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Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2025 January 01.

Published in final edited form as:

Cancer Epidemiol Biomarkers Prev. 2024 July 01; 33(7): 965–967. doi:10.1158/1055-9965.EPI-24-0266.

Appendectomy and risk of prostate cancer in the Health Professionals Follow-up Study

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Abstract

Background: Appendectomy is a common surgical procedure to treat appendicitis. Limited studies examined its association on prostate cancer, with one large cohort study suggesting significant increased risk of overall and advanced prostate cancer, especially among younger men.

Methods: A total of 49,104 men in the Health Professionals Follow-up Study were followed from 1986 to 2016. Cox proportional hazards models were applied to evaluate the association between self-reported history of appendectomy and risk of overall and subtype specific prostate cancer, adjusted for multiple risk factors.

Results: During 30 years of follow-up, we documented 7,253 overall prostate cancer including 579 advanced and 1,092 lethal events. Compared to men without appendectomy, those who reported at baseline having had appendectomy were not at higher risk of overall (hazard ratio (HR)=1.01, 95% CI = 0.95 to 1.07), advanced (HR=0.99, 95% CI = 0.81 to 1.23) or lethal (HR=1.04, 95% CI = 0.89 to 1.20) prostate cancer. The association remained null when stratified by age.

Conclusions: We found no evidence of an association between appendectomy and risk of overall and clinically important prostate cancer.

Impact: We showed that appendectomy was not associated with overall or advanced prostate cancer adjusted for multiple risk factors among a large population of men with 30 years of follow-up.

Introduction

Appendectomy is a common medical procedure usually performed to treat appendicitis. Two small studies reported null associations between history of appendectomy and risk of prostate cancer in the 1990s[1,2]. However, one recent Swedish cohort reported significantly increased risk of overall (HR [95% CI], 1.70 [1.08–2.67]), advanced (4.42 [1.74–11.22])

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Conflict of interest disclosures: The authors declare no potential conflicts of interest.

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and lethal (8.95 [2.98–26.91]) prostate cancer with history of appendicitis before age 20[3]. The authors hypothesized that sensitivity to inflammation during childhood and related inflammatory response may play a role in prostate carcinogenesis[3]. However, it is also plausible that a common factor could increase risk of both appendicitis and of prostate cancer or prostate cancer detection. This association warrants further investigation.

Materials and Methods

We prospectively evaluated the association between history of appendectomy and risk of prostate cancer among 49,104 men in the Health Professionals Follow-up Study, who had no diagnosis of cancer and with available appendectomy information at baseline in 1986 (age range 40 to 75). Participants were mailed questionnaires to collect detailed information on demographics, medication and lifestyle biennially and diet every 4 years[4].

History of appendectomy and date (before 1955, 1955–1964, 1965–1974, 1980–1986) was assessed in 1986. Self-reported prostate cancer diagnoses were confirmed through medical record and pathology report review. Metastatic disease and vital status were ascertained from questionnaires, medical records, autopsy reports, and search of the National Death Index. Underlying causes of death were determined by a physician endpoint review committee (blinded to any exposure information). The mortality ascertainment was >98%[5].

Cox proportional hazards models were applied to estimate the HR(95% CI) between history of appendectomy and risk of prostate cancer. Men were followed from the return of the baseline questionnaire until date of diagnosis, death or end of the follow-up (January 2017), whichever came first. Because only 15% of men had appendectomy after 1965, we combined them with the ‘1955–1964’ group (16%). Our model was stratified by age and calendar year and adjusted for known or suspected risk factors of prostate cancer. We conducted stratified analysis by current age (<65 vs. ≥65 yr) and screening history. We also restrict to men with baseline age<55 years to approximate the young age population in the Swedish study[3].

The study protocol was approved by the institutional review boards of Harvard T.H. Chan School of Public Health, and those of participating registries as required.

Data Availability

Because of participant confidentiality and privacy concerns, data cannot be shared publicly and requests to access the Health Professionals Follow-up Study data must be submitted in writing. Information including the procedures to obtain and access data from the Health Professionals Follow-up Study is described at https://www.nurseshealthstudy.org/researchers (contact email: nhsaccess@channing.harvard.edu) and https://sites.sph.harvard.edu/hpfs/for-collaborators/.

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Results

At baseline, 18% of men reported having a history of appendectomy, with 70% taken place before 1955. At baseline, men with or without appendectomy history had similar lifestyle characteristics (Supplementary Table S1).

Overall, no association was observed between history of appendectomy and risk of prostate cancer after adjusting for multiple lifestyle risk factors. Compared to men without appendectomy history, having appendectomy was not associated with higher risk of overall (1.01 [0.95–1.07]), advanced (0.99 [0.81–1.23]), or lethal (1.04, 0.89–1.20) prostate cancer (Table 1), whether appendectomy was conducted before 1955 or in 1955–1986. The association between appendectomy and risk of prostate cancer remained null both in stratified analysis by current age (Table 2), screening history (Supplementary Table S2) and restricting to men with baseline age<55 years (Supplementary Table S3).

Discussion

Our analysis was motivated by a Swedish study that showed a marked association between appendectomy and prostate cancer risk[3]. However, the observed associations in that study were based on a limited number of cases (number of cases among men with appendicitis/ those without was 20/1664 for overall, 5/187 for advanced, and 4/78 for lethal prostate cancer). Further, data on covariables including screening were limited. In current study, we observed null associations between history of appendectomy and overall or advanced prostate cancer risk, adjusting for multiple lifestyle factors including PSA screening, even when stratifying by current age or restricting to a younger population.

One limitation in our study is that we did not have information on reasons of having appendectomy (appendicitis or incidental). Appendectomy is usually performed to treat appendicitis though it may also be conducted in the absence of appendicitis when patients suffer from chronic abdominal pain. In our study, most appendectomies conducted before 1955 would be at young age and most likely be due to appendicitis. We observed null associations in this subgroup of men.

Although we relied on self-report of appendectomy, the validity of the self-reported medical diagnoses and conditions in these health professionals is high[6,7]. We cannot exclude the possibility that some participants had appendicitis at later time, though most cases occur before age 30, with rates decreasing in older age groups[8]. As an observational study, the possibility of residual confounding could not be completely ruled out. Last, generalizability may be limited because participants were mostly white health professionals. Future studies in diverse populations are needed. The strengths of our study include prospective design with large number of cases, long-term follow-up, detailed and repeated data collection, and comprehensive lifestyle and screening information.

In summary, in a large prospective cohort of U.S. health professionals, history of appendectomy was not associated with risk of prostate cancer or its subtypes.

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Supplementary Material

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Acknowledgment:

E.L. Giovannucci was founded as an American Cancer Society Clinical Research Professor (grant CRP-23-1014041). We are grateful to the participants and research staff of the Health Professionals Follow-up Study and to the Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA.

Funding and Manuscript Deposition:

The Health Professionals Follow-up Study was supported by grant number U01 CA167552. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References:

1. Ilic M, Vlajinac H, Marinkovic J. Case-control study of risk factors for prostate cancer. Br J Cancer. Nov 1996;74(10):1682–6. doi:10.1038/bjc.1996.610 [PubMed: 8932356]
2. Mellemkjaer L, Johansen C, Linet MS, Gridley G, Olsen JH. Cancer risk following appendectomy for acute appendicitis (Denmark). Cancer Causes Control. Mar 1998;9(2):183–7. doi:10.1023/a:1008834311514 [PubMed: 9578295]
3. Ugge H, Udumyan R, Carlsson J, Davidsson S, Andren O, Montgomery S, Fall K. Appendicitis before Age 20 Years Is Associated with an Increased Risk of Later Prostate Cancer. Cancer Epidemiol Biomarkers Prev Jun 2018;27(6):660–664. doi:10.1158/1055-9965.EPI-17-1204 [PubMed: 29588305]
4. Zhang Y, Song M, Mucci LA, Giovannucci EL. Zinc supplement use and risk of aggressive prostate cancer: a 30-year follow-up study. Eur J Epidemiol Dec 2022;37(12):1251–1260. doi:10.1007/s10654-022-00922-0 [PubMed: 36326979]
5. Rich-Edwards JW, Corsano KA, Stampfer MJ. Test of the National Death Index and Equifax Nationwide Death Search. Am J Epidemiol Dec 1 1994;140(11):1016–9. doi:10.1093/oxfordjournals.aje.a117191 [PubMed: 7985649]
6. Joshipura KJ, Pitiphat W, Douglass CW. Validation of self-reported periodontal measures among health professionals. J Public Health Dent Spring 2002;62(2):115–21. doi:10.1111/j.1752-7325.2002.tb03431.x [PubMed: 11989206]
7. Hu FB, Leitzmann MF, Stampfer MJ, Colditz GA, Willett WC, Rimm EB. Physical activity and television watching in relation to risk for type 2 diabetes mellitus in men. Arch Intern Med Jun 25 2001;161(12):1542–8. doi:10.1001/archinte.161.12.1542 [PubMed: 11427103]
8. Guan L, Liu Z, Pan G, Zhang B, Wu Y, Gan T, Ouyang G. The global, regional, and national burden of appendicitis in 204 countries and territories, 1990–2019: a systematic analysis from the Global Burden of Disease Study 2019. BMC Gastroenterol Feb 22 2023;23(1):44. doi:10.1186/s12876-023-02678-7 [PubMed: 36814190]

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Table 1.

History of appendectomy and risk of prostate cancer in the Health Professionals Follow-up Study, 1986–2016

Risk of prostate cancer	History of appendectomy			
	No	Yes	By appendectomy time	
			Yes, <1955	Yes, 1955–1986
All prostate cancer, n	5663	1296	933	363
Age-adjusted model	1.0	1.02 (0.96, 1.08)	1.02 (0.95, 1.09)	1.02 (0.91, 1.13)
Full model	1.0	1.01 (0.95, 1.07)	1.01 (0.94, 1.08)	1.01 (0.90, 1.12)
Localized prostate cancer, n	4144	949	678	271
Age-adjusted model	1.0	1.04 (0.97, 1.11)	1.04 (0.96, 1.13)	1.03 (0.91, 1.17)
Full model	1.0	1.03 (0.95, 1.10)	1.03 (0.94, 1.12)	1.02 (0.90, 1.16)
Advanced prostate cancer, n	468	111	89	22
Age-adjusted model	1.0	1.01 (0.82, 1.24)	1.09 (0.87, 1.38)	0.77 (0.50, 1.18)
Full model	1.0	0.99 (0.81, 1.23)	1.09 (0.86, 1.37)	0.75 (0.48, 1.15)
Lethal prostate cancer, n	866	226	177	49
Age-adjusted model	1.0	1.04 (0.90, 1.21)	1.07 (0.90, 1.26)	0.98 (0.73, 1.31)
Full model	1.0	1.04 (0.89, 1.20)	1.06 (0.90, 1.25)	0.96 (0.72, 1.29)

All cases: T1a excluded; Localized cases: stage T1 or T2 and N0, M0; Advanced cases: stage T3b, T4, N1, or M1; Lethal cases: distant metastases or prostate cancer specific death.

Full model: adjusted for age (underly time scale), race (white/non-white), family history of prostate cancer (yes/no), lagged PSA testing history (yes/no), lagged PSA testing in 50% of possible time periods (yes/no), history of diabetes (yes/no), current aspirin use (yes/no), current body mass index (<18.5, 18.5–24.9, 25.0–29.9 and ≥30.0 kg/m^2), height (continuous), smoking status (never, current, past smoker quit >10 yrs, past smoker quit ≤10 yrs), vigorous physical activity (quintiles), intakes of red meat (quintiles) and tomato-based foods (quintiles).

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Table 2.

History of appendectomy and risk of prostate cancer by age subgroup in the Health Professionals Follow-up Study, 1986–2016

Risk of prostate cancer	History of appendectomy			
	No	Yes	By appendectomy time	
			Yes, <1955	Yes, 1955–1986
All prostate cancer, n				
Age<65	1584	308	189	119
Full model	1.0	1.08 (0.95, 1.22)	1.10 (0.94, 1.28)	1.04 (0.86, 1.26)
Age>=65	4079	988	744	244
Full model	1.0	0.99 (0.92, 1.06)	0.99 (0.91, 1.07)	0.99 (0.87, 1.13)
Localized prostate cancer, n				
Age<65	1161	234	144	90
Full model	1.0	1.13 (0.98, 1.31)	1.17 (0.98, 1.40)	1.07 (0.86, 1.33)
Age>=65	2983	715	534	181
Full model	1.0	0.99 (0.91, 1.08)	0.99 (0.90, 1.09)	1.00 (0.86, 1.16)
Advanced prostate cancer, n				
vAge<65	140	24	19	5
Full model	1.0	0.86 (0.56, 1.34)	1.05 (0.64, 1.71)	0.52 (0.21, 1.27)
Age>=65	328	87	70	17
Full model	1.0	1.04 (0.81, 1.32)	1.10 (0.84, 1.43)	0.85 (0.52, 1.39)
Lethal prostate cancer, n				
Age<65	196	45	36	9
Full model	1.0	1.11 (0.80, 1.54)	1.31 (0.91, 1.89)	0.69 (0.35, 1.35)
Age>=65	670	181	141	40
Full model	1.0	1.02 (0.86, 1.21)	1.01 (0.84, 1.22)	1.06 (0.77, 1.47)

All cases: T1a excluded; Localized cases: stage T1 or T2 and N0, M0; Advanced cases: stage T3b, T4, N1, or M1; Lethal cases: distant metastases or prostate cancer specific death.

Full model: adjusted for age (underly time scale), race (white/non-white), family history of prostate cancer (yes/no), lagged PSA testing history (yes/no), lagged PSA testing in 50% of possible time periods (yes/no), history of diabetes (yes/no), current aspirin use (yes/no), current body mass index (<18.5, 18.5–24.9, 25.0–29.9 and ≥30.0 kg/m^2), height (continuous), smoking status (never, current, past smoker quit >10 yrs, past smoker quit ≤10 yrs), vigorous physical activity (quintiles), intakes of red meat (quintiles) and tomato-based foods (quintiles).