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Antibiotic use predicts an increased risk of cancer

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Antibiotic use has been hypothesized to be associated with the risk of cancer but the evidence is sparse and inconsistent. The aim of the present study was to determine whether antibiotic use predicts the development of various cancers. This nationwide cohort study included 3,112,624 individuals, aged 30–79 years, with no history of cancer. Information on their antibiotic use between 1995 and 1997 was obtained from the Drug Prescription Registry. During the period 1998–2004, 134,070 cancer cases were ascertained from the Finnish Cancer Registry. Cox proportional hazards regression was used to estimate the relative risks (RRs) with 95% confidence intervals (95% CIs). Antibiotic use was associated with an increased risk of cancer: for categories of increasing antibiotic use (0–1, 2–5 and ≥6 prescriptions), RRs (95% CIs) for cancer were 1.0 (reference), 1.27 (1.26–1.29) and 1.37 (1.34–1.40). RRs (for comparison of lowest and highest exposure group) for the most common primary sites *i.e.* prostate, breast, lung and colon were 1.39 (1.31–1.48), 1.14 (1.09–1.20), 1.79 (1.67–1.92), and 1.15 (1.04–1.26), respectively. RRs for other primary sites varied between 0.90 (0.76–1.05) for ovary to 2.60 (1.60–4.20) for endocrine gland (excluding thyroid). In conclusion, antibiotic use predicts an increased risk of cancer. Because of the design of our study the possibility of residual confounding cannot be excluded and further studies are required to confirm the results.
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Key words: antibiotics; cancer; cohort study; risk factor

Antibiotics are one of the most widely used types of medicines. There are large differences in outpatient antibiotic use across countries. For example, France uses over 3 times as many defined daily doses per 1,000 inhabitants per day (DID) as The Netherlands (32.2. DID *vs.* 10.0 DID).[1] Compared with other European countries, there is a moderate rate of antibiotic use (17.1 DID) in Finland.[1]

It has been suggested that up to 75% of antibiotic use has a questionable therapeutic value.[2] The well-known consequence of antibiotic use—whether appropriate or inappropriate—is the resistance of bacteria to antibiotics.[3] At the same time, antibiotic use is increasingly suggested to have unwanted effects on health.[4–7]

An earlier observation from Finland indicated that long-term antibiotic use for urinary tract infections was associated with an increased risk of breast cancer in women under 50 years of age, compared with women who did not use antibiotics.[6] Antibiotic use was also associated with an increased risk of breast cancer in a case-control study conducted in the United States[7] while more recent studies have not, or at most weakly, confirmed the association.[8–12] It has been suggested that antibiotics have an effect on the composition and functioning of intestinal microbiota and on inflammation and immune functions.[13] Through these effects antibiotics could play a role in the development of many types of cancer. On the other hand, antibiotic treatment may reduce the risk of some cancers (*e.g.* gastric cancer).[14] Given the widespread use of antibiotics[1] and high incidence of cancer—over 10 million new cancer cases occur each year worldwide[15]—it is important to determine whether there is an association between the use of antibiotics and the risk of cancer.

To determine whether antibiotic use predicts the development of cancer, we conducted a large-scale cohort study using information from the nationwide Finnish Cancer and Drug Prescription Registries.

Material and methods

Participants

The study cohort was identified from the Population Register in Finland, which maintains basic demographic data on all citizens, each of whom is assigned a personal identification number. We identified all individuals who were alive, between 30 and 79 years of age, and resident in Finland on January 1, 1995 (n = 3,312,509). Subjects who were diagnosed with cancer (n = 106,754) between 1953 and 1997, or died (n = 93,131) between January 1, 1995 and December 31, 1997, were excluded from the study. The final study cohort comprised 1,492,984 men and 1,619,640 women.

Information on cancer

Incident cancer cases were identified through linkage with the Finnish Cancer Registry. The registry provides information on the personal identification number of the patient, the cancer site using the 7th revision of the International Classification of Diseases, the histology and malignancy of tumour, the date of diagnosis, and the cancer-related death. It covers over 99% of cancers identified in Finland with great accuracy.[16] During 7 years of follow-up, from January 1, 1998 to December 31, 2004, 134,070 cancers were identified.

Information on medication

Information on antibiotic use was obtained from the nationwide Drug Prescription Registry kept by the Social Insurance Institution. In Finland, all medicines prescribed by physicians and reimbursed by the National Sickness Insurance Scheme are registered centrally in the Drug Prescription Registry. The only antibiotics excluded from the register are those administered in hospitals (17% of all antibiotics) and those which are not included in the reimbursement system due to their low price. The later, however, mainly concerns children. The Drug Prescription Registry includes information on the personal identification number of patient, the type of medicine prescribed according to the Anatomical Therapeutic Chemical (ATC) classification system and the date the prescription was filled. The register was established in 1993, and its coverage has been almost complete since 1995. For the present study, all antibiotic prescriptions (ATC code J01A), from January 1, 1995 to December 31, 2004, were identified.

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Prescriptions for hormone replacement therapy (HRT) between 1995 and 1997 for women 50 years of age or older (January 1, 1995) were also identified in the Drug Prescription Registry. Participants were categorized as non-users (no HRT prescriptions, 68.6% of women), regular users of estrogens (at least 8 prescriptions of estrogens, ATC code G03C, 8.7%), regular users of progestogens and estrogens in combination (at least 8 prescriptions of combination medicine, ATC code G03F, 5.7%), and occasional users of HRT (less than 8 prescriptions of estrogens and/or combination medicine, 17.0%).

Consistency of antibiotic use

To assess consistency of antibiotic use over time, frequency of use in 1995–1997 was compared with that in 1998–2000, and in 2001–2003. Data on antibiotic use covering each time window (*i.e*. 1995–1997, 1998–2000 and 2001–2003) were combined and participants were categorized into 1 of 3 exposure groups (0–1, 2–5 and $\geq$6) based on the number of antibiotic prescriptions purchased within each 3-year period. The annual antibiotic use was defined as the sum of the years (*i.e*. 0, 1, 2, 3 years) when antibiotics were purchased within each three-year period. The Spearman rank-correlation coefficients for the three-category exposure variable (number of prescriptions) between 1995 and 1997 and 1998 and 2000, and 1995 and 1997 and 2001 and 2003 were 0.50 and 0.44, respectively. The corresponding coefficients for annual antibiotic use were 0.43 and 0.42.

Statistical analysis

This was a cohort study where antibiotic use between 1995 and 1997 was used to determine antibiotic exposure. The follow-up time for each participant was calculated from January 1, 1998 to the date of the first cancer, death from any cause, or December 31, 2004, whichever came first. Cox proportional hazards regression was used to estimate the relative risk (RR) of cancer and its corresponding 95% confidence intervals (95% CIs) associated with antibiotic use. All analyses were adjusted for age and sex. In addition, when postmenopausal breast cancer and female genital cancers were considered, analyses were adjusted for the use of HRT.

Further analyses were restricted to participants with at least 5 years follow-up. We also conducted stratified analyses according to age (65 years or less and more than 65 years). In addition, breast cancer was analyzed according to menopausal status; breast cancer cases aged 51 years or younger at the time of diagnosis were classified as premenopausal and those over 51 years as postmenopausal.[17] Person-time for premenopausal participants was calculated from January 1, 1997 to the date of the first cancer, death from any cause, age of 52 years, or December 31, 2004, whichever came first.

Statistical analyses were performed with SAS software (version 9.1).

Ethics

The study was approved by the National Data Protection Ombudsman, the institutions keeping the registers, and the Institutional Review Board of the National Public Health Institute.

Results

The use of antibiotics was associated with an increased risk of cancer; for categories of increasing antibiotic use (0–1, 2–5 and $\geq$6 prescriptions), RRs (95% CIs) were 1.0 (reference), 1.27 (1.26–1.29) and 1.37 (1.34–1.40) (Table I). The association was found both in men (RR for comparison of lowest and highest exposure group 1.47, 95% CI 1.42–1.53) and women (RR 1.31, 95% CI 1.28–1.35). The most common cancers *i.e*. prostate, breast, lung and colon comprised half of all cancer cases; RR (95% CI) was 1.39 (1.31–1.48) for prostate, 1.14 (1.09–1.20) for breast, 1.79 (1.67–1.92) for lung, and 1.15 (1.04–1.26) for colon cancer. RRs for other primary sites varied between 0.90 (0.76–1.05) for ovary and 2.60 (1.60–4.20) for endocrine gland cancers. In addition to endocrine gland and liver cancers, the risk of nonmelanoma skin, duodenum, pancreas, kidney, bladder, male genitals (excluding prostate) and thyroid cancers as well as myeloma and leukemia was more than 1.5 times higher among participants with 6 or more antibiotic prescriptions compared with the lowest exposure group.

Restricting analyses to participants with 5 or more years follow-up did not produce significantly different results from those covering the entire study population (RR for the comparison of lowest and highest exposure group 1.37, 95% CI 1.34–1.40). Similar results were obtained when the data were stratified according to age (data not shown). We also observed an increased risk of death due to cancer with use of antibiotics (RR 1.33, 95% CI 1.28–1.38).

There was a similar tendency for an increased cancer risk with annual antibiotic use (table is available from authors by request). Compared with non-users of antibiotics, RRs (95% CI) for 1 year, 2 and 3 years of use were 1.33 (95% CI 1.32–1.35), 1.40 (1.38–1.42) and 1.46 (1.43–1.49), respectively. RRs (95% CI) for 3 years of use for different primary sites varied from 0.99 (0.86–1.14) for ovary to 1.81 (95% CI 1.62–2.02) for nonmelanoma skin cancers and was 1.21 (1.15–1.26) for breast and 1.57 (1.49–1.66) for prostate cancers.

Discussion

In our extensive cohort study, antibiotic use did predict an increased risk of cancer. Our results are in accord with a previous study in Finland where young women exposed to antibiotics for treatment of urinary tract infection had a significantly elevated risk of breast cancer.[6] We can also confirm findings from the Seattle case-control study where cumulative exposure to antibiotics for more than 500 days was associated with a greater than two-fold risk of breast cancer.[7] Consistently with our results, the association was found even in the lowest exposure category of 1–50 days of use. Our findings might, however, appear to conflict with those of recent studies[8–12,18] where no consistent associations between antibiotic use and cancer were found. Previous studies have mainly concentrated on breast cancer while our study extends the focus to several cancers.

The major limitation of our study is the lack of information on known risk factors of cancer.[19] Whether this missing information substantially confounds our results is difficult to determine because there is limited data on determinants of antibiotic use. Smoking is potentially important confounder as it is associated with both the risk of some cancers[19] and antibiotic use.[20] Especially the association between lung cancer and antibiotic use may be explained by smoking. On the other hand, as antibiotic use was at least as strongly associated with cancers not related to smoking such as nonmelanoma skin cancer as tobacco-related cancers, it is unlikely that smoking fully explains the antibiotic-cancer association. However, we cannot rule out the possibility that there are some other unknown and/or unmeasured factors which confound our results. For example, the actual or perceived need for antibiotics is probably related to socioeconomic factors and a greater chance of getting medical care and having cancer detected early. Such uncontrolled confounding would explain our findings that use of antibiotics slightly increased risk of several cancer types. It is, however, unlikely that there are other risk factors of cancer which are so strongly related to use of antibiotics that they could explain a substantial increase in cancer risk associated with antibiotic use. Furthermore, adjusting for known risk factors did not materially change the results in previous study.[7] To be able to disentangle confounding factors from the true causal effects of antibiotics on cancer, the determinants of antibiotic use should be clarified. More information on risk factors of cancer is also required.

Another limitation of our study is the lack of information on indications for antibiotic use. Mounting evidence suggests an association between infectious agents, chronic inflammation and cancer.[21] Antibiotic treatment may, thus, be only a marker of an

TABLE I – AGE- AND SEX-ADJUSTED RRS (95% CI) FOR CANCER ACCORDING TO NUMBER OF ANTIBIOTIC PRESCRIPTIONS

Cancer	Number of cancer cases	0–1 Prescription	2–5 Prescriptions		6 or more prescriptions	
Total cancer	134,070	1.00	1.27	(1.26–1.29)	1.37	(1.34–1.40)
Lymphatic tissue, blood tissue						
Leukemia	2,369	1.00	1.37	(1.25–1.50)	1.73	(1.48–2.02)
Lymphomas	5,487	1.00	1.30	(1.22–1.38)	1.41	(1.26–1.57)
Myeloma	1,566	1.00	1.34	(1.20–1.50)	1.61	(1.33–1.95)
Mouth and pharynx	2,594	1.00	1.21	(1.11–1.33)	1.38	(1.17–1.64)
Digestive system						
Esophagus	1,268	1.00	1.03	(0.90–1.17)	0.95	(0.72–1.26)
Stomach, excluding cardia	3,825	1.00	1.10	(1.02–1.19)	1.14	(0.99–1.31)
Stomach, only cardia	759	1.00	1.16	(0.98–1.38)	1.28	(0.93–1.77)
Duodenum	446	1.00	1.51	(1.23–1.85)	1.51	(1.02–2.23)
Colon	7,513	1.00	1.17	(1.11–1.24)	1.15	(1.04–1.26)
Rectum	5,126	1.00	1.14	(1.07–1.21)	1.03	(0.90–1.17)
Liver	1,515	1.00	1.38	(1.23–1.55)	1.93	(1.60–2.33)
Gall bladder	1,365	1.00	1.01	(0.89–1.15)	1.41	(1.16–1.72)
Pancreas	4,556	1.00	1.31	(1.22–1.40)	1.57	(1.40–1.76)
Respiratory organs						
Trachea/lung	12,654	1.00	1.32	(1.27–1.38)	1.79	(1.67–1.92)
Other respiratory organs (nose, larynx)	925	1.00	1.17	(1.00–1.37)	1.45	(1.08–1.94)
Urinary organs						
Kidney	4,286	1.00	1.27	(1.18–1.36)	1.55	(1.37–1.75)
Bladder	4,365	1.00	1.37	(1.28–1.46)	1.52	(1.33–1.73)
Skin						
Melanoma	3,819	1.00	1.16	(1.08–1.25)	1.26	(1.09–1.44)
Other skin (excludes basal cell carcinoma)	3,907	1.00	1.46	(1.36–1.57)	1.86	(1.66–2.08)
Eye	307	1.00	1.28	(0.99–1.65)	1.08	(0.64–1.83)
Central nervous system	4,351	1.00	1.25	(1.17–1.34)	1.31	(1.16–1.48)
Thyroid	1,769	1.00	1.31	(1.18–1.46)	1.67	(1.41–1.99)
Other endocrine glands	176	1.00	1.31	(0.93–1.84)	2.60	(1.60–4.20)
Bone	147	1.00	1.11	(0.76–1.62)	1.08	(0.50–2.32)
Connective tissues	753	1.00	1.35	(1.15–1.58)	1.07	(0.76–1.51)
Other/unspecified	3,214	1.00	1.22	(1.13–1.33)	1.53	(1.34–1.74)
Breast (only women)						
Breast, all[1]	21,869	1.00	1.16	(1.13–1.20)	1.14	(1.09–1.20)
Breast, age 51 years or less (pre)	6,273	1.00	1.19	(1.13–1.26)	1.23	(1.11–1.35)
Breast, age over 51 years (post)[1]	10,988	1.00	1.18	(1.13–1.23)	1.15	(1.07–1.23)
Female genitals[1]						
Cervix uteri	1,385	1.00	1.12	(1.00–1.26)	1.06	(0.85–1.31)
Corpus uteri	4,395	1.00	1.01	(0.94–1.08)	0.95	(0.84–1.07)
Ovary	2,691	1.00	0.99	(0.91–1.08)	0.90	(0.76–1.05)
Other female genitals	715	1.00	1.07	(0.90–1.26)	1.21	(0.92–1.58)
Cervix uteri carcinoma *in situ*	579	1.00	1.10	(0.92–1.32)	0.94	(0.67–1.34)
Male genitals						
Prostate	23,820	1.00	1.36	(1.32–1.40)	1.39	(1.31–1.48)
Other male genitals	362	1.00	0.99	(0.76–1.28)	1.59	(0.96–2.63)

[1]Further adjusted with HRT.

underlying infection predisposing the patient to neoplasia. However, given that three-quarters of antibiotics are prescribed for respiratory tract infections,[22] it is unlikely that the observed association is completely due to the infection. However, we cannot rule out the possibility that antibiotic use is symptomatic of poor health in general and a weakened immune system, which could both lead to more infections requiring antibiotics and failure to destroy cancer cells. The relatively low strength of associations between antibiotic use and cancer suggests that antibiotic use may represent an indicator rather than a cause of cancer.

Although the present study was performed in a cohort design, our data may be criticized on the grounds that the medication period examined was short and relatively close to the time of cancer diagnosis. However, acceptable consistency of antibiotic use was found, suggesting that we used a reasonably valid measure of long-term antibiotic use. Moreover, the restriction of analyses to participants with at least 5 years of cancer-free follow-up did not alter the antibiotic-cancer association. Caution must be taken when interpreting the results because multiple tests were performed and the sample size was so large that even a small increase in the risks, possibly irrelevant, became statistically significant.

The validity, accuracy and completeness of the registers we used are well demonstrated[16] but the limitations of relying on the pharmacy records include a rough estimation of antibiotic exposure. Because of the absence of information on actual usage of the dispensed medication, participants who failed to take their medication have been incorrectly classified as users. Moreover, information on the least expensive medications and antibiotics administered in hospitals were also lacking. These facts dilute the association and bias the relative risks toward unity. Thus, further epidemiological studies with different designs and more detailed analyses including timing, duration, and amount of antibiotic exposure are urgently required.

Although the results of our study should be interpreted conservatively because of the concerns expressed above, there are some plausible biological mechanisms in which antibiotics may increase the risk of cancer.

First, antibiotics themselves may be carcinogenic. Although antibiotics are generally nongenotoxic,[23] some antibiotics have been shown to have genotoxic potential.[24] In animal models, exposure to antibiotics has shown to promote the development of tumors in liver[25] and breast.[26] On the other hand, some antibiotics have shown dose-dependent cytotoxicity against bladder and lung cancer cells.[27,28] In general, evidence of the carcinogenicity of antibiotics is very limited.

Second, antibiotic treatment may promote the development of cancer through its effects on intestinal microbiota which have a

significant impact on the health of the host.[29] The common side effect of treatment with most antibiotics is loss of beneficial anaerobic organisms and increase in potentially pathogenic microbes in intestinal microbiota.[30] These quantitative and qualitative changes are only partly known but may last several months.[31,32] Antibiotic-induced disturbance of intestinal microbiota may increase the risk of cancer because of decreased conversion of health-promoting compounds such as phytochemicals to biologically active compounds that are hypothesized to play an inhibitory role in carcinogenesis.[5,33] Antibiotics may also increase the bacterial production of toxins and decrease the number of bacteria which prevent tumorigenesis.[29] They may also interfere with estrogen metabolism and hence have an effect particularly on the risk of hormone dependent cancers.[34]

Third, antibiotic treatment, especially if long-term and repeated, may have detrimental effects on immune defence, which could predispose the patient to insufficient defence against malignant processes. Some antibiotics such as tetracyclines, macrolides and fluoroquinolones, have an effect on the production of cytokines, prostaglandins, and matrix methalloproteinase, as well as the proliferation of T-lymphocyte.[35–37] Antibiotics can also affect the immune system by disturbing the intestinal microbiota, which plays an important role in maintaining a healthy immune system.[38] Such an explanation would correspond with our findings that the association was observed for a multitude of cancer types in various sites, and that the increase in relative risks was only moderate.

In conclusion, findings of the present study suggest that antibiotic use, especially repeated prescriptions is associated with increased risk of cancer. The observational design of our study does not permit us to determine whether antibiotic use is causally related to cancer or whether there are some other factors, such as infectious agents or behavioral factors to explain our findings. To clarify the reasons for the association, epidemiological studies on determinants of antibiotic use and research on the biological effects of antibiotics are both required. Further epidemiological studies with different designs, study populations and more detailed information on antibiotic exposure are also needed. An appropriate use of antibiotics can certainly be lifesaving and the importance of antibiotics in the treatment of bacterial infections should not be underestimated.

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