastric	5,834	35	1
Colorectal	5,748	121	1

Table 3: Cancer incidence in women in 2017 based on national cancer information center data

Ranking	Type of cancer	Prevalence	%	Crude Rate (CR)	Age-Standardized Rates (ASR*)
1	Breast	22,300	31	86.9	63.0
2	Thyroid	20,135	28	78.5	68.9
3	Colorectal	11,458	16	44.7	23.0
4	Gastric	9,769	14	38.1	21.1
5	Lung	8,328	11	32.5	15.8

*Ages were adjusted to the Korean standard population

Table 4: The 5-year (2013-2017) cancer prevalence rates in women (national cancer information center)

Ranking	Type of cancer	Prevalence	%	Crude Rate (CR)	Age-Standardized Rate (ASR*)
1	Thyroid	111,874	36	463.4	373.9
2	Breast	94,601	31	368.8	254.4
3	Colorectal	42,741	14	166.6	86.9
4	Gastric	37,813	12	147.4	81.5
5	Lung	20,870	7	81.4	42.6

*Ages were adjusted to the Korean standard population

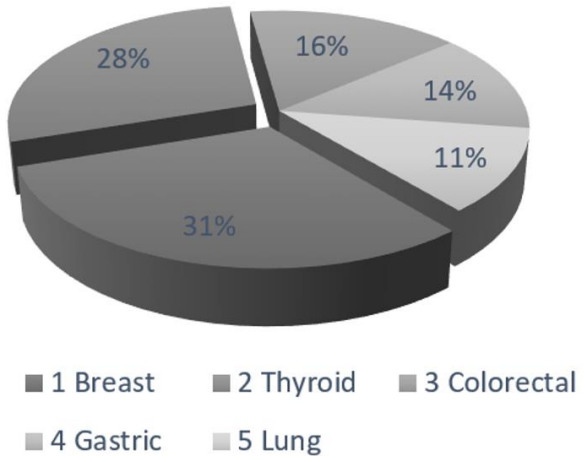

Fig. 1: Cancer incidence in women in 2017

Comparison and analysis of the OA panel results of the samples from 2017 and the data from the National Cancer Information Center showed that the highest-ranking cancer based on the cumulative percentage was breast cancer, followed by thyroid, colorectal, stomach, and lung cancers. These results were consistent with the top five cancer incidences provided by the National Cancer Information Center for Women in 2017. Based on the cumulative percentage of cancer prevalence among Korean women from 2013-2017, thyroid cancer ranked first, followed by breast, colorectal, stomach, and lung cancers.

Discussion

The results of the 2017 female cancer OA panel showed the same pattern as the cancer incidence rates in women announced by the National Cancer Information Center in 2017. The cancers with the incidence rates in descending order were breast cancer, thyroid cancer, colon cancer, stomach cancer, and lung cancer. These results suggest that the OA panel test results accurately reflect the current state of cancer incidence in Korean women. This test can, therefore, be used as an important tool for cancer prevention and early diagnosis and can help track and compare cancer prevalence and incidence. The cumulative data from the National Cancer Information Center between 2013 and 2017 showed different rankings for breast and thyroid cancers compared to the individual results of 2017. Despite this discrepancy, both breast and thyroid cancers consistently appeared among the top-ranked cancers. The fact that breast and thyroid cancers accounted for a significantly higher proportion (49.4%) of cases than colon, stomach, and lung cancers suggests a high correlation. In fact, it highlights the high prevalence of breast and thyroid cancers, which are within the caution and warning ranges (95.3%) of the five-panel OA test for cancers in women.

This study had some limitations. First, it was conducted by a single medical institution in South Korea; thus, the results may not fully represent all SNPs. Second, the ministry of health and welfare and the Korean centers for disease control and prevention lack specific guidelines or regulations regarding SNP testing for individual diseases or cancer types. This implies that different SNPs may be used in SNP tests performed by different institutions. To overcome the limitations of different SNP panel tests, it is necessary to accumulate more data for SNP testing related to the genetic susceptibility prediction for each cancer type or disease. Through the accumulation of results, it is expected that the accuracy of future tests can be further improved. As research continues, SNP testing in the field of preventive medicine can become increasingly important and advanced, contributing to the improvement of the quality of direct-to-consumer tests offered by many institutions.

Conclusion

Based on the results of the five-panel OA test for cancers in women, we confirmed that breast and thyroid cancers have a high incidence among Korean women, accurately reflecting the current state of cancer incidence in the country. This indicates that the test can be utilized as an important tool for cancer prevention and early diagnosis. The high proportion of breast and thyroid cancers compared to that of the other types of cancer underscores their prevalence and significance within the test's alert and warning ranges.

Our findings make significant contributions to the scientific community and have economic implications. They emphasize the importance of SNP testing in preventive medicine and its potential role in public health surveillance by tracking cancer prevalence and incidence rates. Advancements in SNP testing can lead to improved accuracy of future tests and assist in the development of personalized preventive strategies.

Acknowledgment

We express our gratitude to the publisher for their support in pub lishing our research article. The resources and platform provided by the publisher have allowed us to reach a broader audience with our findings.

Funding Information

This study was supported by a research fund provided by Dankook University in 2023.

Author's Contributions

Both authors have equally contributed to this study.

Ethics

This study was approved by the Dankook University Institutional Review Board (IRB No. 2020-10-013).

References

Amos, C. I., Wu, X., Broderick, P., Gorlov, I. P., Gu, J., Eisen, T., ... & Houlston, R. S. (2008). Genome-wide association scan of tag SNPs identifies a susceptibility locus for lung cancer at 15q25. 1. *Nature Genetics*, *40*(5), 616-622. https://doi.org/10.1038/ng.109

Dong, J., Jin, G., Wu, C., Guo, H., Zhou, B., Lv, J., ... & Shen, H. (2013). Genome-wide association study identifies a novel susceptibility locus at 12q23. 1 for lung squamous cell carcinoma in han chinese. *PLoS Genetics*, *9*(1), e1003190. https://doi.org/10.1371/journal.pgen.1003190

Easton, D. F., Pooley, K. A., Dunning, A. M., Pharoah, P. D., Thompson, D., Ballinger, D. G., ... & Bowman, R. (2007). SEARCH collaborators. Meyer KB, Haiman CA, Kolonel LK, Henderson BE, Le Marchand L, Brennan P, Sangrajrang S, Gaborieau V, Odefrey F, Shen CY, Wu PE, Wang HC, Eccles D, Evans DG, Peto J, *et al*: Genome-wide association study identifies novel breast cancer susceptibility loci. *Nature*, *447*, 1087-1093. https://doi.org/10.1038/nature05887

Estrada-Florez, A. P., Bohórquez, M. E., Sahasrabudhe, R., Prieto, R., Lott, P., Duque, C. S., ... & Carvajal-Carmona, L. G. (2016). Clinical features of Hispanic thyroid cancer cases and the role of known genetic variants on disease risk. *Medicine*, *95*(32). https://doi.org/10.1097/MD.0000000000004148

Genome Analysis, (2023). Available from: https://genolifecare.com

Grady, W. M., Willis, J., Guilford, P. J., Dunbier, A. K., Toro, T. T., Lynch, H., ... & Markowitz, S. (2000). Methylation of the CDH1 promoter as the second genetic hit in hereditary diffuse gastric cancer. *Nature Genetics*, *26*(1), 16-17. https://doi.org/10.1038/79120

Gu, C., Zhou, L., & Yu, J. (2013). Quantitative assessment of 2q35-rs13387042 polymorphism and hormone receptor status with breast cancer risk. *PLoS One*, *8*(7), e66979. https://doi.org/10.1371/journal.pone.0066979

Han, W., Woo, J. H., Yu, J. H., Lee, M. J., Moon, H. G., Kang, D., & Noh, D. Y. (2011). Common genetic variants associated with breast cancer in Korean women and differential susceptibility according to intrinsic subtype. *Cancer Epidemiology, Biomarkers & Prevention*, *20*(5), 793-798. https://doi.org/10.1158/1055-9965.EPI-10-1282

He, H., Li, W., Liyanarachchi, S., Wang, Y., Yu, L., Genutis, L. K., ... & de la Chapelle, A. (2018). The role of NRG1 in the predisposition to papillary thyroid carcinoma. *The Journal of Clinical Endocrinology & Metabolism*, *103*(4), 1369-1379. https://doi.org/10.1210/jc.2017-01798

Jendrzejewski, J., Liyanarachchi, S., Eiterman, A., Thomas, A., He, H., Nagy, R., ... & de la Chapelle, A. (2019). Fine mapping of 14q13 reveals novel variants associated with different histological subtypes of papillary thyroid carcinoma. *International Journal of Cancer*, *144*(3), 503-512. https://doi.org/10.1002/ijc.31933

Jones, A. M., Howarth, K. M., Martin, L., Gorman, M., Mihai, R., Moss, L., ... & Bremmer, C. (2012). Consortium TCUKIN, Tomlinson I, Carvajal-Carmona LG: Thyroid cancer susceptibility polymorphisms: Confirmation of loci on chromosomes 9q22 and 14q13, validation of a recessive 8q24 locus and failure to replicate a locus on 5q24. *J Med Genet*, *49*(3), 158-163. https://doi.org/10.1136/jmedgenet-2011-100586

Li, L., Guo, G., Wang, F., Lv, P., Zhu, M., Gu, Y., ... & Pei, X. (2018). TOX high mobility group box family member 3 rs3803662 and breast cancer risk: A meta-analysis. *Journal of Cancer Research and Therapeutics*, *14*(Suppl 1), S208-S212. https://doi.org/10.4103/0973-1482.167611

Lin, Y., Fu, F., Chen, M., Huang, M., & Wang, C. (2014). Associations of two common genetic variants with breast cancer risk in a Chinese population: A stratified interaction analysis. *PloS One*, *9*(12), e115707. https://doi.org/10.1371/journal.pone.0115707

Lin, Y., Yuan, J., Wang, L., Wang, L., Ma, Y., Wang, Y., ... & Zhao, H. (2015). Correlation between SNPs in CDH1 and gastric cancer in Chinese population. *Open Medicine*, *10*(1). https://doi.org/10.1515/med-2015-0007

Liu, L., Su, Q., Li, L., Lin, X., Gan, Y., & Chen, S. (2014). The common variant rs4444235 near BMP4 confers genetic susceptibility of colorectal cancer: An updated meta-analysis based on a comprehensive statistical strategy. *Plos One*, *9*(6), e100133. https://doi.org/10.1371/journal.pone.0100133

Moll, U. M., & Petrenko, O. (2003). The MDM2-p53 interaction. *Molecular Cancer Research*, *1*(14): 1001-1008. PMID: 14707283

Pandey, N., Pal, S., Sharma, L. K., Guleria, R., Mohan, A., & Srivastava, T. (2017). SNP rs16969968 as a strong predictor of nicotine dependence and lung cancer risk in a North Indian population. *Asian Pacific Journal of Cancer Prevention: APJCP*, *18*(11), 3073. https://doi.org/10.22034/APJCP.2017.18.11.3073

Perkel, J. (2008). SNP genotyping: Six technologies that keyed a revolution. *Nature Methods*, *5*(5), 447-453. https://doi.org/10.1038/nmeth0508-447

Pittman, A. M., Webb, E., Carvajal-Carmona, L., Howarth, K., Di Bernardo, M. C., Broderick, P., ... & Houlston, R. S. (2008). Refinement of the basis and impact of common 11q23. 1 variation to the risk of developing colorectal cancer. *Human Molecular Genetics*, *17*(23), 3720-3727. https://doi.org/10.1093/hmg/ddn267

Ragazzo, M., Puleri, G., Errichiello, V., Manzo, L., Luzzi, L., Potenza, S., ... & Giardina, E. (2021). Evaluation of OpenArray™ as a genotyping method for forensic DNA phenotyping and human identification. *Genes*, *12*(2), 221. https://doi.org/10.3390/genes12020221

Tatem, A. J., Guerra, C. A., Atkinson, P. M., & Hay, S. I. (2004). Momentous sprint at the 2156 Olympics?. *Nature*, *431*(7008), 525-525. https://doi.org/10.1038/431525a

Thanh, N. T. N., Lan, N. T. T., Phat, P. T., Giang, N. D. T., & Hue, N. T. (2018). Two polymorphisms, rs2046210 and rs3803662, are associated with breast cancer risk in a Vietnamese case-control cohort. *Genes & Genetic Systems*, *93*(3), 101-109. https://doi.org/10.1266/ggs.17-00053

Wang, F., Yan, D., Ji, X., Han, J., Chen, M., Qiao, H., & Zhang, S. (2016). rs965513 polymorphism as a common risk marker is associated with papillary thyroid cancer. *Oncotarget*, *7*(27), 41336. https://doi.org/10.18632/oncotarget.9324

Yao, K., Hua, L., Wei, L., Meng, J., & Hu, J. (2015). Correlation between CASC8, SMAD7 polymorphisms and the susceptibility to colorectal cancer: An updated meta-analysis based on GWAS results. *Medicine*, *94*(46). https://doi.org/10.1097/MD.0000000000001884

Young, R. P., Hopkins, R. J., Hay, B. A., Epton, M. J., Black, P. N., & Gamble, G. D. (2008). Lung cancer gene associated with COPD: Triple whammy or possible confounding effect?. *European Respiratory Journal*, *32*(5), 1158-1164. https://doi.org/10.1183/09031936.00093908

Zheng, X., Wang, L., Zhu, Y., Guan, Q., Li, H., Xiong, Z., ... & Cheng, L. (2012). The SNP rs961253 in 20p12. 3 is associated with colorectal cancer risk: A case-control study and a meta-analysis of the published literature. *PloS One*, *7*(4), e34625. https://doi.org/10.1371/journal.pone.0034625